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Contents

Information-based Holistic Electronic Healthcare

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Abstract

The article discuss important development in medical informatics from the past and in the present by way of examples. The word 'informatics' is discussed as well as the relationship of the disciplines like biomedical informatics, health informatics and healthcare informatics to medical informatics. These cross-sectional disciplines form one of the bases for biomedicine and healthcare. They play the significant role in the new presented concept of the holistic information-based healthcare.

Keywords

Medical informatics, biomedical informatics, health informatics, healthcare informatics, electronic healthcare

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1 Introduction

Opinions that I present in the article are influenced by many open-minded persons that I have had the opportunity to meet during my life. Some of them have passed away and I cannot ask them for valuable advices now.

Figure 1: Jaroslav Hájek and graduates at Carolinum in 1965.

During my studies of mathematical statistics at Charles University in Prague, Faculty of Mathematics and Physics I received a lot new knowledge from Jaroslav Hájek († 1974), an outstanding scientist and university professor that unfortunately died at the age of 48 years after the transplantation of kidney. After my graduation in 1965 (Figure 1), I started to work with the Faculty of Pediatrics of Charles University in Prague. I realized the huge complexity of medical research and I decided to continue in doctoral studies focusing on such parts of mathematics that can support applications of mathematical methods in medicine and healthcare.

In 1967 I started my Ph.D. studies in theory of information under the supervision of Albert Perez from the Institute of Theory of Information and Automation of the Czechoslovak Academy of Sciences. Albert Perez († 2003) was a leader of the Czech school of information theory and also member of IFIP. The IFIP-TC4 was founded by Francois Grémy in 1967. Albert Perez introduced two of his Ph.D. students to medical informatics topics and mediated first interactions with activities in IFIP-TC4. Due to the political changes in Czechoslovakia in the late sixties, I could apply for the postgraduate studies at the Medical Faculty, University of Edinburgh in 1967. My application was successful, but normalization processes that started in Czechoslovakia after 21st August 1968 forced me to interrupt my postgraduate studies and return to Czechoslovakia in July 1969. Nevertheless, the one year stay in the United Kingdom gave me new knowledge on practice of medical computing. At the Department of Social Medicine, Medical Faculty, University of Edinburgh, I met many new approaches and ideas on medical data analysis and computing. Some of them were published later in [1]. The International Medical Informatics Association (IMIA) grew out of the former TC4 of the IFIP in 1979. Francois Gremy († 2014) from France (the first IMIA president) and Peter Reichertz († 1987) from Germany, one of presidents of EFMI (European Federation of Medical Informatics) deserve credit for the spread of the term medical informatics all over the world. In 1978 I established medical informatics group in frame of the present Czech

Society of Biomedical Engineering and Medical Informatics (CSBME&MI). This Society became later the member of EFMI and IMIA and has contributed to the organization of many scientific events dealing with medical informatics topics. Francois Gremy participated in several medical informatics events in Czechoslovakia and he influenced me by the views on context of informatics and information sciences. In 1985 the IMIA conference 'Computer-aided medical decision making' was organized in Prague, Czechoslovakia. The Programme committee was chaired by Jan van Bemmel and among the members were also Francois Gremy and Albert Perez (Figure 2).

Figure 2: Albert Perez, Jan H. van Bemmel, Jana Zvárová, Leodegar Cigánek and Jan Münz members of the committees of the first IMIA conference in Prague 1985.

All participants of the conference received the proceedings [2] and apart of the scientific sessions they enjoyed also societal meeting at Charles University in Prague (Figure 3).

Figure 3: Shigekoto Kaihara, Jana Zvárová, Francois Gremy and J.H. van Bemmel.

Here we can see not only the first IMIA president Francois Gremy, but also two other IMIA presidents Shigekoto Kaihara († 2011) from Japan and Jan van Bemmel from The Netherlands. The sudden death of Shigekoto Kaihara was a great loss for medical informatics community over all the world. The second IMIA conference 'Medical Informatics and Medical Education' was organized in Prague 1990 (Figure 4). It brought together participants from 18 countries from all over the world and the proceedings, titled 'Knowledge, Information and Medical Education', were published by Elsevier in 1991. The proceedings contained over 60 contributions describing the influence of computers on medical education and the education in medical informatics in general.

Medical informatics education has been one of the main objectives of IMIA. First the 'Recommendations of IMIA on Education in Medical Informatics' were published in [4] and the updated version in [5]. After the political changes in Czechoslovakia 1989 we prepared the project 'Education in the Methodology Field of Healthcare' with the acronym EuroMISE (European education in Medical Informatics, Statistics and Epidemiology) under the Tempus program [6, 7, 8]. The EuroMISE project for higher education developed the courses that were taught in Prague in the period 1993-1995. The EuroMISE centre as the joint workplace of Charles University in Prague and Academy of Sciences of the Czech Republic was established in 1994. The courses continued after the end of the project till the year 1998 receiving support not only from many teachers participating in the EuroMISE project but also from new teachers, e.g. Jean-Raoul Scherrer († 2002) the giant in the field of medical informatics and one of the EFMI Presidents. The EuroMISE courses showed new approaches to higher education in the methodology field of healthcare (Figure 5) and contributed to the development to Ph.D. studies in the field of biomedical informatics at Charles University in Prague [9].

In April 2004, more than 250 experts from 30 countries gathered in Prague, Czech Republic, to participate in the International Joint Meeting EuroMISE 2004, which was composed of several scientific events. At this event participated Jean Claude Healy († 2008) who made a speech at the Aula Magna of Charles University in Prague (Figure 6). I am completely convinced that the foundation of eHealth concept by J.C. Healy extremely accelerated electronic healthcare development promoting a transfer of new remarkable technologies to healthcare. He was the driving force behind the adoption of the WHO eHealth Resolution in 2005 [10]. The achievements of J.C. Healy are documented in details in the paper [11] and the book [12].

The field of medical informatics started to be broaden to the field of biomedical informatics that was discussed in detail at the symposium organized by R. Haux in Heidelberg, Germany June 2011 [13]. In 2013 the EFMI Special Topic conference 'Data and Knowledge for Medical Decision Support' was organized in Prague [14]. This conference opened the new problems in research and education and contributed to the EuroMISE Mentor Association establishment [15].

Figure 4: Participants of the second IMIA conference in Prague 1990.

2 Holistic approach to Information-based Electronic Healthcare

Healthcare is an information intensive sector, generating huge volumes of information in form of data and knowledge every day [16]. Data are generated in hospitals, primary care, clinics, surgeries and laboratories and often stored in electronic form. Nowadays, knowledge can be formalized from medical literature, clinical guidelines or protocols into electronic form. New knowledge can be also extracted from large biomedical databases using current information technologies. However, huge amount of knowledge can be also formalized from highly educated and knowledgeable health personnel, especially medical experts, who are providing their individual knowledge and experience to medical diagnoses, treatment and healthcare management.

Figure 5: Participants and teachers at the EuroMISE courses in Harrachov 1994.

Figure 6: The speech of J.C. Healy at Aula Magna of the Charles University in Prague.

The concept of Information-based Holistic Electronic HealthCare (IHE-HC) focuses on information in the form of data or knowledge that can be stored, processed or transmitted in electronic form. However, we have to take into account also economic and environmental aspects of handling data and knowledge in electronic form. Therefore, not only electronic component in healthcare is important, but also simultaneous impact of economic and environmental components on healthcare, called as e_3Health concept [17]. The environmental component is considered at large, including culture, legislation, language, geographic position, healthcare and social systems.

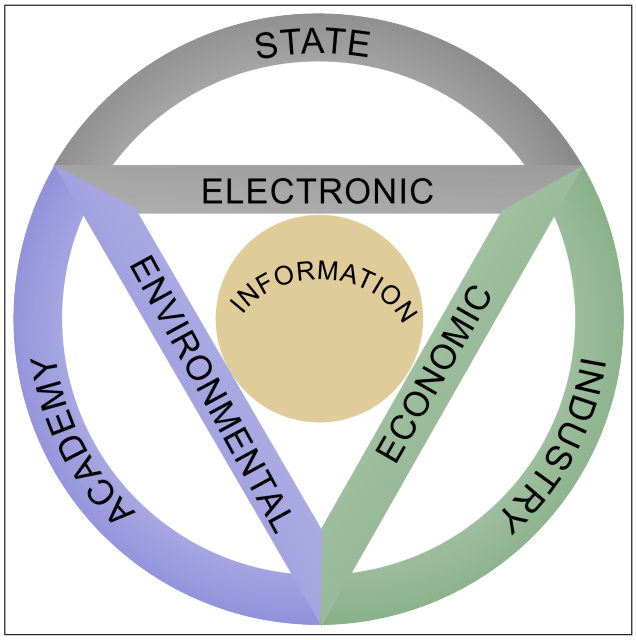

Figure 7: Information-based Holistic Electronic Healthcare.

IHE-HC is connecting the e_3Health concept with the application in a given healthcare system via co-operation among three main stakeholders (State, Academy and Industry). The inability to share information across these main stakeholders is just one of the major obstacles towards quality, efficiency, security and cost-effectiveness of healthcare.

The gap between the demand for IHE-HC from an increasingly well-informed citizens and the ability of the government and healthcare organizations to meet this demand is widening all the time. In any state the center of its interest should be the wellness of citizens that otherwise suffer from under-investment in information technologies, lack of political will to improve healthcare, fragmented markets with inadequate development of new systems, lack of standards, complexity of medical data, data entry problems, security and confidentiality. Coordinated and integrated healthcare with an efficient use of information technologies and available resources is really adding value to patients and professionals by improving health.

3 Medical, Health, Biomedical and Healthcare Informatics

The meaning of some words is not the same for everybody speaking the same language. The scientific approach to this important issue has been highly developed for English language in the research project UMLS (Unified Medical Language System). Donald Lindberg, Director of the National Library of Medicine (USA), played the key role in the project development. The UMLS is a concise compilation of many controlled vocabularies in biomedical sciences that mandate the use of predefined, authorized terms that have been preselected by the designer of the vocabulary. The detail information on UMLS can be found at [18].

It has been intended to be used mainly by the developers of systems in medical informatics. The term 'medical informatics' originated in Europe where it was first used by Francois Gremy and Peter Reichertz. The term 'informatics' was used to distinguish the discipline from 'computer science' as it was called in the United States.

Now we will show several problems with different understanding of medical informatics discipline. For this reason we will analyze each word 'medical' and 'informatics' in English and Czech languages separately.

First, we will analyze the word 'informatics'. In Chapter 1 of the book [19] Izet Masic wants to answer the question what the informatics is. He shows that definitions of informatics differentiate from one user to another. In Chapter 3 Francis Roger France [19] highlights that the term 'Informatics' was created in 1962 (Académie Francaise) from two words, information and automatic, and covers all techniques, information concepts and applications of computers. Morris Collen traces the term 'informatics' back to Russian origins in the fifties of the 20th century [20]. Jochen Moehr [21] shows that in some European countries, e.g. Germany and France, the term 'informatics' was adopted for computer science in the sixties of 20th century. In [22] Grémy discusses 'informatics' as the discipline that deals with information. He also pointed out different information sciences that work with information in different forms. In [23] Reinhold Haux opened the discussion on essential aims and tasks of medical informatics. In Jana Zvárová's article [24] informatics is viewed as the discipline that deals with information and specifies different positions of information sciences and information processes (Figure 8).

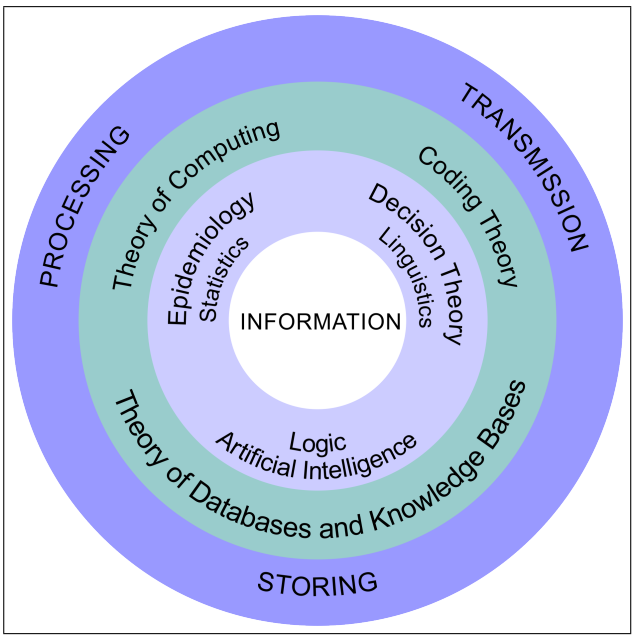

Figure 8: Structure of informatics.

In the Czech Republic the word 'informatics' is mostly interpreted in three ways as (i) computer science, (ii) information science focused on scientific information gathered in libraries, (iii) discipline dealing with information. However, we can meet also other views on informatics, e.g. as a discipline working with algorithms.

Second, medical informatics started with a focus on medicine. Instead of 'medical informatics' the term 'health informatics' started to be used. These two disciplines medical informatics and health informatics have been mostly considered as the same disciplines, see e.g. [25], but the words medical and health are not synonymous. Sometimes we meet also the term 'Healthcare informatics'. 'Health' and 'Healthcare' are two words with distinct meanings in both English and Czech languages. The word 'Health' can be interpreted as the noun 'Health' (Zdraví), e.g. Public Health (Veřejné zdraví) or as the adjective 'Health' (Zdravotní), e.g. Health Insurance (Zdravotní pojištění). Similarly, the word 'Healthcare' can be interpreted as the noun 'Healthcare' (Zdravotnictví) or as the adjective 'Healthcare' (Zdravotnický), e.g. Healthcare documentation (Zdravotnická dokumentace). But not only in Information and Communication Technologies (ICT) context the words 'Health' and 'Healthcare' are sometimes used synonymously. We can see the same situation in healthcare domains in both Czech and English languages. For example Ministerstvo zdravotnictví (Healthcare) České republiky is officially translated as Ministry of Health of the Czech Republic and a similar situation is visible in many other documents.

Medical Informatics as the discipline has been discussed in many papers. Reinhold Haux (IMIA president 2007-2010) in the paper 'Medical Informatics: Past, present, future' gives 96 references on this topic [26]. Marion Ball (IMIA president 1992-1995) in her keynote lecture 'Medical informatics – back to the future' presented at MEDINFO congress in Cape Town 2010 goes back to the concept of Shannon information.

Biomedicine is a broader field than Medicine. Biomedical Informatics is often understood as the intersection of Informatics and Biomedicine. Biomedical informatics should accelerate research in the boarder of biomedicine and informatics. The role of biomedical informatics for translational medicine was mentioned in the paper [27] titled Biomedical and Health Informatics in Translational Medicine. Here I understand the word 'Health' more in the sense of 'Healthcare'. Healthcare informatics, in my opinion, is using research results of biomedical informatics for applications in a given healthcare system to maximize health and fitness of citizens in the state. The future research in biomedical and healthcare informatics should introduce and explore new theories, concepts, and methods and contribute to better information processing in biomedicine as well as to more efficient and high-quality healthcare.

3.1 Important future research topics

There are many research topics in the broad field of Biomedical and Healthcare Informatics that need deeper studies. I will mention only three items, where the research could overcome barriers for further progress.

- Data in biomedicine and healthcare are not collected appropriately;
- Biomedical knowledge is rarely stored and formalized;

- There are many obstacles (e.g. legislation) for running appropriate applications in electronic healthcare.

We will shortly describe needs for future research in the above mentioned fields. Simultaneously, we will mention some applications tested in the Czech healthcare.

3.2 Data in biomedicine and healthcare are not collected appropriately

The most important source of information for biomedicine and healthcare is data. We can see a huge amount of data collected in an unstructured form, e.g. in narrative medical reports. Unstructured data is very difficult to analyze and most information in unstructured data is used rarely or never. With penetration of ICT in healthcare comprehensive electronic health records (EHRs) combined with appropriate representing, accessing and visualizing health data have been developed. There are many articles dealing with this topic, e.g. the article [28] that gives a very deep overview of activities about this topic. There are research efforts to minimize unstructured data in electronic health records to make information reusable for other tasks. I would like to mention at least the European projects I4C and Triple C and the ORCA Open Record for Care (ORCA) with primary applications in cardiology [29, 30]. Some of these research results we have later used for development of electronic health record in dentistry, in broader sense electronic oral health record (EOHR) [31, 32, 33]. It is necessary to stress that physicians cannot lose any information and they need to store both structured and unstructured data. Because of the Lifetime DentCross Component (user interface collecting data in dentistry even using voice commands) we found that the parts of the electronic health record, where narrative reports could be stored, were left empty. All information needed by dentists was stored in the structured data. Future research should focus on development of electronic health records for each state (considering $e_3$health components) and minimizing size of unstructured data.

3.3 Biomedical knowledge is rarely stored and formalized

The art of medicine is the skilled application of biomedical and information sciences and medical experience. In medicine the knowledge how to treat diseases in the optimal way in different healthcare systems is often described in clinical guidelines. This knowledge can be formalized and used in combination with data in the electronic health record to support the treatment. Knowledge in clinical guidelines is updated regularly by medical experts to keep the highest possible standard of treatment, see e.g. [34]. In the Czech Republic the catalogue of clinical guidelines was developed [35] and some of these clinical guidelines were enhanced to formalized clinical guidelines that can be executed together with electronic health records [36]. Clinical guidelines knowledge should be well represented and support medical decision-making [37].

It is important to formalize medical knowledge for its future reuse in medical decision making. Clinical uncertainty is reality today. It is mostly caused by incomplete knowledge and incomplete data about the clinical problem, erroneous recording and interpretation of information by the physician. Knowledge gathered by physicians is called subjective knowledge. Subjective know-ledge from medical experts is sometimes formalized to be reused in so called expert systems. However, subjective knowledge has to be verified by data and other knowledge sources continuously. Future research should focus on the development of medical decision support systems, where not only reused data but also knowledge (including subjective knowledge) is stored, formalized and verified with other data and knowledge sources continuously.

3.4 There are many barriers (e.g. legislation) for running appropriate applications in healthcare

In the special edition of the European Journal for Biomedical Informatics titled 'Support of eHealth Applications by Legal Systems in Europe' there are published four papers concerned with legal interoperability which allows different jurisdictions to enable secured access to and processing of patient information transferred electronically [38]. The papers in this collection make clear that Europe still has some way to go in establishing a full legal framework for electronic healthcare. In the paper [39], authors look into such questions related to one of the most basic elements of any eHealth solution – electronic health records – in Czech law. Also in other papers legal questions concerned electronic health records are discussed. A legal system of the state is an environmental factor with a great influence on electronic healthcare. Different legal systems in European countries are blocking legal interoperability among states as well as new electronic applications. Till now there has still not been a multidisciplinary biomedical and healthcare informatics research focusing on the impact of legal systems on electronic healthcare. Future research should focus on the consistency of legal systems and formalization of legal knowledge for its reuse in medical practice.

References

[1] Whitby LG, Lutz W. (Eds.) Principles & Practice of Medical Computing. Churchill Livingstone, Edinburgh and London, 1971

[2] Van Bemmel JH, Gremy F, Zvárová J. (Eds.) Diagnostic Strategies and Expert Systems. Amsterdam: North Holland, 1985.

[3] Van Bemmel JH, Zvárová J. (Eds.) Knowledge, Information and Medical Education.Amsterdam: North Holland, 1991

[4] Haux R. et members of IMIA WG1: Recommendations of the International Medical Informatics Association (IMIA) on Education in Health and Medical Informatics. Methods Inf Med 2000, 39:267–277

[5] Mantas J, Ammenwerth E, Demiris G, Hasman A, Haux R. et all. Recommendations of the International Medical Informatics Association (IMIA) on Education in Biomedical and Health Informatics – First Revision. Methods Inf Med 2010; 49: 105–12

[6] Hasman A, Albert A, Wainwright P, Klar R, Sosa M. (Eds.) Education and Training in Health Informatics in Europe. SHTI vol.25. Amsterdam: IOS Press, 1995.

[7] Zvárová J, Engelbrecht R, van Bemmel JH., Education in Medical Informatics, Statistics and Epidemiology. Int JMed Inform. 1997; 4:3–8

[8] Zvárová J.: Education in Methodology Field of Healthcare – EuroMISE. Methods of Information in Medicine. 1994; 33: 315–317.

[9] Zvárová J, Svačina Š. New Czech Postgraduate Doctoral Program in Biomedical Informatics In: G. Surjan, R. Engelbrecht, P. McNair (Eds.) Health Data in the Information Society, Proceedings of MIE2002, Amsterdam, IOS Press; 2002, 766–769

[10] Resolution WHA58.28. eHealth. In: Fifty-eighth World Health Assembly, Geneva, May 16 –25, 2005. Resolutions and decisions, annex. Geneva:World Health Organization; 2005: 108–110.

[11] Iakovidis I. A Tribute to Jean-Claude Healy, a Free Thinker and Visionary Leader for Biomedical Informatics. IMIA Yearbook of Medical Informatics, Stuttgart: Schattauer, 2008: 16.

[12] Rosenenmoller M, Whitehouse D, Wilson P. (Eds.) Managing eHealth From Vision to Reality. Palgrave Macmillan 2014

[13] Haux R. On the Methodology and Scientific Fundamentals of Organizing,Representing and Analysing Data, Information and Knowledge in Biomedicine and Health Care Methods Inf Med 2011; 50: 487–490

[14] Blobel B, Hasman A, Zvárová J. (Eds.) Data and Knowledge for Medical Decision Support. IOS Press, Amsterdam 2013

[15] EuroMISE Mentor Association, www.euromise.net (accessed December 31, 2014).

[16] Zvárová J, Veselý A, Vajda I. Data, information and knowledge. In: Berka P, Rauch J, Zighed D. (Eds.) Data mining and medical knowledge management. Information science reference. Hershey, PA: IGI Global; 2009: 1–36.

[17] Zvárová J, Zvára K. e_3Health: Three Main Features of Modern Healthcare. In: Moumtzoglou A, Kastania A. (Eds.) E–Health Systems Quality and Reliability: Models and Standards, IGI Global Press, New York, 2010; 18–27

[18] National Library of Medicine, UMLS `http://www.nlm.nih.gov/research/umls/quickstart.html` (accessed December 31, 2014).

[19] Masic I, Mihalas G. (Eds.) Contributions to the history of medical informatics, Avicena Sarajevo, 2014

[20] Colen MF. Origins of medical informatics, West. J. Med. 1986, 145: 778–785.

[21] Moehr JR. Teaching medical informatics: Teaching on the seams of disciplines, cultures, traditions. Method Inf Med. 1989; 28(4):273–280.

[22] Gremy F. Crisis of Meaning and Medical Informatics Education: A burden and/or a relief? Methods Inf Med. 1989; 28(4): 189–195.

[23] Haux R. Aims and tasks of medical informatics, Int J Med Inform. 1997; 44:9–20

[24] Zvárová J. On the medical informatics structure. Int J Med Inform. 1997; 44: 75–81.

[25] Protti DJ, Van Bemmel JH, Gunzenhauser R, Haux R, Warner H, Douglas JV, Lang E. Can Health/Medical Informatics be regarded as a separate discipline? Meth Inf. Med. 1994; 33:318–326.

[26] Haux R. Medical Informatics: Past, present, future. Int J Med Inform 2010, 79:599–610

[27] Kulikowski, CW, Kulikowski W. Biomedical and Health Informatics in Translational Medicine. Methods Inf Med 2009;, 48(1):4–10

[28] Häyrinen K, Saranto K, Nykänen P. Definition, structure, content, use and impacts of electronic health records: a review of the research literature. Int J Med Inform. 2008;77(5):291–304

[29] van Ginneken AM. The computerized patient record: balancing effort and benefit. Int J Med Inform. 2002; 65 :97–119

[30] van Ginneken AM, Stam H, van Mulligen EM, de Wilde M, van Mastrigt R, van Bemmel JH. ORCA: The versatile CPR. Method Inform Med 1999; 38: 332–338.

[31] Zvárová J, Dostálová T, Hanzlíček P, Teuberová Z, Nagy M, Pieš M, et al. Electronic health record for forensic dentistry. Methods Inf. Med. 2008; 47:8–13.

[32] Chleborád K, Zvára K Jr, Dostálová T, Zvára K, Hippmann R, Ivančáková R, Trmal Z, Psutka J. Evaluation of voice-based data entry to an electronic health record system for dentistry. Biocybernetics and biomedical engineering 2013; 33: 204–210.

[33] Hippmann R, Dostálová T, Zvárová J, Nagy M, Seydlová M,, Hanzlíček P, et al. Voice supported electronic health record for temporomandibular joint disorders. Methods Inf Med. 2010; 49:168–172

[34] Ten Teije A, Miksch S, Lucas P. (Eds.) Computer-based Medical Guidelines and Protocols: A Primer and Current Trends. IOS Press, Amsterdam 2008

[35] Zvolský M. The Database of the Catalogue of Clinical Practice Guidelines Published via Internet in the Czech Language – The Current State. European Journal for Biomedical Informatics 2010,6 (1):83–89, `http://www.ejbi.org/img/ejbi/ejbi2010-1.pdf` (accessed December 31st, 2014)

[36] Veselý A, Zvárová J. Determination of Guidelines Compliance: Comparison of Clinical Guidelines with the Patientâ^{TM}s Record. Eur J Biomed Inform. 2012;, 8(1):16–28, `http://www.ejbi.org/img/ejbi/ejbi2012-1.pdf` (accessed December 31st, 2014)

[37] Buchtela D, Peleška J, Veselý A, Zvárová J, Zvolský M. Guideline Knowledge Representation Model. Eur J Biomed Inform. 2008; 4(1):17–23, `http://www.ejbi.org/img/ejbi/ejbi2008.pdf` (accessed December 31st, 2014)

[38] Wilson P, Zoi K. Do the Legal Systems of Europe and its Member States Meet the Needs of eHealth? Eur J Biomed Inform. 2012; 8(2):1–2, `http://www.ejbi.org/img/ejbi/ejbi2012-2.pdf` (accessed December 31st, 2014)

[39] Dostál O, Šárek M. Support for Electronic Health Records in Czech Law. Eur J Biomed Inform. 2012; 8(2):29–33, `http://www.ejbi.org/img/ejbi/ejbi2012-2.pdf` (accessed December 31st, 2014)

Importance of Cerebral Folate Deficiency for Development and Treatment of Autism Spectrum Disorder

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Abstract

Autism or Autism Spectrum Disorders (ASD) is serious lifelong neurobehavioral impairment, significantly complicating the integration of an individual into the normal life. Etiology of ASD is usually complex combination of different disturbances, and remains unknown in a majority of cases. Cerebral Folate Deficiency (CFD) is a neurodegenerative syndrome characterized by reduced concentrations of metabolically active folate in cerebrospinal fluid (CSF) and normal serum levels in most cases. While a serious CFD can be easily diagnosed because of presence of obvious motor and sensory impairment, a mild CFD can play a role in the development of various behavioral disabilities including ASD with no apparent physical disability. Severity of CFD is highly variable. The CFD is usually partially, rarely completely, compensable syndrome and some publications reported also positive therapeutic effect on the core ASD symptoms (impaired communication, social interaction, abstraction and stereotypic behavior), commonly referred to as incurable. Rarely, the full recovery from the ASD symptoms in the patients with proven CFD, have been published. Although the CFD has been described already in 2002, the first study aimed at the effect of the treatment focused on the idiopathic ASD core symptoms was published in 2013. The aim of this review was to summarize available information on the coincidence of CFD and ASD, to describe the importance of folate depletion for development and function of the Central Nervous System (CNS) and to point out the potential relationships to other pathological findings in ASD. Another objective was to map the most common causes of CFD, to quantify coincidence of CFD and ASD and to evaluate the treatment effectiveness tested so far, again focused on improving the ASD core symptoms. Further research in this area could lead to new therapeutic options of idiopathic autism.

Keywords

Autism, Cerebral Folate Deficiency, Folate, Folate Receptor Autoantibody, EHR

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Introduction

Autism Spectrum Disorders (ASD) comprise a group of pervasive developmental disorders characterized by the communication difficulties, impaired reciprocal social interaction, imagination insufficiency and stereotypic behavior. ASD is a lifelong disability with an uncertain prognosis. Full social integration is currently unachievable for the majority of ASD patients. The estimated prevalence of ASD varies in different populations ranging from $0,1$ to $1,5\%$, thus represents a substantial socioeconomic burden. The ASD is neurobehavioral impairment with an unknown etiology in most cases [1]. The current research extends, in addition to genetic causes, to other areas such as epigenetic changes, exogenous intoxication, autoimmunity etc. This review summarizes available information about the coincidence of ASD and Cerebral Folate Deficiency (CFD). CFD is a syndrome characterized by reduced levels of 5-MTHF (5-methyl tetrahydrofolate) in the cerebrospinal fluid (CSF) but normal levels of 5-MTHF in serum and erythrocytes. CFD symptoms and their severity are highly variable. Some published papers show that CFD can contribute to the ASD development and progression and that the CFD compensation can suppress the core ASD symptoms [2, 3, 4, 5, 6, 7].

Folate Transport and Utilization Value for CNS

Folate transport begins in the proximal ileum [8], wherein the folates are hydrolyzed to the monoglutamic forms, absorbed, chemically reduced and converted mainly into the 5-MTHF. The initial reduction occurs in enterocytes or liver, but the corresponding enzyme DHFR (Dihydrofolate reductase) is present in all tissues.

Three types of receptors ensure the intracellular transport: RFC (Reduced Folate Carrier) and PCFT (Proton-Coupled Folate Transporter) operating on the principles of Na^+ antiport [9] or H^+ synport respectively [10]. The third receptor type - FOLR1 (Folate receptor 1 or FR-α) is based on endocytosis, is ATP-dependent and, as the only one, provides significantly different concentrations of folate between intra- and extracellular space [11]. FOLR1 is expressed mainly in the cell membranes of choroid plexus, placentar tissue, thyroid gland, kidney proximal tubules and other tissues, wherein it provides an active unidirectional transport of folates [12]. The physiological folates concentrations in cerebrospinal fluid (CSF) compared to the systemic circulation is about 3 times higher and decreases with age [13].

The intracellular folate retention is ensured by polyglutamination by the enzyme FPGS (Folypolyglutamate synthase). Folate transport into mitochondria is ensured with another specific transporter SLC25A32 [14]. Folate polyglutamic forms cannot be transported across membranes but they are a suitable substrate for metabolic utilization. The catalytic activities between enzymes in folate metabolic pathways and FPGS are interconnected and interacts each another via a negative feedback preventing an excessive intracellular folate retention [15].

Folate in its 9 biochemical forms is involved in more than one hundred of metabolic reactions. Folates are cofactors of purines and pyrimidines synthesis, the DNA and mRNA precursors and are necessary for cell growth and division [16].

The gene expression is significantly affected by the methylation of specific DNA loci and also its chromatin carrier. Substrate for methylation is S-adenosylmethionine (SAM), the product of homocysteine to methionine metabolic regeneration, which is folate-dependent [17]. SAM is also necessary for the conversion of serotonin to melatonin, which is involved in the circadian rhythm control. Abnormalities in the melatonin levels in ASD have been observed in 9 studies [18].

In the absence of folate, the body regenerates SAM using an alternative metabolic pathway and consumes choline, which is conditionally essential for the CNS development [19]. The choline depletion leads to a reduction in lipoprotein synthesis, disruption of myelin membranes, CNS demyelination and atrophy [20]. The choline is also a part of the sphingomyelin molecules; its lack therefore may also disrupt the myelin synthesis itself. Choline is a precursor of acetylcholine, and thus a disruption of acetylcholine synthesis can be expected as well [19]. An extremely limited diet, frequent in ASD, with following malnutrition, may synergistically contribute to the choline depletion [21]. Folate is also a cofactor in the metabolic regeneration of glycine from choline, (more precisely in conversion of dimethylglycine to sarcosine). The catalysis proceeds also without a folate cofactor, but the resulting products are different and a toxic formaldehyde arises [22].

Folate is necessary for the synthesis of serine. Serine does not cross the blood brain barrier and after its formation, the developing fetus depends on the local synthesis in the CNS [23]. Serin has proven trophic effect on neural tissue [24]. Inhibition of serine utilization in CNS is associated with increased apoptosis of neurons [25] . In addition, the L-serine is required for the myelin and phospholipids synthesis, and thus also for the formation and growth of dendrites and axonal connections. Phospatidyl-L-serine, a serine metabolite, is active in the regulation of apoptosis and synaptic pruning (the elimination of excess neural connections during the brain development and maturation) in the early postnatal period. D-serine, glycine, the other serine metabolites also work as the inhibitory neurotransmitters, have neuromodulating effect and act as signaling molecules affecting growth and brain development and synaptic maturation [23].

Decreased CSF level of 5-MTHF is associated with impaired tetrahydrobiopterin (BH4) regeneration [26]. The BH4 is an essential cofactor in the synthesis of serotonin, dopamine and nitric oxide (NO). Disruption of the serotoninergic and dopaminergic pathways is associated with the ASD pathophysiology and can affect not only the synaptic transmission but also the previously described synthesis of the end products (melatonin) or accumulation of precursors (serotonin) [27]). NO is a potent local vasodilator. Several studies have found a focal CNS hypoperfusion in patients with ASD [28, 29, 30]. In BH4 deficiency the 5-MTHF is an alternative cofactor of NO synthesis.

Reduction of NO synthesis leads to the superoxide production and to the oxidative damage of tissues [31]. Oxidative damage of cell membranes and cell compartments, including mitochondria, can be caused by the very SAM depletion, resulting from the lack of 5-MTHF. Free radicals can, not only interfere with lipoproteins in the cell membranes and contribute to axonal growth and formation disruption, to the damage of dendrites and whole synaptic connections, but also directly interfere with the inner mitochondrial membrane integrity and significantly affect the ATP production. Reduction of ATP synthesis can lead to structural disruption in cell division growth and synaptic pruning, as well as to the functional disruption of synaptic activity and, last but not least, to the further reduction of ATP-dependent folate import into the CNS. Increased oxidative stress or disrupted ATP production in ASD patients were described in 3 controlled trials and 9 case reports [32].

It cannot be passed that mutations in genes for folate catalytic enzymes or transport receptor proteins can significantly contribute to the folate metabolism disruption. The examples can be cases of ASD or similar neurobehav-

ioral disorders due to the mutations of *MTHFR* (Methlytetrahydrofolatereductase) [33], *DHFR* [34] and *FOLR1* [35] genes. Besides the genetic polymorphisms, the epigenetic modifications like the atypical DNA methylation or histone structure modifications published in ASD, have to be taken into account [36]. The 5-MTHF depletion in CNS is probably in a direct connection with the hypo- and hypermethylation of genes associated with ASD, e.g.: *AFF, GABRB3, MECP2, NLGN3, NRXN1, SLC6A4, UBE3A* [37], *OXTR* [38], *SHANK3* [39]. Folate deficiency in a critical period of pre- and early postnatal development may contribute to the disruption of expression of these genes and thus to the development of ASD.

Objectives

Our aim was to quantify the coincidence of ASD in published CFD cases since 2002, when the disease was first systematically described to this day (October 2014). The second objective was to quantitatively evaluate the treatment efficacy of CFD with a particular focus on improving the core ASD symptoms.

Methods

To search for publications, we used the public interface of the U.S. National Library of Medicine - PubMed. We sought publications matching the phrase "Cerebral Folate Deficiency", found a set of selected clinical studies and case reports. Type of study has not been distinguished due to a relatively small number of sources. For each found publication, we obtained the number of patients, clinical picture, diagnosis or description of ASD, related neurobehavioral symptoms, etiology, treatment protocol and outcome, with special focus on the treatment effect on the ASD symptoms. Partial ASD symptoms (communication disorders, impaired social interaction ...) or similar, were not included in the ASD and CFD concomitance evaluation, unless the ASD was directly diagnosed in the study or described in a wider range of symptoms. Mutually different structures of individual studies and wide range of interest of this review excluded a deeper statistical analysis. Therefore, the findings were evaluated only quantitatively.

Results

Clinical Picture of CFD

Ramaekers et al. described in 2002 the CFD in 5 patients as a progressive disease with normal development to 4 or 6 months of age and subsequent manifestation of irritability, progressive microcephaly, psychomotor retardation, cerebellar ataxia and movement disorders of lower extremities. Epilepsy often manifested at 3 years and the disturbances of vision have been found in a part of patients after the 6 years of age. The authors found significantly reduced levels of 5-MTHF in CSF and normal serum concentration in 5 cases [40].

The same authors published another 20 cases in 2004. Some patients, in addition to the symptoms listed above, suffered from spastic paraplegia and hearing loss. In some cases pathological findings on brain MRI were observed (frontotemporal atrophy with periventricular and subcortical demyelinizations and atrophy of the cerebellum). Authors did not find mutations in the FOLR1 gene, but confirmed the nonfunctional FOLR1 receptor, therefore they hypothesized a possible epigenetic damage or the blocking of FORL1 receptor with another compound including autoantibody (Folate Receptor Auto Antibody FRAA) [41].

A symptomatic treatment with high doses of 5-formyltetrahydrofolate (5-FTHF) has been tested in both studies. The treatment leads to the improvement of the neurological problems, amelioration of seizures, EEG normalization, improvement in postural control and coordination of intentional movements, as well as a reduction of hyperexcitability and impulsive behavior. Patients also improved in cognitive functions, but a full recovery was not observed in any patient.

The CFD clinical picture in further studies proved to be highly variable, with heterogeneous etiology and with no clear correlation between the 5-MTHF levels in CSF and clinical symptoms, their type, number and level of expression [40, 41].

Coincidence of CFD and Another Findings Including ASD

In the above mentioned study [41] was ASD, according to the ADOS (Autism Diagnostic Observation Schedule), diagnosed in 7 of 20 CFD patients. One-year supplementation with 5-FTHF led to 5-MTHF and pterins levels normalization in CSF in 18 patients. The authors also created the first therapeutic protocol based on supplementation with high doses of 5-FTHF.

Ramaekers et al. published the CFD without known etiology in 4 patients with Rett syndrome in 2003. The treatment with 5-FTHF brought a partially beneficial effect [42].

Moretti et al. published in 2005 a case report of a 6-year-old girl with CFD, developmental delay, psychomotor regression, seizures, mental retardation and autistic features. The treatment with 5-FTHF led to improvement of motor skills [43].

Hansen et al. published in 2005 a case report of a girl with idiopathic progressive neurological disease refractory to treatment manifesting at the age of 3 years. The girl suffered from progressive developmental delay. Poor postural control, spasticity and ataxia occurred at the age of 12 years. At this age, the authors also proved a significant CFD. After initiation of 5-FTHF therapy a very remarkable motoric and cognitive improvement occurred within 1 week with subsequent stagnation after one year

of treatment, when the 5-FTHF therapeutic dose had to be doubled to 30 mg/day [44].

Ramaekers et al. published in 2005 a study comparing CSF levels of 5-MTHF and serum FRAA in the group of 28 children with clinically diagnosed CFD. 25 of the 28 patients were FRAA positive, in contrast with the comparable healthy control group where hasn't been positive even one FRAA test. 4 FRAA positive CFD patients were diagnosed with ASD (according to ADOS). All FRAA positive patients were treated with 5-FTHF. In 2 youngest autistic patients (2 and 3 years) had a significant improvement in neurological and autistic symptoms, but in 2 older (12 and 15 years) was treatment much less effective and they remain autistic. In one other autistic patient the symptoms disappear completely after the treatment [2].

Ormazabal et al. measured in 2006 the CSF levels of neurotransmitters, pterins, and 5-MTHF in 283 pediatric patients with neurologic disorders of unknown etiology. She found significantly decreased CSF levels of 5-MTHF in 15% of cases [45]. The same authors in the same year published another study of 165 patients with severe epileptic encephalopathies, movement disorders, Rett syndrome or mitochondrial diseases. They found mild to profound CFD in 74% of cases [13].

Pineda et al. published a case report of Kearns-Sayre Syndrome (KSS) in 2006. KSS is caused by deletions in the mitochondrial genome which leads to the impairment of respiratory chain, and subsequent lack of the ATP production. KSS is manifested by progressive neurological and muscular dystrophies. The ATP depletion causes a disruption of the ATP-dependent intracellular folate transport by FOLR1 and subsequent CFD. After supplementation with high doses of 5-FTHF the gait improved and also the myelination restored gradually. However, the long-term treatment, failed to suppress areflexia and cerebellar symptoms [46].

Ramaekers et al. published a study of 25 patients with low-functional autism in 2007. Serum folate levels were normal, but in 23 of 25 patients were found the decreased CSF 5-MTHF levels. 19 of these 23 were FRAA positive. One-year 5-FTHF supplementation led to normalization of 5-MTHF levels in CSF. Furthermore, partial or complete recovery of clinical state has been noted [47].

Ramaekers et al. published a comparative study of the CSF analysis in 33 patients with Rett syndrome in 2007. He found the CFD in 14 samples. Six out of these 14 patients were FRAA positive while in the group without CFD were only 2 FRAA positive individuals [48].

Mercimek-Mahmutoglu et al. published in 2007 an atypical case of H-ABC Syndrome (Hypomyelination with Atrophy of the Basal Ganglia and Cerebellum) with concomitant CFD and normal CSF neurotransmitters levels. The H-ABC syndrome is a complex of the CNS anomalies visible on brain MRI scan, movement disorders and mental retardation of variable severity. Etiology H-ABC is unknown. In the published case a 5-FTHT therapy, combined with levodopa / carbidopa, suppress the opiostonic and oculogyric seizures. After discontinuation of levodopa / carbidopa therapy the CSF 5-MTHF levels decreased again [49].

Ramaekers et al. tested in 2008 the effectiveness of milk-free diet on the serum FRAA levels, because the mammalian milk contains the free FOLR1 protein. Therefore authors tested the hypothesis that the body produces FRAA in an immune response to the free animal FOLR1 and the FRAA can block also the FOLR1 membrane receptors subsequently. This study included 24 children and 10 of them were diagnosed with low-functional autism according to the ADOS and ADI (Autism Diagnostic Interview). Long-term 5-FTHF therapy brought the improvements in a number of neurological symptoms to all patients. Significant improvement in attention, communication, and stereotypic behavior was observed in 2 out of 10 autistic patients. In other 4 patients the improvement was partial [3].

Moretti et al. published 7 cases of atypical CFD (psychomotor retardation, developmental delay, dyskinesias, seizures) in 2008. The polymorphisms in FOLR1 or in genes active in folate metabolic pathways have not been found. 5 of the 7 patients were diagnosed with autism or ASD (according to the ADI-R and ADOS), with the most notable symptoms in the areas of sensitivity to change, rituals, repetitive movements and in fascination by sensoric perceptions. The group was not etiologically consistent. After the 5-FTHF treatment occurred in 4 of these 7 patients improvements in both the neurological and the autistic symptoms [4].

The case of unsuccessful treatment in a patient with developmental delay, epilepsy and coma, CFD and FRAA positivity published Bonkowski et al. in 2008. Treatment with 5-FTHF did not affect the clinical status [50].

Hasselmann et al. described in 2010 a case of Alper's disease (fatal neurodegenerative prionic disease) in 3,5 years old girl with a concomitant CFD, probably based on FRAA positivity. The patient was treated by administration of 5-FTHF. Despite further disease progress, the treatment had a positive impact on the CSF 5-MTHF level, on the frequency of seizures and on the communication skills. Gradually also CSF concentrations of some inflammatory mediators (IL-8, IFN-γ) decreased. Supportive treatment with 5-FTHF, as well as in other cases mentioned in our review, did not affect the serum FRAA levels. The patient died at the age of 5,5 years [51].

In 2010 Serrano et al. described 6 cases of CFD in KSS. She described disturbances in white matter myelination, cerebral atrophy, as well as reduced CSF 5-MTHF levels and elevation of serotonin and dopamine metabolic products. The authors present the treatment of 5-FTHF as clearly beneficial [52].

In 2011 Mangold et al. published her retrospective study of 103 CFD cases from the years 1999 to 2007. Clinically diagnosed autism in the medical records were found in 4 patients with CFD, mostly with moderate than with severe lack of CSF 5-MTHF. The diagnosis was clear in only 22 of the 103 patients and this retrospective study did not examine the other patients for the ASD. However,

it states e.g.: mental retardation in 84 cases, epilepsy in 53 cases or motoric disorder in 75 patients with CFD. This study also does not mention neither therapy nor its effectiveness, however, reports the CFD as a relatively common syndrome in many different serious neurological diseases [53].

Dill et al. published in 2011 a case of 8-year-old boy with LAMM syndrome (Congenital Deafness with Labyrinthine Aplasia, Microtia and Microdontia) and CFD based on homozygous *FOLR1* mutation. The brain MRI and MRS (spectroscopy), in addition to the typical findings of LAMM syndrome, also reveals myelination disorders and depletion of choline in frontoparietal areas and in the brain stem. The patient required an artificial ventilation support. The 5-FTHF therapy rapidly improved consciousness, postural control and gait and alleviated epilepsy and the permanent ventilation support could be terminated. Nevertheless, after 2 weeks the epilepsy relapsed and pyridoxal-5-phosphate had to be indicated [54].

Banka et al. published in 2011 the 3 cases of homozygous mutations in the *DHFR* gene, with severe progressive CNS, gastrointestinal and circulatory manifestation and with a fatal outcome in one of the cases. The findings include megaloblastic anemia, profound CFD, frontal and cerebellar hypoplasia, dilatation of cerebral ventricles and other structural abnormalities visible on brain MRI. Serum folic acid levels were normal in all cases, but CSF 5-MTHF and BH4 levels were significantly low. Treatment with 5-FTHF brought little benefit in the form of CSF levels improvements and epilepsy alleviation. The surviving patients remained in a serious clinical state [55].

Cario et al. published in 2013 another 3 cases of homozygous *DHFR* mutations and milder symptoms. The patients had megaloblastic anemia, impaired erythropoiesis and neurological symptoms including epilepsy, ocular myoclonus and serious learning disabilities. In all cases a profound CFD were found, as well as a good clinical response to high dose 5-FTHF supplementation. The publication also describes the recurrence of symptoms after repeated interruption of treatment in one noncompliant patient [56].

Leuzzi et al. published in 2012 a CFD case with strongly impulsive behavior, autoagresivity, impaired gross motor skills and speech, but without typical autistic symptoms. At 6 years of age the CSF 5-MTHF level was undetectable. Pathogenic mutations in the *MTHFR* and *FOLR1* genes were not found. The patient was also FRAA negative and the CFD cause was not revealed. After initiation of 5-FTHF treatment the CSF 5-MTHF level improved, but the patient's clinical status did not improved [57].

Sadighi et al. published in 2012 a case of previously healthy 58-year-old woman with sudden retrograde amnesia and myoclonus. In patient the reduced concentrations of 5-MTHF and BH4 in the CSF have been revealed and subsequently the presence of FRAA too. 6-month long therapy with 5-FTHF completely suppressed the symptoms [58].

Steele et al. published in 2012 2 patients with progressive epilepsy, movement disorders, hypotonia and seizures of unknown etiology with subsequently proven CFD. Autistic traits have been identified in 1 patient. The 5-FTHF has been administered to both patients. Long-term therapy gradually brought about a significant improvement in epilepsy, motor skills, speech and general mental ability [5].

Ho et al. reports in 2014 a case of a 13-year-old boy with mutism, psychomotor retardation and catatonic schizophrenia. Brain MRI scan and metabolic blood tests were normal. Lumbar puncture showed CFD and subsequent blood test revealed the FRAA elevation. 9-month long treatment with 5-FTHF did not bring improvements in the patients status [59].

A CFD case based on MTHFR deficiency with late manifestations published Wang et al. in 2014 in a 13-year-old boy with schizophrenia. 3-months long treatment with 5-FTHF, cobalamin, pyridoxine and betaine (cofactors and intermediates of folate metabolism) adjusted the CFD, completely suppressed the clinical symptoms and patient then returned into the normal life [60].

Al-Baradie et al published in 2014 a case of twins with developmental delays, epilepsy and CFD. One patient demonstrated clear autistic symptoms. Molecular genetic testing detected the homozygous mutation in *FOLR1* gene in both twins. The 5-FTHF administration completely suppressed epilepsy and significantly improved social interaction and motor skills of both patients [7].

Wang et al. published in 2014 a CFD case in anemic girl with tremor and weakness of lower limbs, intracranial calcifications, regression of cognitive abilities and sleep disturbances. The authors found not only CFD but also systemic folate deficiency and the homocysteine elevation. The CSF level of 5-MTHF was undetectable. The patient had mutation of *SLC46A1* gene, encoding a folate transporter PCFT. Supplementation with 5-FTHF brought a full withdrawal symptoms at 6 years of age [61].

CFD in Idiopathic Infantile Autism

All of the above mentioned publications, either aiming on the presence FRAA or on other causes, were always focused on CFD as a primary diagnosis and incidental autism kept only as possible comorbidity. Publications about the CFD without diagnosed ASD commonly reported the other neurodevelopmental disorders and most of them did not include information about the differential diagnostic examination to rule the ASD out.

Frye et al. published in 2013 an open study of the ASD core symptoms efficacy treatment using 5-FTHF in 93 patients with idiopathic autism. The prevailing finding was the mild CFD without the typical clinical manifestation. The predominant CFD cause was the FRAA positivity detected in 75% of patients. Known causes of ASD were excluded, respectively the patients with a known genetic disorder were not enrolled in the study. After a 4-months therapy with high-doses of 5-FTHF (2 mg/kg/day) a

moderate to remarkable improvement was noted in one third of patients. Significant improvement was observed particularly in receptive and expressive language, attention and stereotyped behavior. To our knowledge, this is the first study dealing with the effect of the 5-FTHF supplementation for idiopathic ASD only and has its limits and restrictions. Although all patients were clinically diagnosed with ASD before the study enrollment, the outcome was evaluated only by parents according to the Clinical Global Impression Scale. The study was not blind and placebo-controlled. The control group consisted of the children waiting for therapy initiation [6].

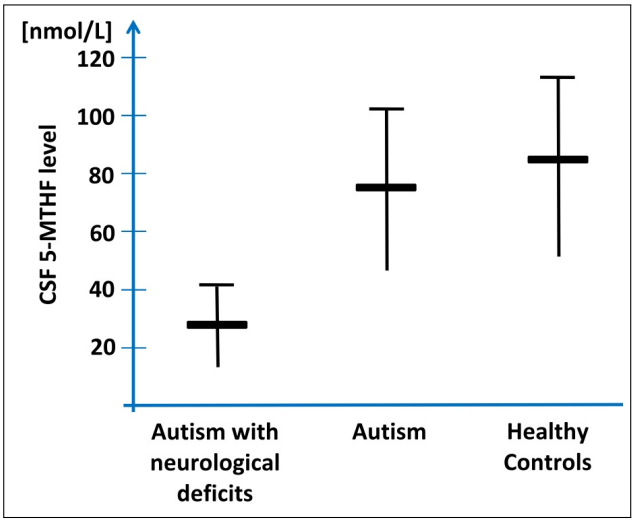

Figure 1: Comparison of CSF 5-MTHF levels among the 3 groups. Based on [19].

In 2013 Ramaekers et al. in his review compared the CSF 5-MTHF concentrations of previously published CFD cases. The authors show that the reduction rate of CSF 5-MTHF significantly correlated with the severity of disability. Significantly lower CSF 5-MTHF levels are associated with more severe neurological deficit when the primary diagnosis is supported by the finding of the typical CFD symptoms (neurological deficits). Conversely, in the primary diagnosis of idiopathic autism or ASD respectively, the CSF 5-MTHF level reduction remains in the range of normal values (1). The authors also confirm the negative correlation between the CSF 5-MTHF levels and serum FRAA levels [19]. This study processed some data from the studies already mentioned here, in which the 5-FTHT treatment efficacy on neurological and autistic symptoms was described.

Conclusions

We found a total of 351 published cases of CFD in the years 2002 - 2014 (1). With regard to the enrolled authors we cannot exclude that a smaller proportion of cases has been published repeatedly. ASD was reported in 44% of patients. However a number of studies do not indicate whether patients were subjected to differential diagnostic test for the ASD evaluation. Furthermore, in very severe CFD cases the precise diagnostic examination for ASD could not be realized. Many of these studies have reported impaired social interaction and communication in a patient's history. Thus it is possible that the overall proportion of ASD was higher than 44%. Variable positive treatment effect on the core ASD symptoms (communication, social interaction ...) was reported in 29% of patients with ASD and CFD. Most cases were administered by 5-FTHT in monotherapy, combined therapy has been used infrequently [54],[60].

Table 1: Summary of ASD findings in CFD and the 5-FTHF treatment efficacy.

Num. of patients		*Th. efficacy*		*Etiology*	*Ref.*
Total	*ASD*	*ND*	*ASD*		
5	n/a	5	n/a	n/a	[40]
20	7	n/a	n/a	n/a	[41]
1	1	1	0	n/a	[43]
1	n/a	1	n/a	n/a	[44]
28	4	18	2	FRAA	[2]
4	n/a	4	n/a	Rett	[45]
1	n/a	1	n/a	KSS	[46]
25	25	n/a	n/a	FRAA	[47]
14	n/a	n/a	n/a	FRAA	[48]
1	n/a	0	n/a	n/a	[49]
24	10	n/a	6	FRAA	[3]
7	5	4	4	various	[4]
1	n/a	0	n/a	n/a	[50]
1	0	0	n/a	Alper	[51]
6	n/a	n/a	n/a	KSS	[52]
103	4	68	n/a	various	[53]
1	0	n/a	n/a	FOLR1	[54]
3	0	2	0	DHFR	[55]
3	2	n/a	n/a	DHFR	[56]
1	0	0	0	n/a	[57]
1	1	0	0	FRAA	[58]
2	1	2	1	n/a	[5]
1	0	n/a	n/a	FRAA	[59]
1	n/a	1	n/a	MTHFR	[60]
2	1	2	1	FOLR1	[7]
1	0	1	0	SLC46A1	[61]
93	93	93	31	FRAA	[6]
351	**154**	**203**	**45**	**TOTAL**	

Treatment with 5-FTHF is primarily symptomatic. Especially in more severe neurological deficits it leads to a partial improvement in a relatively short time, some cases reported further gradual improvement during a long-term administration. The effect can be explained by the general metabolic role of folates, embracing the function (synthesis of neurotransmitters, hormones, amino acid metabolism ...) and also the structure (synthesis of sphingomyelin, protective antioxidant effect, DNA methylation ...) of CNS. The administration of 5-FTHT does not affect the FRAA levels. Adverse effects are usually assessed as less frequent and mild - sleep disturbances, increased

hyperactivity [6]. In patients with epilepsy may the treatment increase the seizures frequency in some cases [60]. In patients treated with Risperidone, the 5-FTHF may again increase the aggressivity [6]. In some genetic disorders it was necessary an additional medication (pyridoxal-5-phosphate) for suppressing the epileptic effect. A comprehensive therapeutic trial of core ASD symptoms in mild CFD, placebo-controlled, evaluating the efficacy and safety of 5-FTHT or 5-MTHF has not been published yet. Likewise, a long-term study of the effects of mutually different, concurrently or sequentially acting subclinical causes disrupting the folate metabolism locally in the CNS during critical periods of prenatal and early postnatal development, is absent at present.

The most common cause of the published CFD cases were the FRAA positivity, the second largest group consists of an CFD of unknown etiology. The remainder belongs mostly to the genetic defects (2). Significantly elevated FRAA titers results in a typical CFD, however, the significance of slightly elevated FRAA levels for the ASD pathophysiology is not yet precisely known, although many patients responded positively to the treatment (2).

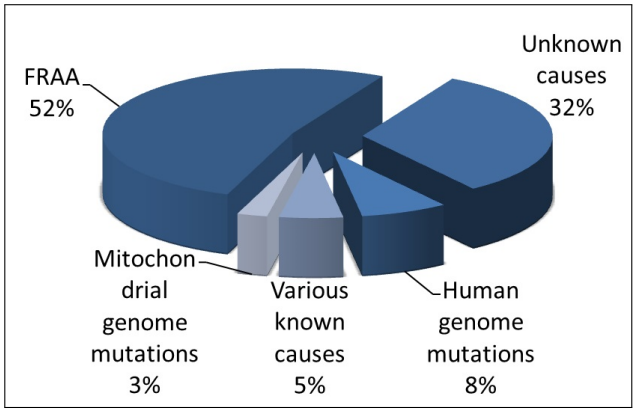

Figure 2: The common CFD etiologies.

Discussion

Disruption of folate and folate-dependent metabolic pathways localized only in the CNS is in ASD quite hard to diagnose. The only available and completely reliable method is the lumbal puncture with examination of 5-MTHF level in CSF, which is not routinely indicated in ASD for its invasivity. Less invasive methods, such as MR spectroscopy has not the needed resolution in nmol/L at present. The FRAA assay is available only in a few laboratories in the world. It is therefore possible that mild CFD in ASD escapes the attention in diagnosis and treatment for a long time, and that it may contribute to the development and progression of idiopathic ASD. This disorder is partially or rarely completely compensable. Although the first findings of ASD in CFD were identified 10 years ago and ASD prevalence is estimated from $0,1$ to $1,5\%$, we found only a few dozens of published cases (1).

The prevalence of mild CFD in ASD is not sufficiently mapped, as well as the contribution of individual causes. This is a very small population tested (total 351 published cases). Even the therapeutic effect on ASD symptoms in mild CFD has not yet been sufficiently documented. Published results clearly show the need for further research in this area, primarily because the ASD is currently considered as an incurable lifelong disorder of unknown etiology with a high socio-economic burden. In ASD patients with proven CFD have been repeatedly described improvements of neurological symptoms and also in core ASD symptoms. Many publications show the negative correlation between the age of the patient and treatment outcome. Therefore, an early intervention seems to be essential.

The potential importance of folate metabolism also illustrates the fact that there has been published other experimental studies of ASD treatment based on administration of substances, whose synthesis or concentration is directly or indirectly folate-dependent or folate-controlled or they act as cofactors in folate metabolic pathways (2).

Table 2: Other experimental ASD therapies based on administration of substances associated with folate.

Susbtance	*Publications*	*Ref.*
melatonin	18 clinical trials	[18]
tetrahydrobiopterin	4 clinical trials	[62]
cobalamin	1 clinical trial	[63]
pyridoxin	3 studies	[64]
cholin	1 animal studies	[65]
antioxidants	4 clinical trials	[62]
SSRI	9 studies	[66]

The large part of CFD etiology of (32%), the significance of mild CFD for the ASD and the relationships to the other potentially causes as oxidative stress, exogenous intoxication, infection and others points to the need for further research of these epigenetic influences. We assume that the ASD etiology may be strongly associated with a synergistic effect of several epigenetic causes, which together manifest as a neurobehavioral syndrome but each independently represents only a subclinical, not manifest problem. Research of this hypothesis is fully appropriate. Potential confirmation would significantly affect the further clinical research of ASD medications according to the rules of evidence based medicine. Heterogeneous causes which can occur simultaneously and synergistically reinforcing each other if they are not examined all together, make practically impossible to correctly select the test group for a clinical trial. Mixed test groups composed of more mutually different ASD phenotypes would affect the outcome of each trial in a random manner and the results of these studies would have always the significant differences. Gradually, it would be possible to identify only the dominant causes, as appears to be in serious CFD based on FRAA.

Conversely, if it were possible to identify and classify particular, separately insignificant, but collectively manifest causes, it would contribute significantly to the identification of novel ASD etiologies, and to the respective phenotypes classification. However, the identification and classification of multiple causes, manifestations, and their relationships across specializations of internal medicine, neurology, genetics and psychiatry, obviously requires a specific approach to capture the issues and the need of a structured information and knowledge modeling using the apparatus of ontologies and formal languages. Further applications of such broader information model are numerous: standardization of examination panels, interdisciplinary decision support in the diagnosis, the basis for population screening for fragile children and parents with a higher risk of ASD development, data collection for comparable research, interoperable electronic health record profile for data exchange and more.

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References

[1] Z. Sedlacek and M. Havlovicova, "Detsky autismus," in Detsky autismus, 1st ed., M. Hrdlicka and V. Komárek, Eds. Praha: Portál s.r.o., 2004, pp. 130–137.

[2] V. T. Ramaekers, S. P. Rothenberg, J. M. Sequeira, T. Opladen, N. Blau, E. V Quadros, and J. Selhub, "Autoantibodies to folate receptors in the cerebral folate deficiency syndrome.," N. Engl. J. Med., vol. 352, no. 19, pp. 1985–1991, May 2005.

[3] V. T. Ramaekers, J. M. Sequeira, N. Blau, and E. V Quadros, "A milk-free diet downregulates folate receptor autoimmunity in cerebral folate deficiency syndrome.," Dev. Med. Child Neurol., vol. 50, no. 5, pp. 346–52, May 2008.

[4] P. Moretti, S. U. Peters, D. Del Gaudio, T. Sahoo, K. Hyland, T. Bottiglieri, R. J. Hopkin, E. Peach, S. H. Min, D. Goldman, B. Roa, C. a Bacino, and F. Scaglia, "Brief report: autistic symptoms, developmental regression, mental retardation, epilepsy, and dyskinesias in CNS folate deficiency.," J. Autism Dev. Disord., vol. 38, no. 6, pp. 1170–1177, Jul. 2008.

[5] S. U. Steele, S. M. Cheah, A. Veerapandiyan, W. Gallentine, E. C. Smith, and M. A. Mikati, "Electroencephalographic and seizure manifestations in two patients with folate receptor autoimmune antibody-mediated primary cerebral folate deficiency.," Epilepsy Behav., vol. 24, no. 4, pp. 507–12, Aug. 2012.

[6] R. E. Frye, J. M. Sequeira, E. V Quadros, S. J. James, and D. A. Rossignol, "Cerebral folate receptor autoantibodies in autism spectrum disorder.," Mol. Psychiatry, vol. 18, no. 3, pp. 369–81, Mar. 2013.

[7] R. S. Al-Baradie and M. W. Chaudhary, "Diagnosis and management of cerebral folate deficiency. A form of folinic acid-responsive seizures.," Neurosciences (Riyadh)., vol. 19, no. 4, pp. 312–6, Oct. 2014.

[8] R. Zhao and I. D. Goldman, "Folate and thiamine transporters mediated by facilitative carriers (SLC19A1-3 and SLC46A1) and folate receptors.," Mol. Aspects Med., vol. 34, no. 2–3, pp. 373–85, 2013.

[9] I. Ifergan, G. Jansen, and Y. G. Assaraf, "The reduced folate carrier (RFC) is cytotoxic to cells under conditions of severe folate deprivation. RFC as a double edged sword in folate homeostasis.," J. Biol. Chem., vol. 283, no. 30, pp. 20687–95, 2008.

[10] H. Yuasa, K. Inoue, and Y. Hayashi, "Molecular and functional characteristics of proton-coupled folate transporter.," J. Pharm. Sci., vol. 98, no. 5, pp. 1608–16, May 2009.

[11] J. B. Wollack, B. Makori, S. Ahlawat, R. Koneru, S. C. Picinich, A. Smith, I. D. Goldman, A. Qiu, P. D. Cole, J. Glod, and B. Kamen, "Characterization of folate uptake by choroid plexus epithelial cells in a rat primary culture model.," J. Neurochem., vol. 104, no. 6, pp. 1494–503, Mar. 2008.

[12] K. Hyland, J. Shoffner, and S. J. Heales, "Cerebral folate deficiency.," J. Inherit. Metab. Dis., vol. 33, no. 5, pp. 563–70, Oct. 2010.

[13] A. Ormazabal, A. García-Cazorla, B. Pérez-Due?as, V. Gonzalez, E. Fernández-Alvarez, M. Pineda, J. Campistol, and R. Artuch, "Determination of 5-methyltetrahydrofolate in cerebrospinal fluid of paediatric patients: reference values for a paediatric population.," Clin. Chim. Acta., vol. 371, no. 1–2, pp. 159–162, 2006.

[14] S. A. Lawrence, S. A. Titus, J. Ferguson, A. L. Heineman, S. M. Taylor, and R. G. Moran, "Mammalian Mitochondrial and Cytosolic Folylpolyglutamate Synthetase Maintain the Subcellular Compartmentalization of Folates.," J. Biol. Chem., Aug. 2014.

[15] K. Pietrzik, L. Bailey, and B. Shane, "Folic acid and L-5-methyltetrahydrofolate: comparison of clinical pharmacokinetics and pharmacodynamics.," Clin. Pharmacokinet., vol. 49, no. 8, pp. 535–48, Aug. 2010.

[16] M. Serrano, B. Pérez-Due?as, J. Montoya, A. Ormazabal, and R. Artuch, "Genetic causes of cerebral folate deficiency: clinical, biochemical and therapeutic aspects.," Drug Discov. Today, vol. 17, no. 23–24, pp. 1299–306, Dec. 2012.

[17] J. Kaluzna-Czaplińska, E. Zurawicz, M. Michalska, and J. Rynkowski, "A focus on homocysteine in autism.," Acta Biochim. Pol., vol. 60, no. 2, pp. 137–142, 2013.

[18] D. A. Rossignol and R. E. Frye, "Melatonin in autism spectrum disorders: a systematic review and meta-analysis.," Dev. Med. Child Neurol., vol. 53, no. 9, pp. 783–92, Sep. 2011.

[19] V. Ramaekers, J. M. Sequeira, and E. V Quadros, "Clinical recognition and aspects of the cerebral folate deficiency syndromes.," Clin. Chem. Lab. Med., vol. 51, no. 3, pp. 497–511, Mar. 2013.

[20] A. Y. Hardan, N. J. Minshew, N. M. Melhem, S. Srihari, B. Jo, R. Bansal, M. S. Keshavan, and J. A. Stanley, "An MRI and proton spectroscopy study of the thalamus in children with autism.," Psychiatry Res., vol. 163, no. 2, pp. 97–105, 2008.

[21] J. C. Hamlin, M. Pauly, S. Melnyk, O. Pavliv, W. Starrett, T. A. Crook, and S. J. James, "Dietary intake and plasma levels of choline and betaine in children with autism spectrum disorders.," Autism Res. Treat., vol. 2013, p. 578429, Jan. 2013.

[22] Z. Luka, S. Pakhomova, L. V Loukachevitch, M. E. Newcomer, and C. Wagner, "Folate in demethylation: the crystal structure of the rat dimethylglycine dehydrogenase complexed with tetrahydrofolate.," Biochem. Biophys. Res. Commun., vol. 449, no. 4, pp. 392–8, 2014.

[23] T. J. de Koning, K. Snell, M. Duran, R. Berger, B.-T. Poll-The, and R. Surtees, "L-serine in disease and development.," Biochem. J., vol. 371, no. Pt 3, pp. 653–61, May 2003.

[24] R. Savoca, U. Ziegler, and P. Sonderegger, "Effects of L-serine on neurons in vitro.," J. Neurosci. Methods, vol. 61, no. 1–2, pp. 159–67.

[25] S. Furuya, J. Mitoma, A. Makino, and Y. Hirabayashi, "Ceramide and its interconvertible metabolite sphingosine function as indispensable lipid factors involved in survival and dendritic differentiation of cerebellar Purkinje cells.," J. Neurochem., vol. 71, no. 1, pp. 366–77, Jul. 1998.

[26] A. L. Miller, "The methylation, neurotransmitter, and antioxidant connections between folate and depression.," Altern. Med. Rev., vol. 13, no. 3, pp. 216–226, 2008.

[27] C. Pagan, R. Delorme, J. Callebert, H. Goubran-Botros, F. Amsellem, X. Drouot, C. Boudebesse, K. Le Dudal, N. Ngo-Nguyen, H. Laouamri, C. Gillberg, M. Leboyer, T. Bourgeron, and J.-M. Launay, "The serotonin-N-acetylserotonin-melatonin pathway as a biomarker for autism spectrum disorders.," Transl. Psychiatry, vol. 4, p. e479, Jan. 2014

[28] W.-H. Yang, J. Jing, L.-J. Xiu, M.-H. Cheng, X. Wang, P. Bao, and Q.-X. Wang, "Regional cerebral blood flow in children with autism spectrum disorders: a quantitative 99mTc-ECD brain SPECT study with statistical parametric mapping evaluation.," Chin. Med. J. (Engl)., vol. 124, no. 9, pp. 1362–1366, May 2011.

[29] M. Sasaki, E. Nakagawa, K. Sugai, Y. Shimizu, A. Hattori, Y. Nonoda, and N. Sato, "Brain perfusion SPECT and EEG findings in children with autism spectrum disorders and medically intractable epilepsy.," Brain Dev., vol. 32, no. 9, pp. 776–782, 2010.

[30] S. K. Gupta and B. V. Ratnam, "Cerebral perfusion abnormalities in children with autism and mental retardation: a segmental quantitative SPECT study.," Indian Pediatr., vol. 46, no. 2, pp. 161–164, Feb. 2009.

[31] M. E. Hyndman, S. Verma, R. J. Rosenfeld, T. J. Anderson, and H. G. Parsons, "Interaction of 5-methyltetrahydrofolate and tetrahydrobiopterin on endothelial function.," Am. J. Physiol. Heart Circ. Physiol., vol. 282, no. 6, pp. H2167–72, Jun. 2002.

[32] A. Ghanizadeh, M. Berk, H. Farrashbandi, A. Alavi Shoushtari, and K.-A. Villagonzalo, "Targeting the mitochondrial electron transport chain in autism, a systematic review and synthesis of a novel therapeutic approach.," Mitochondrion, vol. 13, no. 5, pp. 515–9, Sep. 2013.

[33] D. Pu, Y. Shen, and J. Wu, "Association between MTHFR gene polymorphisms and the risk of autism spectrum disorders: a meta-analysis.," Autism Res., vol. 6, no. 5, pp. 384–92, Oct. 2013.

[34] M. Adams, M. Lucock, J. Stuart, S. Fardell, K. Baker, and X. Ng, "Preliminary evidence for involvement of the folate gene polymorphism 19bp deletion-DHFR in occurrence of autism.," Neurosci. Lett., vol. 422, no. 1, pp. 24–9, 2007.

[35] B. Pérez-Due?as, C. Toma, A. Ormazábal, J. Muchart, F. Sanmartí, G. Bombau, M. Serrano, A. García-Cazorla, B. Cormand, and R. Artuch, "Progressive ataxia and myoclonic epilepsy in a patient with a homozygous mutation in the FOLR1 gene.," J. Inherit. Metab. Dis., vol. 33, no. 6, pp. 795–802, Dec. 2010.

[36] D. Siniscalco, A. Cirillo, J. J. Bradstreet, and N. Antonucci, "Epigenetic findings in autism: new perspectives for therapy.," Int. J. Environ. Res. Public Health, vol. 10, no. 9, pp. 4261–4273, 2013.

[37] L. Thompson, M. Thompson, and A. Reid, "Functional neuroanatomy and the rationale for using EEG biofeedback for clients with Aspergerâ^{TM}s syndrome.," Appl. Psychophysiol. Biofeedback, vol. 35, no. 1, pp. 39–61, 2010.

[38] S. Mamrut, H. Harony, R. Sood, H. Shahar-Gold, H. Gainer, Y.-J. Shi, L. Barki-Harrington, and S. Wagner, "DNA methylation of specific CpG sites in the promoter region regulates the transcription of the mouse oxytocin receptor.," PLoS One, vol. 8, no. 2, p. e56869, Jan. 2013.

[39] L. Zhu, X. Wang, X.-L. Li, A. Towers, X. Cao, P. Wang, R. Bowman, H. Yang, J. Goldstein, Y.-J. Li, and Y.-H. Jiang, "Epigenetic dysregulation of SHANK3 in brain tissues from individuals with autism spectrum disorders.," Hum. Mol. Genet., vol. 23, no. 6, pp. 1563–78, Mar. 2014.

[40] V. T. Ramaekers, M. Häusler, T. Opladen, G. Heimann, and N. Blau, "Psychomotor retardation, spastic paraplegia, cerebellar ataxia and dyskinesia associated with low 5-methyltetrahydrofolate in cerebrospinal fluid: a novel neurometabolic condition responding to folinic acid substitution.," Neuropediatrics, vol. 33, no. 6, pp. 301–8, Dec. 2002.

[41] V. T. Ramaekers and N. Blau, "Cerebral folate deficiency.," Dev. Med. Child Neurol., vol. 46, no. 12, pp. 843–51, Dec. 2004.

[42] V. T. Ramaekers, S. I. Hansen, J. Holm, T. Opladen, J. Senderek, M. Häusler, G. Heimann, B. Fowler, R. Maiwald, and N. Blau, "Reduced folate transport to the CNS in female Rett patients.," Neurology, vol. 61, no. 4, pp. 506–15, Aug. 2003.

[43] P. Moretti, T. Sahoo, K. Hyland, T. Bottiglieri, S. Peters, D. del Gaudio, B. Roa, S. Curry, H. Zhu, R. H. Finnell, J. L. Neul, V. T. Ramaekers, N. Blau, C. A. Bacino, G. Miller, and F. Scaglia, "Cerebral folate deficiency with developmental delay, autism, and response to folinic acid.," Neurology, vol. 64, no. 6, pp. 1088–90, Mar. 2005.

[44] F. J. Hansen and N. Blau, "Cerebral folate deficiency: life-changing supplementation with folinic acid.," Mol. Genet. Metab., vol. 84, no. 4, pp. 371–373, Apr. 2005.

[45] A. Ormazabal, A. García Cazorla, B. Pérez Due?as, M. Pineda, A. Ruiz, E. López Laso, M. García Silva, I. Carilho, C. Barbot, B. Cormand, M. Ribases, L. Moller, E. Fernández Alvarez, J. Campistol, R. Artuch, A. Garcâ^{TM}ia Cazorla, and M. Garcâ^{TM}ia Silva, "[Usefulness of analysis of cerebrospinal fluid for the diagnosis of neurotransmitters and pterin defects and glucose and folate transport deficiencies across blood brain barrier].," Med. Clin. (Barc)., vol. 127, no. 3, pp. 81–5, Jun. 2006.

[46] M. Pineda, A. Ormazabal, E. López-Gallardo, A. Nascimento, A. Solano, M. D. Herrero, M. A. Vilaseca, P. Briones, L. Ibá?ez, J. Montoya, and R. Artuch, "Cerebral folate deficiency and leukoencephalopathy caused by a mitochondrial DNA deletion.," Ann. Neurol., vol. 59, no. 2, pp. 394–398, Feb. 2006.

[47] V. T. Ramaekers, N. Blau, J. M. Sequeira, M.-C. Nassogne, and E. V Quadros, "Folate receptor autoimmunity and cerebral folate deficiency in low-functioning autism with neurological deficits.," Neuropediatrics, vol. 38, no. 6, pp. 276–81, Dec. 2007.

[48] V. T. Ramaekers, J. M. Sequeira, R. Artuch, N. Blau, T. Temudo, A. Ormazabal, M. Pineda, A. Aracil, F. Roelens, F. Laccone, and E. V Quadros, "Folate receptor autoantibodies and spinal fluid 5-methyltetrahydrofolate deficiency in Rett syndrome.," Neuropediatrics, vol. 38, no. 4, pp. 179–83, Aug. 2007.

[49] S. Mercimek-Mahmutoglu and S. Stockler-Ipsiroglu, "Cerebral folate deficiency and folinic acid treatment in hypomyelination with atrophy of the basal ganglia and cerebellum (H-ABC) syndrome.," Tohoku J. Exp. Med., vol. 211, no. 1, pp. 95–6; author reply 97, Jan. 2007.

[50] J. L. Bonkowsky, V. T. Ramaekers, E. V Quadros, and M. Lloyd, "Progressive encephalopathy in a child with cerebral folate deficiency syndrome.," J. Child Neurol., vol. 23, no. 12, pp. 1460–3, Dec. 2008.

[51] O. Hasselmann, N. Blau, V. T. Ramaekers, E. V Quadros, J. M. Sequeira, and M. Weissert, "Cerebral folate deficiency and CNS inflammatory markers in Alpers disease.," Mol. Genet. Metab., vol. 99, no. 1, pp. 58–61, Jan. 2010.

[52] M. Serrano, M. T. García-Silva, E. Martin-Hernandez, M. del M. OâTMCallaghan, P. Quijada, A. Martinez-Aragón, A. Ormazábal, A. Blázquez, M. A. Martín, P. Briones, E. López-Gallardo, E. Ruiz-Pesini, J. Montoya, R. Artuch, and M. Pineda, "Kearns-Sayre syndrome: cerebral folate deficiency, MRI findings and new cerebrospinal fluid biochemical features.," Mitochondrion, vol. 10, no. 5, pp. 429–32, Aug. 2010.

[53] S. Mangold, N. Blau, T. Opladen, R. Steinfeld, B. Wessling, K. Zerres, and M. Häusler, "Cerebral folate deficiency: a neurometabolic syndrome?," Mol. Genet. Metab., vol. 104, no. 3, pp. 369–72, Nov. 2011.

[54] P. Dill, J. Schneider, P. Weber, D. Trachsel, M. Tekin, C. Jakobs, B. Thöny, and N. Blau, "Pyridoxal phosphate-responsive seizures in a patient with cerebral folate deficiency (CFD) and congenital deafness with labyrinthine aplasia, microtia and microdontia (LAMM).," Mol. Genet. Metab., vol. 104, no. 3, pp. 362–8, Nov. 2011.

[55] S. Banka, H. J. Blom, J. Walter, M. Aziz, J. Urquhart, C. M. Clouthier, G. I. Rice, A. P. M. de Brouwer, E. Hilton, G. Vassallo, A. Will, D. E. C. Smith, Y. M. Smulders, R. A. Wevers, R. Steinfeld, S. Heales, Y. J. Crow, J. N. Pelletier, S. Jones, and W. G. Newman, "Identification and characterization of an inborn error of metabolism caused by dihydrofolate reductase deficiency.," Am. J. Hum. Genet., vol. 88, no. 2, pp. 216–25, Feb. 2011.

[56] H. Cario, D. E. C. Smith, H. Blom, N. Blau, H. Bode, K. Holzmann, U. Pannicke, K.-P. Hopfner, E.-M. Rump, Z. Ayric, E. Kohne, K.-M. Debatin, Y. Smulders, and K. Schwarz, "Dihydrofolate reductase deficiency due to a homozygous DHFR mutation causes megaloblastic anemia and cerebral folate deficiency leading to severe neurologic disease.," Am. J. Hum. Genet., vol. 88, no. 2, pp. 226–31, Feb. 2011.

[57] V. Leuzzi, M. Mastrangelo, A. Celato, and C. Carducci, "A new form of cerebral folate deficiency with severe self-injurious behaviour.," Acta Paediatr., vol. 101, no. 11, pp. e482–3, Nov. 2012.

[58] Z. Sadighi, I. J. Butler, and M. K. Koenig, "Adult-onset cerebral folate deficiency.," Arch. Neurol., vol. 69, no. 6, pp. 778–779, 2012.

[59] A. Ho, D. Michelson, G. Aaen, and S. Ashwal, "Cerebral folate deficiency presenting as adolescent catatonic schizophrenia: a case report.," J. Child Neurol., vol. 25, no. 7, pp. 898–900, 2010.

[60] Q. Wang, J. Liu, Y.-P. Liu, X.-Y. Li, Y.-Y. Ma, T.-F. Wu, Y. Ding, J.-Q. Song, Y.-J. Wang, and Y.-L. Yang, "[Methylenetetrahydrofolate reductase deficiency-induced schizophrenia in a school-age boy].," Zhongguo Dang Dai Er Ke Za Zhi, vol. 16, no. 1, pp. 62–6, Jan. 2014.

[61] Q. Wang, X. Li, Y. Ding, Y. Liu, Y. Qin, and Y. Yang, "The first Chinese case report of hereditary folate malabsorption with a novel mutation on SLC46A1.," Brain Dev., 2014.

[62] R. E. Frye and D. A. Rossignol, "Treatments for biomedical abnormalities associated with autism spectrum disorder.," Front. Pediatr., vol. 2, p. 66, Jan. 2014.

[63] K. Bertoglio, S. Jill James, L. Deprey, N. Brule, and R. L. Hendren, "Pilot study of the effect of methyl B12 treatment on behavioral and biomarker measures in children with autism.," J. Altern. Complement. Med., vol. 16, no. 5, pp. 555–560, May 2010.

[64] R. E. Frye, D. Rossignol, M. F. Casanova, G. L. Brown, V. Martin, S. Edelson, R. Coben, J. Lewine, J. C. Slattery, C. Lau, P. Hardy, S. H. Fatemi, T. D. Folsom, D. Macfabe, and J. B. Adams, "A Review of Traditional and Novel Treatments for Seizures in Autism Spectrum Disorder: Findings from a Systematic Review and Expert Panel.," Front. public Heal., vol. 1, p. 31, 2013.

[65] E. A. Langley, M. Krykbaeva, J. K. Blusztajn, and T. J. Mellott, "High maternal choline consumption during pregnancy and nursing alleviates deficits in social interaction and improves anxiety-like behaviors in the BTBR T+Itpr3tf/J mouse model of autism.," Behav. Brain Res., Oct. 2014.

[66] K. Williams, A. Brignell, M. Randall, N. Silove, and P. Hazell, "Selective serotonin reuptake inhibitors (SSRIs) for autism spectrum disorders (ASD).," Cochrane database Syst. Rev., vol. 8, p. CD004677, Jan. 2013.

Introduction to technology acceptance

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Abstract

This contribution introduces a number of user satisfaction and technology acceptance approaches. User satisfaction appears to be a bad predictor for system acceptance and usage but is a good diagnostic to be used for system design. Since information systems are still underutilized, application of models of user technology acceptance can provide important clues about what can be done to increase system usage. The more so when models for user satisfaction and technology acceptance are integrated. Various user technology acceptance models are introduced.

Keywords

Health IT acceptance, user satisfaction, TRA, TAM, evaluation, integration of user satisfaction and technology acceptance aspects

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Introduction

Information technology adoption and use in the workplace remains a concern of information systems research and practice. Underutilized systems still exist. Therefore understanding and creating the conditions under which information systems will be adopted by a human organization remains a high-priority research issue. There is a need for methods with which one can predict – on the basis of information from (potential) users - whether an information system will be successful. The method would be even more useful when in case of a negative prediction it is able to indicate which factors should be changed to get a successful system. And finally, it would be very nice if the method would work even when the potential users are only briefly introduced to the system.

In this contribution we will focus on user acceptance, defined as the demonstrable willingness within a user group to employ information technology for the tasks it is designed to support. In their effort to explain system use, researchers first developed tools for measuring and analyzing computer user satisfaction [1]. User satisfaction is often considered as a surrogate of system success. But how do we define a successful system and is user satisfaction indeed a surrogate of system success? First this question will be discussed and then we will continue with some approaches that focus on user satisfaction. Next we will introduce the Theory of Reasoned Action (TRA), stemming from social psychology. TRA is a general model applicable to many domains. Then we discuss the three versions of the technology acceptance model (TAM). TAM is based on TRA. Finally we will introduce the Unified Theory of Acceptance and Use of Technology model.

1 How to define information system's success?

As stated above, user satisfaction was often considered as a surrogate measure for success. DeLone and McLean [2] investigated how IS success can be defined. They reviewed many studies that were conducted to identify factors that contribute to IS success, but the definition of IS success – the dependent variable – was an elusive one to define. They noted that information flows through a series of stages from its production through its use or consumption to its influence on individual and/or organizational performance, leading to six different aspects or categories of information systems: System quality, Information quality, Use, User satisfaction, Individual impact and Organizational impact. IS success clearly is multidimensional. In the literature for each of the mentioned success categories many different measures of success were proposed. User satisfaction appeared to be the most widely used single measure of IS success. DeLone and McLean developed an IS success model on the basis of the results of their literature review. Success not only is a multidimensional concept but the six aspects also appeared to be interde-

pendent. The model shows the following interdependencies: System quality and Information quality affect both Use and User satisfaction. Additionally the amount of Use can affect the degree of User satisfaction. Use and User satisfaction are direct antecedents of Individual impact and impact on individual performance should eventually have some Organizational impact. In 2001 the model was updated [3]. A third quality aspect was included: Service Quality. Individual and Organizational impact were merged into the aspect Net benefits. In addition the authors suggest that Intention to use may be a worthwhile alternative for Use in some contexts.

2 User satisfaction

In the seventies of the last century the need was felt to evaluate information system (IS) services and user satisfaction, from the organization's point of view to estimate the benefits of IS services and from the EDP (electronic data processing) department's point of view to improve performance [1]. User satisfaction is defined by Ives et al [4] as the extent to which users believe that the information system available to them meets their information requirements.

As indicated by Bailey and Pearson [5], it was natural to turn to the efforts of psychologists, who study satisfaction in a broader perspective. Bailey and Pearson used as operational definition for user satisfaction the weighted sum of an individual's feelings toward all factors affecting that attitude. To measure satisfaction with this definition, one must have a theoretically complete set of factors. Bailey and Pearson developed a computer user satisfaction questionnaire consisting of 39 factors, covering the organization, the hardware system, the application software, user factors and EDP staff. They used the semantic differential technique to express the feelings toward the various factors. Four appropriate pairs of bipolar adjectives were used for each factor. For example, the factor 'Reliability of the system' consisted of four quality ratings with the bipolar adjectives: consistent – inconsistent, high- low, superior- inferior, sufficient- insufficient. The adjectives were separated in seven intervals, labeled with intensity modifiers: extremely, quite, slightly, neither or equally, slightly, quite, and extremely. Assigning numeric values to the scales from -3 to +3 allows for quantification. A fifth rating is used to measure the importance of the factor relative to the other factors with again seven intervals ranging from extremely unimportant to extremely important. This scale varied from 0 to 1.0. The importance rating was used for weighing the four individual's feelings.

A problem was that the computer user satisfaction questionnaire required 195 individual seven-point scale responses (five per factor). This is a rather large number. Ives et al [4] reduced the questionnaire to 13 items and two scales per item. Bailey [6] adapted the questionnaire for measuring user satisfaction in hospitals. He was not able to reduce the number of factors. Instead the questionnaire now contained 41 factors. However, the number of quality ratings was reduced to two as already done by Ives et al.

With the advent of personal workstations and end-user computing the tools measuring user satisfaction developed by Bailey and Pearson and by Ives et al. became outdated. Doll and Torkzadeh [7] developed a new instrument to measure satisfaction of end users who directly interact with a specific application. It was a questionnaire with 12 items and 2 global measures of perceived overall satisfaction and success, which was widely used. Roy and Bouchard reviewed a number of user satisfaction instruments [8].

User satisfaction is a potentially useful diagnostic for system design. A lot of research is done on the factors and processes that intervene between IT investments and the realization of their economic value. These factors and processes are commonly tied to user perceptions about IT and how it impacts their work. User satisfaction however appears to be not a good predictor of system use.

3 Theory of Reasoned Action (TRA)

TRA is a popular theory from social psychology, investigating the determinants of consciously intended behaviors of individuals [9, 10]. The model, based on this theory, can be applied quite generally.

According to the theory, the performance of a behavior (such as using an information system) is determined by an individual's Behavioral intention. Behavioral intentions are self-instructions to perform a particular behavior. A Behavioral intention is the result of deliberations about what one will do and indicates how hard one is prepared to try to perform the behavior. The Behavioral intention in turn is determined by the individual's Attitude and Subjective norm towards the behavior. Attitudes are an individual's positive or negative feelings towards the behavior (good/bad, harmful/beneficial, etc.). Attitude is operationally defined as the sum of a person's Behavioral beliefs (the individual's subjective probability that performing the behavior results in a certain consequence of the behavior, numerically expressed), multiplied by the individual's Evaluation of those consequences (again numerically expressed). Since the model is general and the beliefs depend on the type of behavior to be studied, they have to be determined for every behavior, usually via interviews.

The Subjective norm refers to the degree to which an individual perceives that most people who are important to him think he should or should not perform the behavior. The Subjective norm is determined by the sum of products of one's Normative beliefs (whether specific groups or people encourage or discourage the behavior) and one's Motivation to comply with these expectations. Again it should be investigated via interviewing who are the rel-

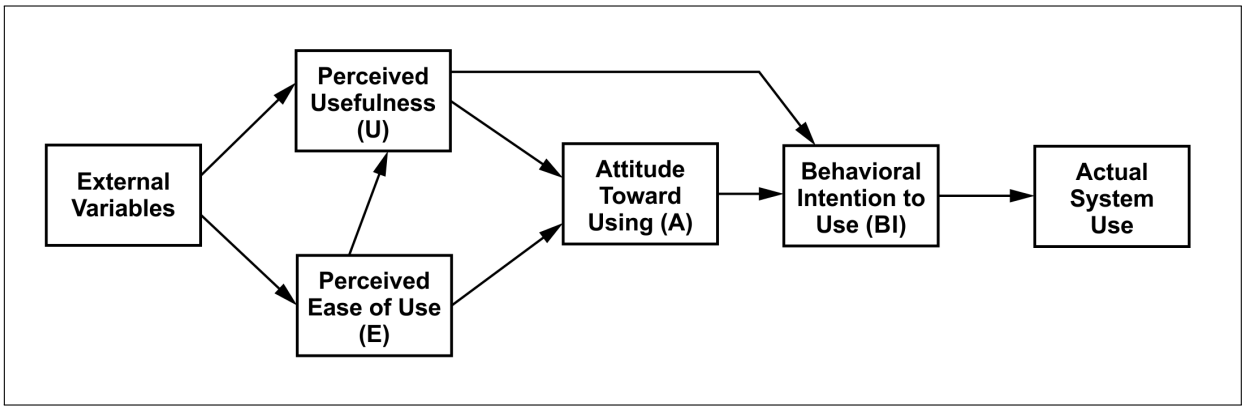

Figure 1: The TAM model (based on [20]).

evant referent individuals and groups. According to the theory external variables influence the beliefs about the outcomes associated with performing a behavior. Certain external variables can be the reason that a certain behavior is not performed very often. With a model that includes the external variables one can determine which external variables caused the low performance of the behavior.

The values of the various constructs in TRA are determined via questionnaires consisting of a number of items that are scored by the respondents on a seven point Likert scale. For beliefs two scales are used: one for the belief strength itself and one for its evaluation. An item for measuring Behavioral belief strength could be: 'Using the information system in my job would enable me to accomplish a task more quickly', to be scored on a Likert scale with values ranging for example from extremely likely to extremely unlikely. An item for evaluating the consequence of the behavior could be: 'Accomplishing a task more quickly is' followed by a seven point scale starting with Extremely bad and ending with Extremely good, for example. For the contents of the questionnaires the reader is referred to [11].

After the model is validated (indicating that a large part of the variance of behavioral intention is explained by the model) it can be used to determine how specific types of behavior are influenced by external variables, beliefs and attitudes.

Various studies reported that the correlations between attitudinal predictors and behavioral criteria were rather low, making the use of attitudes in the TRA model questionable. However, Ajzen and Fishbein [12] argued that there should be a correspondence between attitude and behavior and that that was not always the case in the studies, reporting low correlations. What does correspondence mean? Attitudinal and behavioral entities are characterized by four different elements: the action; the target, at which the action is directed; the context in which the action is performed and the time at which it is performed. Attitude will only successfully predict behavior when the four elements of attitude correspond with the four elements of the behavior. To give an example: as mentioned earlier, user satisfaction appeared to be a weak predictor of system use. This is attributable to the fact that beliefs and attitudes about objects (such as an information system) are poor predictors of behaviors, such as system usage because the targets are different and therefore there is no total correspondence: user satisfaction has as target the system, whereas the behavior concerns the use of the system. Wixom and Todd [13] state that the two dominant approaches in systems research, patient satisfaction and technology acceptance, have been developed in parallel and have not been reconciled or integrated. They acknowledge that that is due to the fact that these approaches study a different target so that patient satisfaction does not predict attitude toward usage very well. They integrated both approaches using the above mentioned ideas about correspondence as we will discuss later.

TRA was related to voluntary behavior. But behavior is usually not totally voluntary and under control. Therefore in the successor of TRA, the theory of planned behavior, TpB, an additional element is included: perceived behavioral control, which is determined by control beliefs [14]. Control beliefs refer to specific factors or circumstances that make behavior easier or more difficult. A direct measure of perceived behavioral control should capture people's confidence that they are capable of performing the behavior under investigation. Again two scales are needed for measuring control beliefs: its strength (perceived likelihood of the occurrence of each facilitating or constraining condition) and its perceived power (perceived effect of a condition in making doing the behavior hard or easy). For the items of both scales the reader is again referred to [11].

4 TAM - Technology Acceptance model

TAM was developed by Davis [15] to predict the individual adoption and use of new information systems. It is based on TRA and models user acceptance of information systems. TAM should be able to explain why an information system is not accepted, so that corrective actions

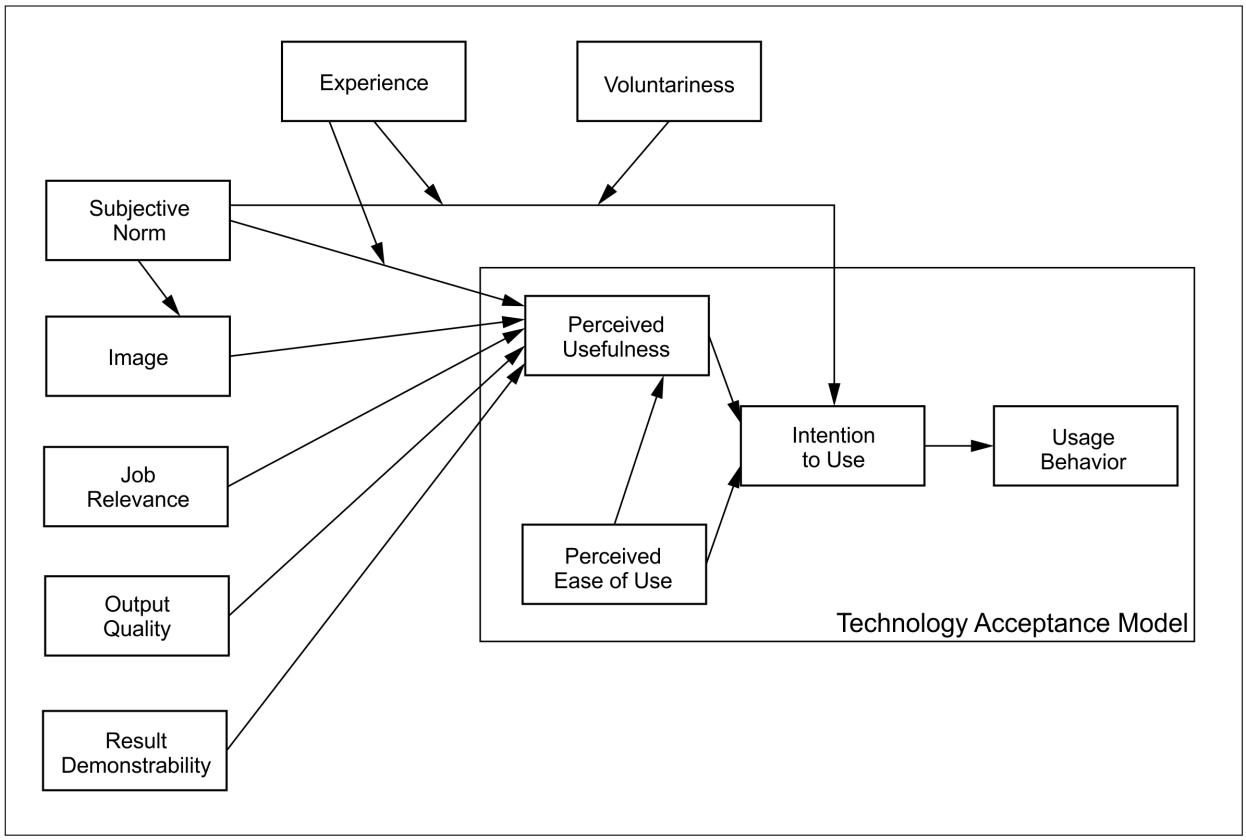

Figure 2: The TAM2 model (based on [20]).

can be carried out. TAM can already be applied after the potential users have been shortly introduced (an hour or so) to a new system.

It appeared that technology acceptance is determined by only two beliefs: Perceived usefulness and Perceived ease of use. Perceived usefulness is an outcome expectancy, defined as the prospective user's subjective probability that using a specific application system will increase his or her job performance. Perceived ease of use is a process expectancy that refers to the degree to which the prospective user expects the target system to be free of effort. Both beliefs are fairly general determinants of user acceptance, valid for different computer systems and user populations. In contrast to TRA, in TAM one of the beliefs (Perceived usefulness) directly influences Behavioral intention (see fig. 1). TAM does not include Subjective norm (no significant effect on Behavioral intention was detected) or Perceived behavioral control (TAM was derived from TRA) as a determinant of Behavioral intention. According to TAM, Perceived usefulness is also influenced by Perceived ease of use because, other things being equal, the easier the system is to use the more useful it can be. The effect of external variables (e.g. design characteristics, system characteristics, development process, training) on Behavioral intention are mediated by Perceived usefulness and Perceived ease of use. Questionnaires were designed for both types of belief [16]. For Behavioral Intention and Attitude the same scales are used as in TRA. Attitude towards using a technology was omitted in the final model presented in [10] because Attitude only partially mediated the effects of Perceived usefulness and Perceived ease of use to Behavioral intention (see insert in fig. 2). In addition the weak direct link between Perceived usefulness and Attitude and the strong direct link between Perceived usefulness and Intention were reasons to remove Attitude form the model. According to Venkatesh [17] the removal of Attitude helps to better understand the influence of Perceived ease of use and Perceived usefulness on the key dependent variable of interest – Intention. Studies show that around 40% of the variance of Behavioral intention to use the system can be explained by TAM (for medical applications see [18, 19]).

Because TAM uses general beliefs it is not clear which external variables make technology useful and easy to use. Some work has been done to address this limitation by identifying determinants of the key predictors in TAM: Perceived usefulness and Perceived ease of use. Some researchers have developed context-specific determinants of the two TAM constructs.

Venkatesh and Davis [21] added context independent determinants of Perceived usefulness to the model and tested the extension of the model. The extended model was called TAM2. Subjective norm, already used in TRA, was included in TAM2. It appeared that Subjective norm had a significant effect on Intention in mandatory but not in voluntary settings. To distinguish between these usage

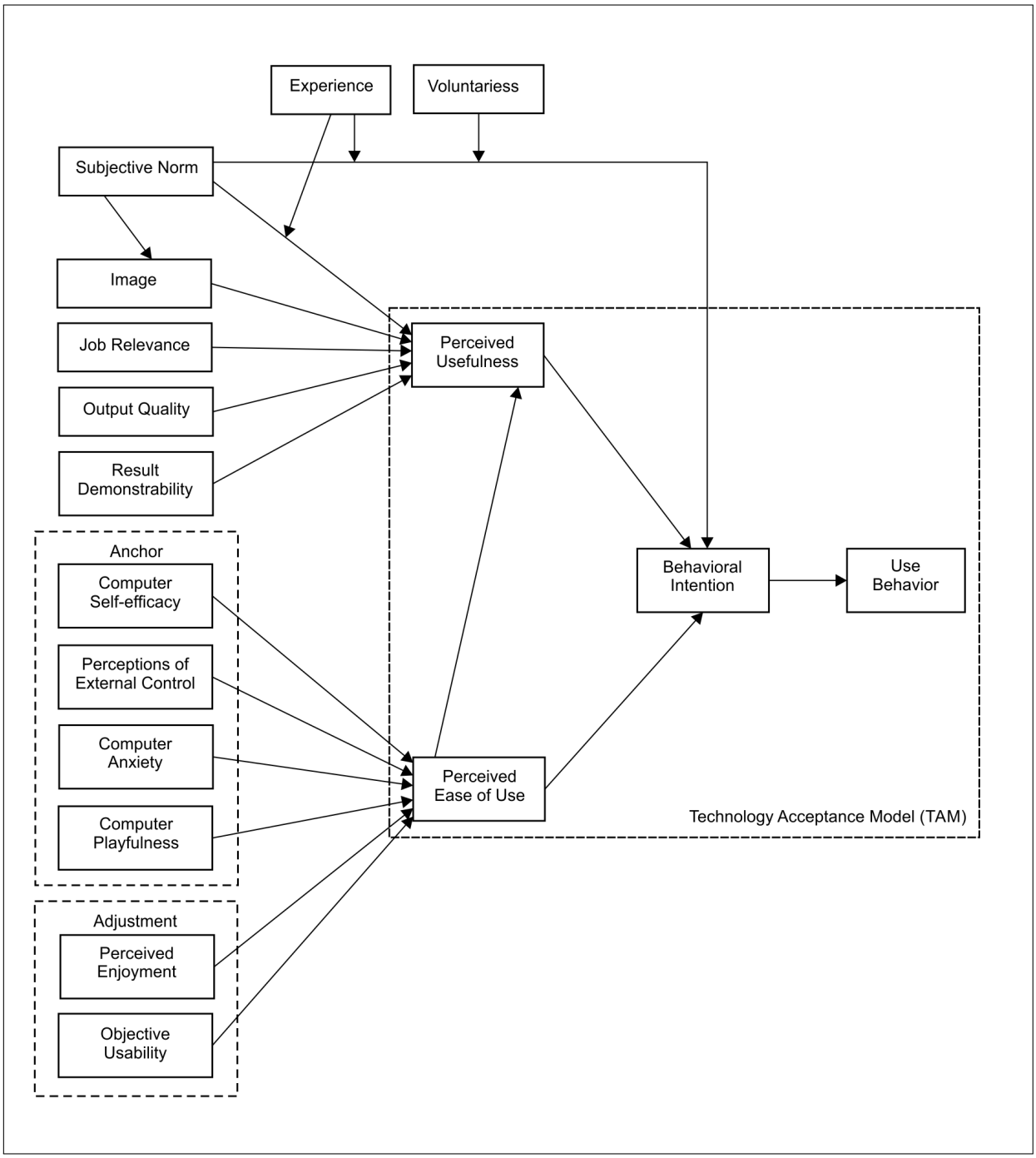

Figure 3: The TAM3 model.

settings, the model introduces Voluntariness as a moderating variable. Subjective norm also has a positive direct effect on Perceived usefulness. Another determinant of Perceived usefulness is Image, the degree to which use of an innovation is perceived to enhance one's status in one's social system. TAM2 theorizes that Subjective norm will positively influence Image. The positive direct effect of Subjective norm on Behavioral intention for mandatory systems will attenuate with increased experience. Also the positive direct effect of Subjective norm on Perceived usefulness will attenuate with increased experience for both mandatory and voluntary systems. Experience was therefore also added as a moderating variable. Next to these social determinants four cognitive instrumental determinants of Perceived usefulness were included: Job relevance (an individual's perception regarding the degree to which the target system is applicable to his or her job), Output quality (the degree to which an individual believes that the system performs his or her job tasks well), Result demonstrability (the degree to which an individual believes that the results of using a system are tangible, observable, and communicable). Venkatesh and Davis [21]

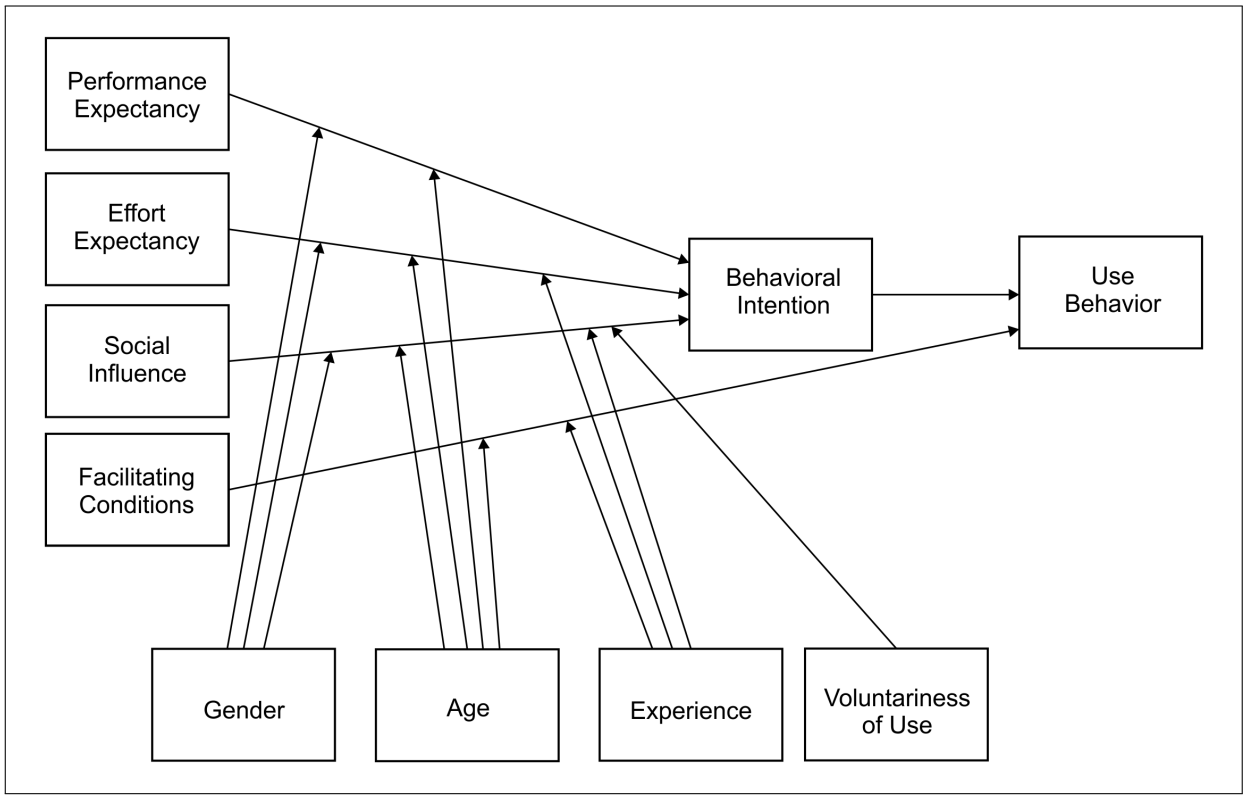

Figure 4: The Unified Theory of Acceptance and Use of Technology model.

could prove that the added variables (see fig. 2) indeed were determinants of Perceived usefulness. They together explained up to 60% of the variance of Perceived usefulness.

TAM3 [17, 22, 23]] adds determinants of Perceived ease of use to TAM2 (see fig. 3, based on [20]). A theoretical framework, based on behavioral decision theory, was developed describing the determinants of system-specific Perceived ease of use as individuals evolve from the early stage of experience with the target system to stages of significant experience [23]. Behavioral decision theory suggests that "anchoring and adjustment" is an important general decision making heuristic often used by individuals: in the absence of specific knowledge, individuals rely on general information that serves as an "anchor". When they get direct experience with the target system, the anchors are adjusted but not renewed, since individuals are often unable to ignore such anchoring information in decision-making processes. The determinants therefore can be divided into anchors (general beliefs about computers and computer usage) and adjustments (beliefs that are based on direct experience with the target system).

The anchor determinants are: Computer self-efficacy (the degree to which an individual believes that he or she has the ability to perform a specific task/job using the computer), Perception of external control (the degree to which an individual believes that organizational and technical resources exist to support the use of the system), Computer anxiety (the degree of an individual's apprehension, or even fear, when she/he is faced with the possibility of using computers) and Computer playfulness (the degree of cognitive spontaneity in microcomputer interactions). The first two mentioned determinants are constructs related to control, a concept that was introduced in TpB.

The adjustment determinants are: Perceived enjoyment (the extent to which the activity of using a specific system is perceived to be enjoyable in its own right, aside from any performance consequences resulting from system use) and Objective usability (a comparison of systems based on the actual level (rather than perceptions) of effort required to completing specific tasks). Again experience and voluntariness are considered as moderators. TAM3 was tested and it was shown that the suggested determinants of Perceived ease of use explained between 43% and 52% of the variance in Perceived ease of use. Also from 40% to 53% of the variance of Behavioral intention was explained [23].

5 Unified Theory of Acceptance and Use of Technology (UTAUT)

Venkatesh et al [24] note that IT technology acceptance research has yielded many competing models, each with different sets of acceptance determinants. They compared the acceptance determinants of eight different models: TRA, TAM/TAM2, the motivational model, TpB, a model combining the TAM and TpB, the model of PC

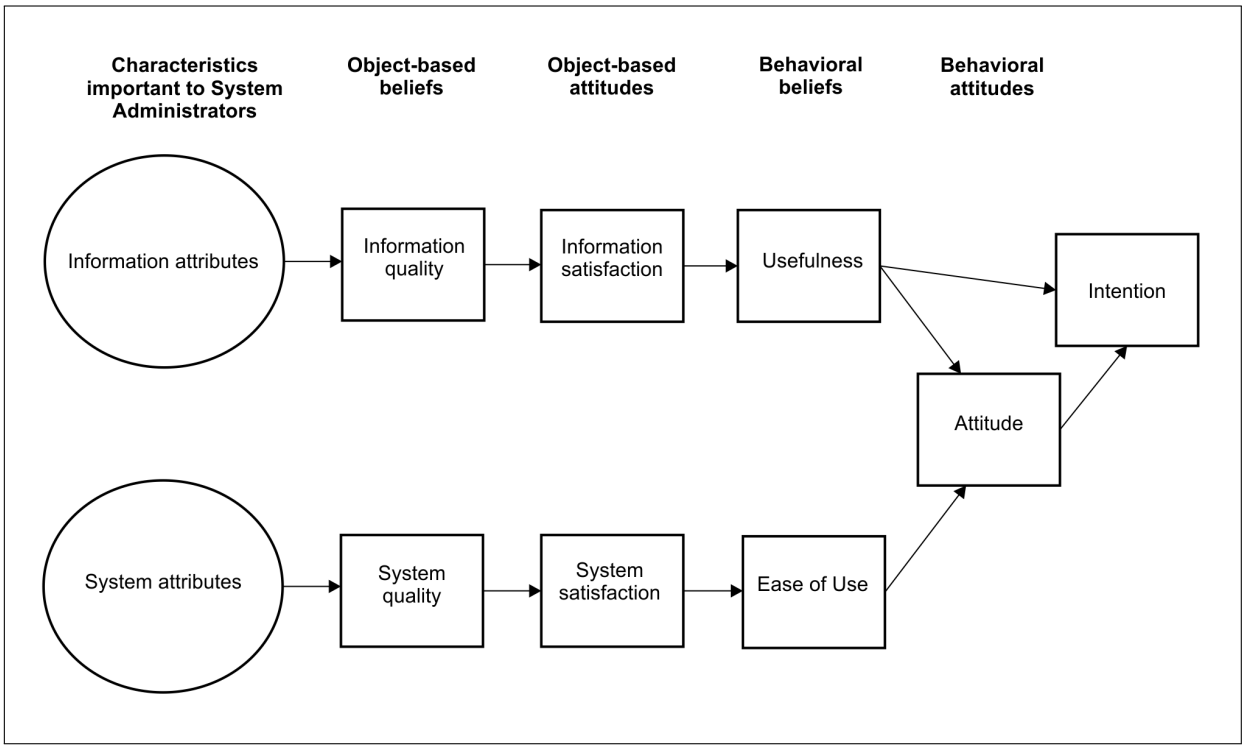

Figure 5: The integrated model (based on [13].

utilization, the innovation diffusion theory, and the social cognitive theory. Then a unified model was formulated based on commonalities between the investigated models. They also tested the model (see fig. 4, based on [20]).

Although seven constructs appeared to be significant direct determinants of Intention or Usage in one or more of the individual models, it was theorized that four constructs play a significant role: Performance expectancy (the degree to which an individual believes that using the system will help him or her to attain gains in job performance), Effort expectancy (the degree of ease associated with the use of the system), Social influence (the degree to which an individual perceives that important others believe he or she should use the new system) and Facilitating conditions (the degree to which an individual believes that an organizational and technical infrastructure exists to support the use of the system). Also four modifying variables were included: age, gender, experience and voluntariness. The Performance expectancy construct is the strongest predictor of Behavioral intention and is comparable with the construct Perceived usefulness in TAM. The influence of Performance expectancy on Behavioral intention is moderated by gender and age such that the effect is stronger for men and particularly for younger men. Effort expectancy is comparable to TAM's Perceived ease of use. The influence of effort expectancy on Behavioral intention is moderated by gender, age, and experience, such that the effect is stronger for women, particularly older women, and particularly at early stages of experience. Social influence is comparable to TAM2's Subjective norm. The influence of Social influence on Behavioral intention is moderated by gender, age, voluntariness, and experience, such that the effect will be stronger for women, particularly older women, particularly in mandatory settings in the early stages of experience. Facilitating conditions was not a construct in TAM. Facilitating conditions do not influence Behavioral intention but influence usage directly. The influence of facilitating conditions on usage are moderated by age and experience, such that facilitating conditions only matter for older workers in later stages of experience.

UTAUT was able to account for 70 percent of the variance in Usage intention. The authors conclude that since UTAUT explains as much as 70 percent of the variance in intention, the practical limits of our ability to explain individual acceptance and usage decisions in organizations have probably be reached.

6 Integrating user satisfaction and technology acceptance approaches

Despite its predictive capability, TAM provides only limited guidance about how to influence usage through design and implementation. Designers receive feedback regarding ease of use or usefulness in a general sense, but they do not receive actionable feedback about important aspects of the information system itself (e.g. flexibility, integration, completeness of information, and information currency). Such guidance was a core objective in the de-

velopment of TAM, but one that has received limited attention [13].

Wixom and Todd [13] describe how the patient satisfaction and technology acceptance models can be integrated. User satisfaction had been measured by various subsets of beliefs about specific systems, information and other related characteristics. They conclude that user satisfaction is an object-based attitude that functions as an external variable influencing Behavioral intention and Usage via behavioral beliefs and attitudes (see fig. 5 for a general idea of the model). In this way one has taken care of the correspondence principle as discussed above. Beliefs about using the system will be shaped in part by the attitude toward the system itself.

The integrated model has as input key antecedents of the System and Information quality beliefs, derived from the user satisfaction literature. For system quality, antecedents like Reliability, Accessibility and Timeliness are introduced. Information quality is determined by antecedents like Completeness, Accuracy and Currency. System quality and Information quality beliefs shape attitudes about System satisfaction and Information satisfaction. Satisfaction with the information produced by the system will influence perceptions of usefulness. System satisfaction represents a degree of favorableness with the system and the mechanics of interaction. The more satisfied one is with the system itself, the more likely one is to find the system easy to use. So these two attitudes connect with the Usefulness and Ease of use beliefs of the TAM model. The integrated model also indicates that System satisfaction influences Information satisfaction.

The integrated model has been tested. The value of each construct was determined using three items per construct (only information satisfaction and system satisfaction had two items [13]). Timeliness appeared not to be a significant determinant of System quality. But this may have been caused by the fact that a data warehousing data access software was evaluated. The model explained 59% of the variance of Intention. The advantage of the integrated model is that system and information characteristics can be assessed together with their influence on system use.

7 Discussion

Above we have presented user satisfaction and technology acceptance approaches. We finished by presenting an attempt to integrate both approaches. The discussed models explain a high percentage of the variance of Behavioral intention. The integrated model provides a mechanism for understanding and assessing the relative influence of detailed system and information characteristics.

The presented model versions can be used for evaluating the acceptance of information systems. The model is known and the values of the several constructs of the model can be determined using the corresponding questionnaires, published in the literature. When the potential users have answered the questionnaires the relations between the various constructs of the model and the explained variance can be determined via regression analysis or Structured Equation Modeling. In this way it can be determined which constructs influence which other constructs.

References

[1] Legris P, Ingham J, Collerette P. Why do people use information technology? A critical review of the technology acceptance model. Information Management 2003, 40: 191â“204.

[2] DeLone WH and McLean ER. Information systems success: the quest for the dependent variable. Information Systems Research, 1992, 3(1): 60-95.

[3] DeLone WH and McLean ER. The DeLone and McLean model of information systems success: a ten-year update. Journal of Management Information Systems, 2001, 19(4): 9-30.

[4] Ives, B, Olson MH and Baroudi JJ. The measurement of user information satisfaction. Communications of the ACM, 1983, 26 (10), 785-793.

[5] Bailey, JE and Pearson, SW. Development of a tool for measuring and analyzing computer user satisfaction. Manage. Sci. 1983, 29(5): 530-545.

[6] Bailey, JE. Development of an instrument for the management of computer user attitudes in hospitals. Methods Inf. Med. 1990, 29(1): 51-56.

[7] Doll, W. J. and Torkzadeh, G. The Measurement of End-User Computing Satisfaction, MIS Quarterly 1988, 12(2): 259-274.

[8] MC Roy and Bouchard, L. Developing and evaluating methods for user satisfaction measurement in practice. Journal of Information Technology Measurement, 1999, X (3-4): 49-58.

[9] M. Fishbein, I. Ajzen, Belief, Attitude, Intention, and Behavior: An Introduction to Theory and Research, Addison-Wesley, Reading, MA, 1975.

[10] Davis FD, Bagozzi RP and Warshaw PR. User acceptance of computer technology: a comparison of two theoretical models. Management Science, 1989, 25 (8): 982-1003.

[11] Ajzen I. Constructing a TpB Questionnaire: conceptual and methodological considerations. Available from http://people.umass.edu/aizen/pdf/tpb.measurement.pdf

[12] Ajzen I and Fishbein M. Attitude-Behavior relations: a theoretical analysis and review of empirical research. Psychological Bulletin. 1877, 14(1): 888-918.

[13] Wixom BH and Todd PA. A theoretical integration of user satisfaction and technology acceptance. Information Systems Research, 2005, 16(1): 85-102

[14] Ajzen I. The theory of planned behavior. Organizational behavior and human decision processes. 1991, 50: 179-211.

[15] Davis FD. A technology acceptance model for empirically testing new end-user information systems: theory and results. Doctoral dissertation. Sloan School of Management, Massachusetts Institute of Technology, 1986.

[16] Davis FD. Perceived usefulness, Perceived ease of use, and user acceptance of information technology. MIS Quarterly, 1989, 13(3):319-340.

[17] Venkatesh V. Determinants of perceived ease of use: integrating control, Intrinsic motivation, and emotion in the technology acceptance model. Information Systems Research 2000, 11(4): 342-365.

[18] Yarbrough AK and Smith TB. Technology Acceptance among Physicians: A New Take on TAM. Med Care Res Rev. 2007, 64: 650-672.

[19] Holden RJ and Karsh B-T. A theoretical model of health information technology usage behaviour with implications for patient safety. Behaviour and Information Technology. 2009, 28(1): 21-38.

[20] Vvenkatesh.com/IT/organizations/models.asp [cited 06.05.14]

[21] Venkatesh V and Davis FD. A Theoretical Extension of the Technology Acceptance Model: four longitudinal field studies. Management Science, 2000, 46(2): 186-204.

[22] Venkatesh V and Davis FD. 1996. A model of the antecedents of perceived ease of use: Development and test. Decision Sci. 1996, 27: 451â“481.

[23] Venkatesh V and Bala H. Technology acceptance model 3 and a research agenda on interventions. Decision Sciences 2008, 39(2): 273-315.

[24] Venkatesh V, Morris MG, Davis GB and Davis FD. User acceptance of information technology: toward a unified view. MIS Quarterly, 27, 2003, 425-478.

Clinical Algorithms: purpose, content, rules, and benefits

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Abstract

This paper describes the advantages and disadvantages of Clinical Algorithms (CAs) in the graphical format of Flow Charts, their design and symbology, their current use in clinical practice, their implementation on computer systems, software used in their production, proposals for international CA standards, and novel ideas for incorporation into future Algorithms.

In this Paper, detailed rules and techniques for drawing Flow Charts will be discussed. This will be followed by illustrations of the value of Clinical Algorithms in Medicine and examples of well-designed such Algorithms.

Keywords

Algorithms, Clinical Algorithms, Decision Making, Flow Charts, Medicine

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1 Introduction

With the establishment of Evidence-based Medical Practice, Clinical Algorithms (CAs) for all aspects of medical care are appearing in research papers, guidelines, and protocols, in increasing numbers. Unfortunately many Algorithms published in the medical literature contain logic errors that may ultimately impact on patient safety and the quality of care provided. The objective of a CA is to present a sequence of medical processes and decisions with its associated logic in a clear, concise and simple way using a well-designed graphical format of a Flow Chart. It is a step-by-step set of instructions for carrying out a medical procedure or solving a medical problem e.g. a diagnosis.

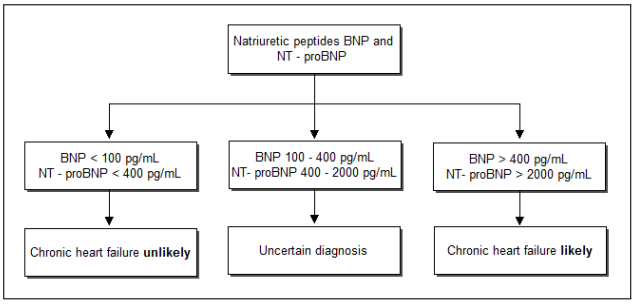

Figure 1: An Algorithm stratifying BNP and NT-proBNP levels in normal individuals, patients with an uncertain diagnosis and patients with CHF. (From [4] with permission).

A CA can also be described using prose and is one method of modelling a medical decision process, the others being disease-state maps that link decision points in patient management over time, scenarios that specify sequences of clinical activities that contribute towards a goal, and workflow specifications that model care processes in a health care organisation [1]. Sailors [2] has identified 5 types of CA that encompass the aforementioned paradigms starting with level 0 – a macro view of the decision process up to level 5 – a micro view of the individual decisions being made and processes executed including computer-based implementation. A CA Flow Chart can also be constructed from, and analysed, using a Decision Table [3].

2 The Flow Charting of Clinical Algorithms

2.1 Is a Clinical Algorithm the best way of solving the clinical problem?

An Algorithm may not be the best format for displaying and solving a clinical problem. Figure 1 shows a simple Algorithm illustrating how BNP and NT-proBNP levels vary in normal patients and those with chronic heart failure (CHF). Elevated blood levels of the natriuretic peptides, BNP (Brain Natriuretic Peptide) and NT-proBNP (the N-terminal prohormone of BNP), are found in the

blood of patients with CHF. Figure 2 shows a graphical representation of the Algorithm shown in Figure 1 that is much easier to understand and has a greater visual impact.

Figure 2 shows how this data is best displayed in a graphical format rather than an Algorithm.

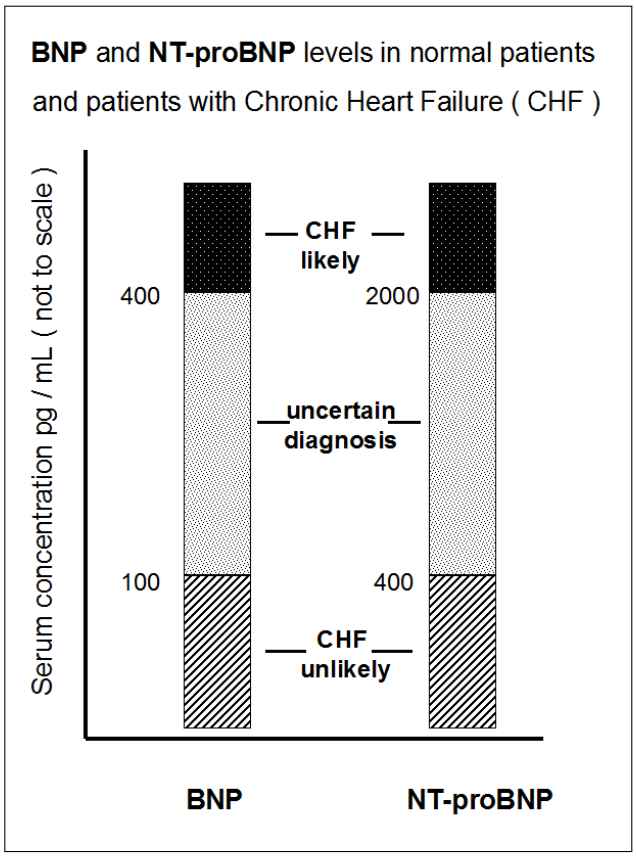

Figure 2: A graphic presentation of the data in Figure 1 which has a much greater visual impact than the Algorithm in the Figure.

2.2 The general structure of a Clinical Algorithm

All Algorithms can be described using Flow Charts, but not all Flow Charts are Algorithms. Figure 3 shows three Flow Charts, two of which are Algorithms. Figure 3(a) is a flow chart but not an Algorithm because it only consists of a linear sequence of processes and lacks any decision-based logic. Sadler remarked in 1983 [5] that a CA is no more than a type of Flow Chart, which is incorrect. He is unaware of the excellent work done on CAs for Dysphagia in 1970, and 'Fever of Unknown Origin' in 1977.

Figure 3(b) is a Flow Chart and non-iterative Algorithm – Process 2 is only executed if the answer to Decision 1 is "Yes" otherwise only Process 1 is executed. Figure 3(c) is a Flow Chart and iterative Algorithm – Process 2 is only executed if the answer to Decision 1 is "Yes" otherwise control moves back to Process 1 which is repeatedly executed until the answer to Decision 1 is "Yes" when Process 2 is executed.

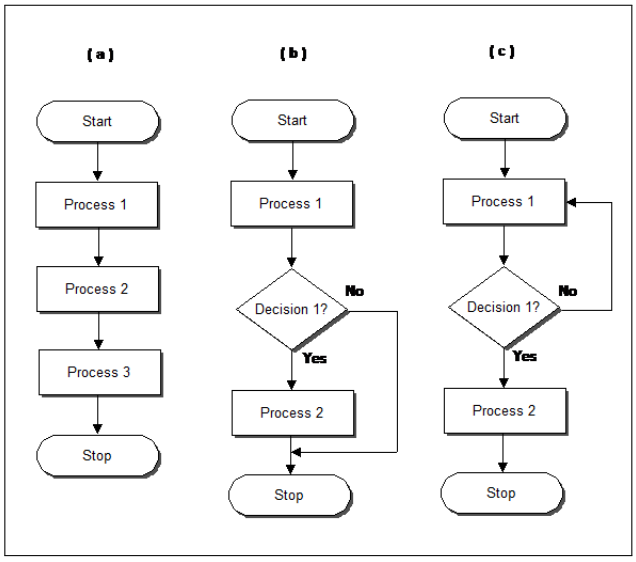

Figure 3: A Flow Chart (a) and two Algorithms (b) and (c) which are also Flow Charts.

2.3 Data Entity Types

A "Data Entity Type" is an abstract group descriptor whose group-members have similar properties. An example is a collection of items consisting of an apple, pear, orange, and banana. The apple, pear, orange, and banana are all of the same Data Entity Type called fruit. Similarly, Figure 4(a) contains Statement boxes on 'blood test results' and 'echocardiography' – both of Data Entity Type 'clinical investigation'. The Statement box 'Chronic Heart Failure' is a different Data Entity Type called 'Medical Diagnosis'. As these Data Entity Types on the same level in the Flow Chart do not match, Figure 4(b) shows how an additional Statement box can be added to match the latter Data Entity Type.

2.4 Data Flow

Data flow in a CA is vertical top-down. Many Algorithms display mutually exclusive options in a format that spreads out horizontally (Figure 6(a)). This may be related to them being able to fit on the double A4 page of a paper journal. The correct vertical-format Algorithm is shown in Figure 6(b).

The style of presentation shown in Figure 6(a) is therefore not recommended.

2.5 Symbols used in Clinical Algorithms

These are all illustrated in Figure 7.

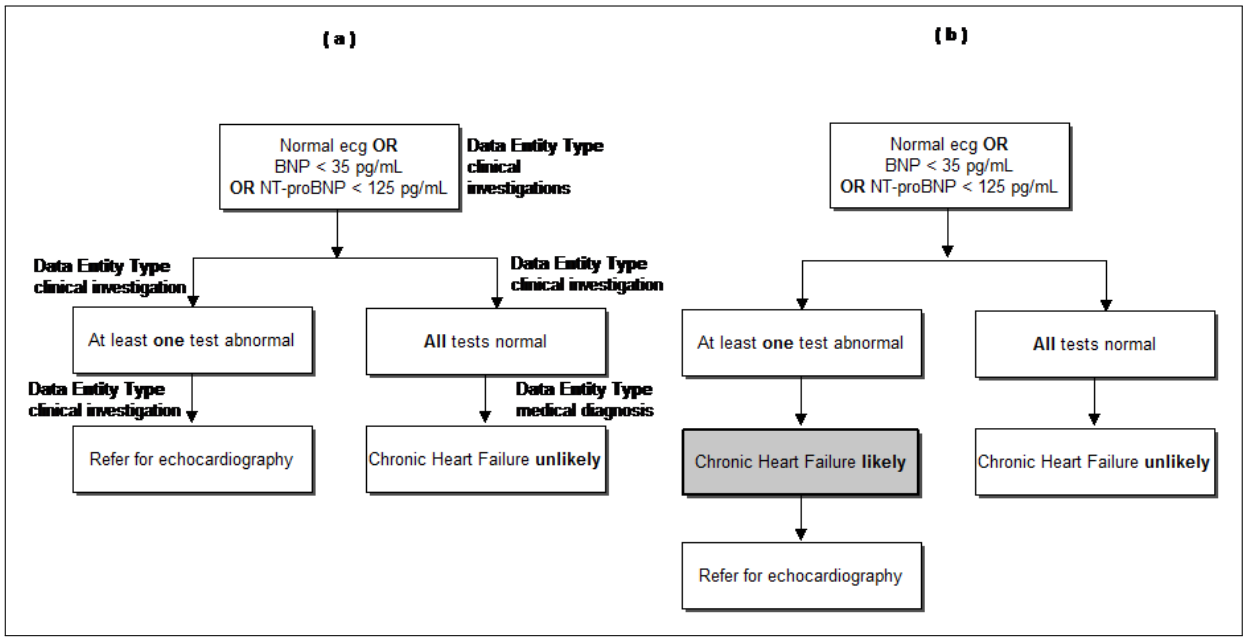

Figure 4: (a) A Clinical Algorithm illustrating Data Entity Type and how symbols on the same level in the CA should be of the same Data Entity Type. (From [6] with permission); (b) is corrected for Data Entity Type. Note the ambiguous logic in the top Decision box which is dis-ambiguated in Figure 5.

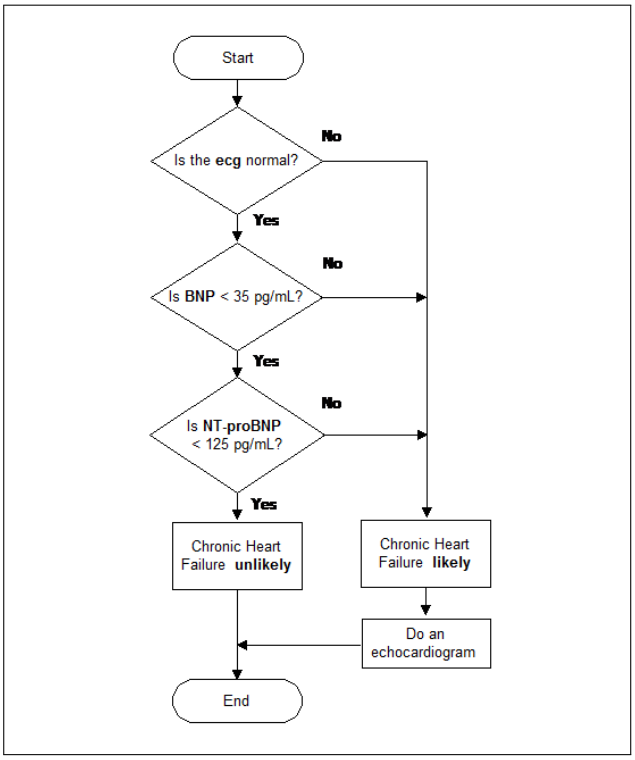

Figure 5: The re-designed Algorithm from Figure 4 with Statement boxes on the same level containing the same Data Entity Type, 'Chronic Heart Failure', and the dis-ambiguated logic from the top Decision box shown in multiple Decision boxes.

Start / Stop box

A Start box is lozenge-shaped and appears at the top of the Algorithm (Item 7a). It has no input and can only have one output. There can only be one Start box in an Algorithm. A vertical line terminated with a downward-pointing arrow arises from its lower horizontal edge.

A Stop or End box is lozenge-shaped and appears at the bottom of the Algorithm. A Stop box can have multiple inputs but never has an output and there may be more than one Stop box in an Algorithm. The word "End" is preferable to "Stop" as the latter may infer "stopping" treatment which is not the case. A vertical line terminated with a downward-pointing arrow usually enters its upper horizontal edge.

Process / Statement box

A Process / Statement box is a rectangular box containing an "action statement" indicating the execution of a process such as "Treat the patient with drug X" or a "statement" such as "The diagnosis is X". The text cannot contain a question and may contain a single Boolean operator such as AND or OR separating the two statements. The box has a vertical line terminated with a downward-pointing arrow entering its upper horizontal edge and a vertical line terminated with a downward-pointing arrow leaving its lower horizontal edge.

Decision box

A Decision box is a diamond-shaped or hexagonal box containing a single question ending with a question mark that allows the user to make a decision such as ("Is the blood pressure low?"). The text cannot be a statement and may not contain a Boolean operator such as AND or OR. The box has a vertical line terminated with a

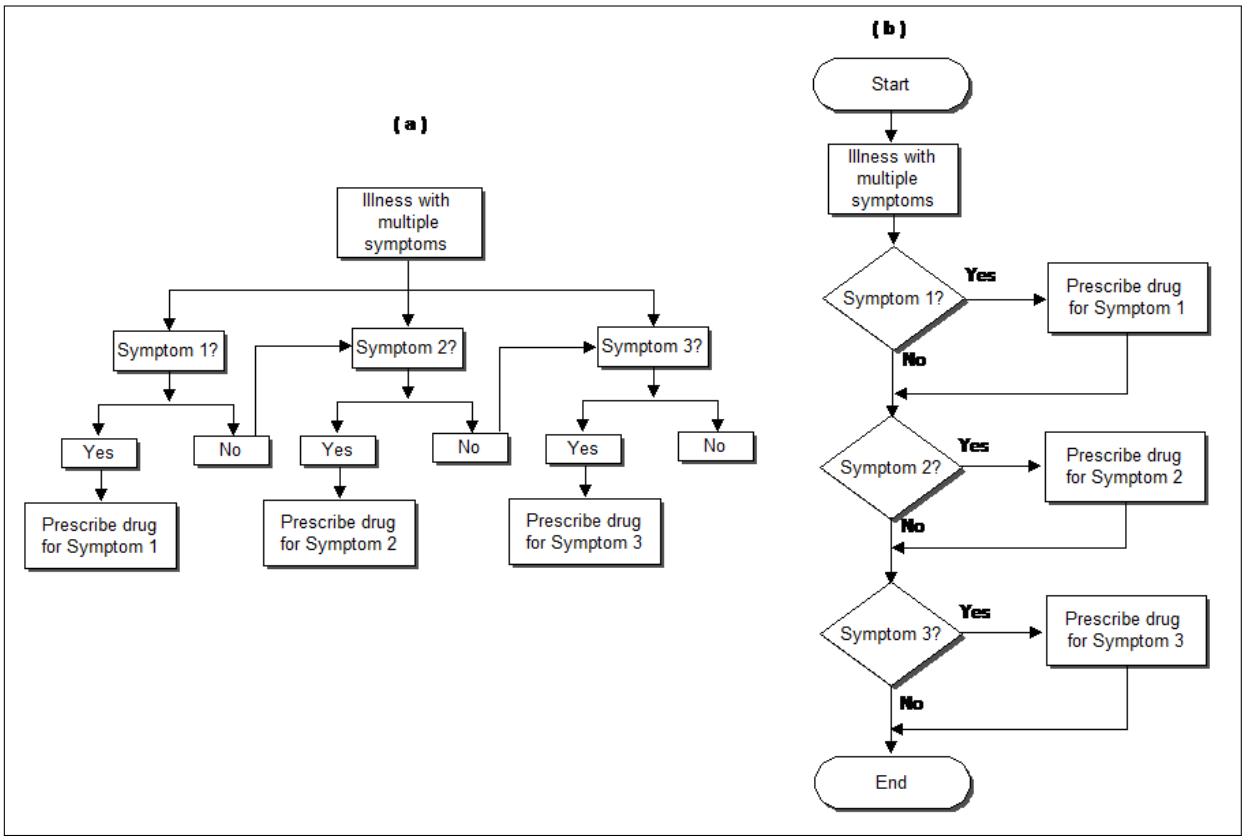

Figure 6: (a) An Algorithm that incorrectly illustrates selections which are not mutually exclusive so the data flows horizontally from left to right. Modified from the Algorithm in [7]. (b) The re-designed Algorithm showing how multiple selections should be presented in a top-down fashion.

downward-pointing arrow entering its upper vertex and a vertical line terminated with a downward-pointing arrow leaving its lower vertex. The horizontal lines of the hexagon are commonly longer than its sloping sides. Diamond-shaped and hexagonal Decision boxes should not be mixed in the same Algorithm. A hexagonal Decision box demands less text wrap and permits longer text strings inside the box than a similar size diamond-shaped box. A Decision box must have TWO exits.

Simple Decisions

Figure 8 shows examples of binary decisions.

Complex Decisions

Figure 9 shows how more complex decisions are made in a CA. A vertical line emanates from the lower edge / vertex of the Decision box and connects to a horizontal line of several rectangular boxes, the number required depending on the number of selections needed. Figure 9(a) shows how selections are made from a range of integers (continuous variables). Note the overlapping ranges, the value "50" being present in both selections. Figures 9(b) and 9(c) show how selections are made from discontinuous variables such as "Yes", "No", "Don't know", and "Positive", "Equivocal", and "Negative". Figure 9(d) contains a choice called "Otherwise" which is selected if the response does not fit "Choice 1" or "Choice 2". The selections should be of the same Data Entity Type.

Termination of the current Algorithm and transfer of control to another Algorithm

A Circular box indicates termination of the Algorithm at that point and transfer of control to another Algorithm.

Lines connecting symbols

Solid straight lines running horizontally and vertically should connect all the symbols in the Algorithm.

3 Common Pitfalls in the Design of Clinical Algorithms

These are illustrated in Figure 4(a) (Chronic Heart Failure), Figure 6(a) (Diagnosing Syncope), Figure 9(a) (Haematology) , Figure 10(a) (Management of Alcohol Withdrawal Syndromes), Figure 11(a) (Dyspepsia Management) and documented in Table 1.

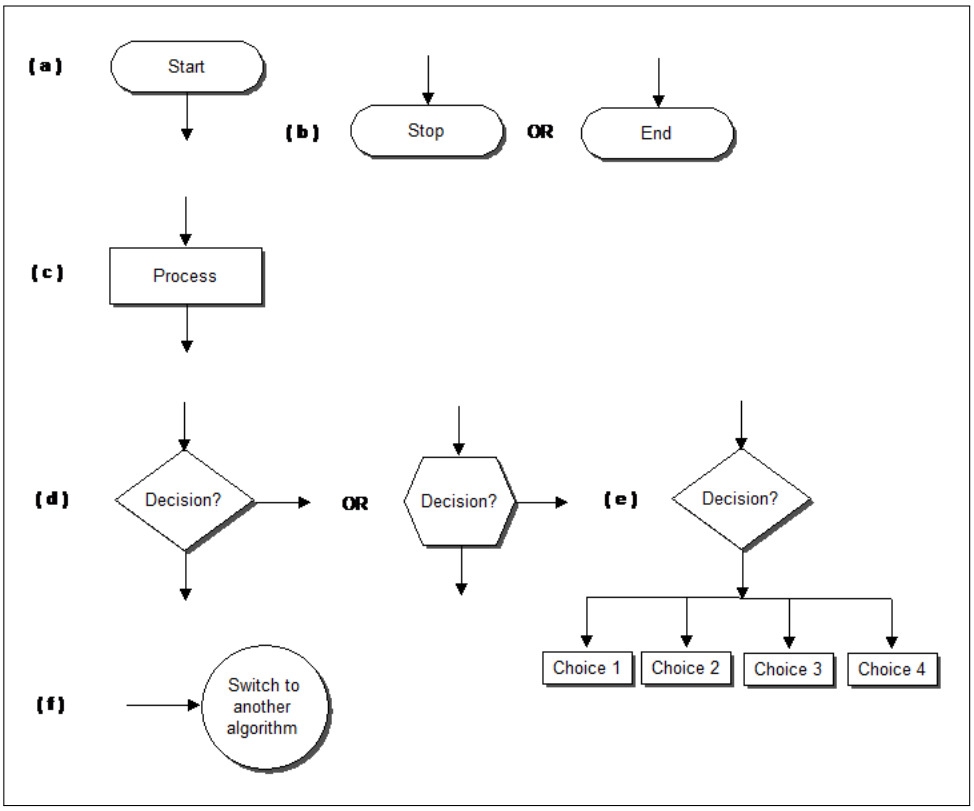

Figure 7: The individual components of a Clinical Algorithm (a) Start box, (b) Stop / End box, (c) Process / Statement box, (d) Diamond-shaped and hexagonal Decision boxes with two choices, (e) Decision box with more than two choices and (f) Circular box indicating termination of the Algorithm at that point and immediate transfer of control to another Algorithm.

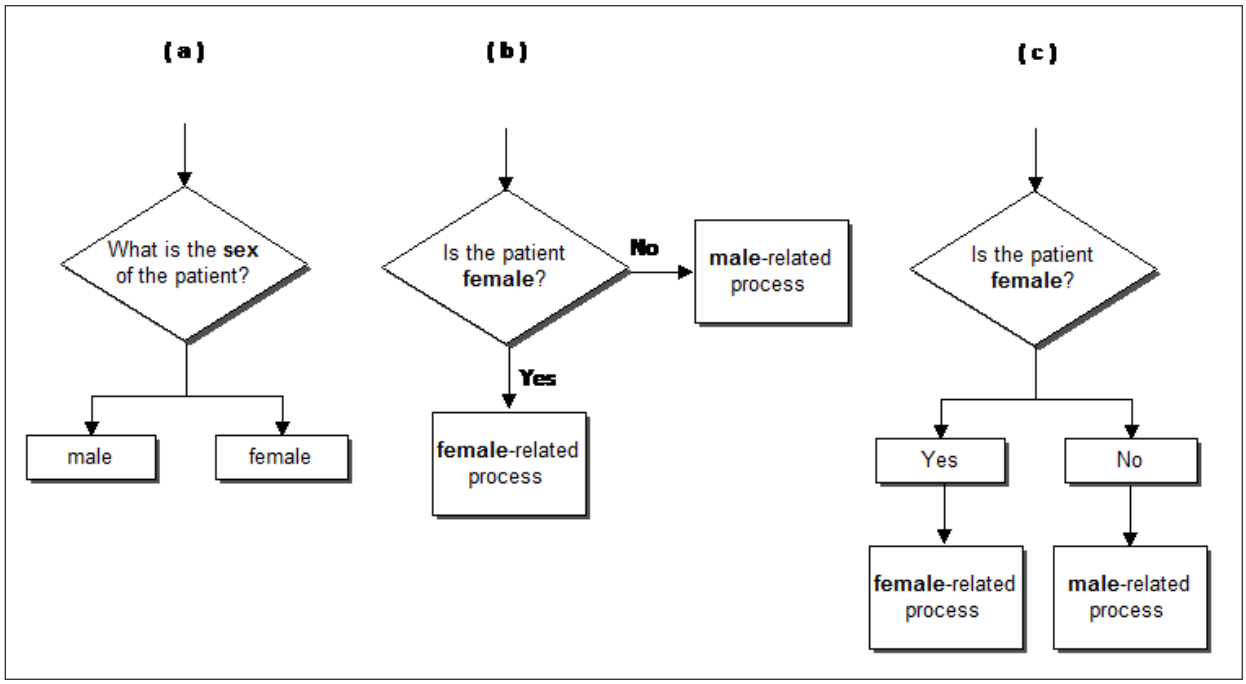

Figure 8: The design options available for making a binary "Yes", "No" decision in a CA. (a) A neutral selection of Data Entity Type "sex", (b) Display of the female option with the "No" choice corresponding to the male selection (c) Less commonly notation displaying the "Yes" and "No" options in separate Statement boxes is used.

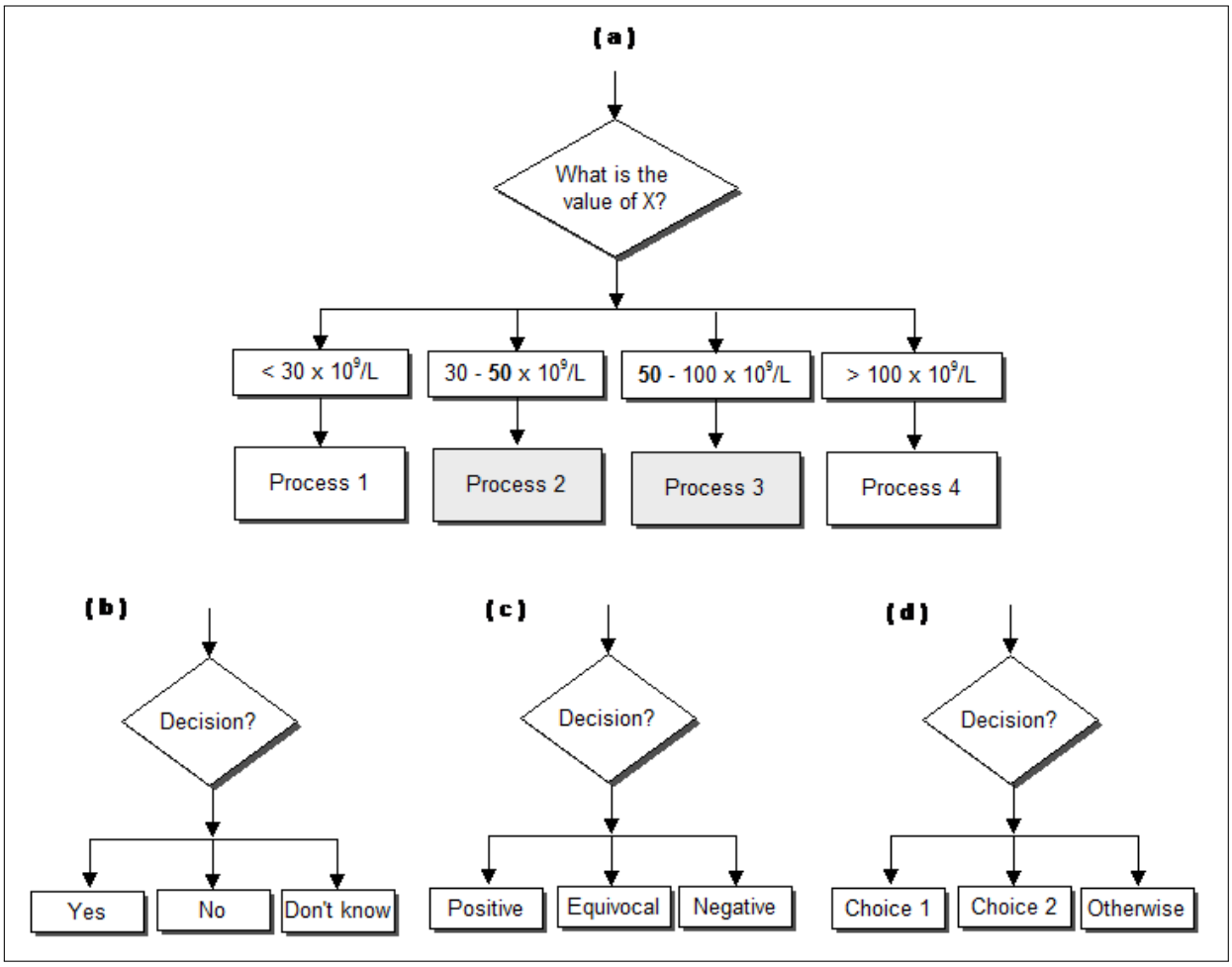

Figure 9: How complex decisions with more than two choices (other than "Yes" and "No") are made in CAs. (a) An error demonstrating overlap of the integer value "50" (b). Adapted from the Figure in [8]. (b) A "Don't know" selection added to "Yes", "No" Decision box (c) An "Equivocal" selection added to a "Positive", "Negative" Decision box. (d) An "Otherwise" selection added to a "Choice 1", "Choice 2" Decision box to trap choices other than "Choice 1" and "Choice 2.

4 Clinical Algorithms: their existence and value

4.1 Advantages of Clinical Algorithms

If the Algorithm is kept simple the graphical format can make the decision-making process easy to recall. Remember newspaper editor Arthur Brisbane's 1911 expression "Use a picture. It's worth a thousand words." CAs are helpful in the diagnosis of complex and uncommon clinical problems but one needs to think outside the Algorithm and be aware of its limitations. A CA presents the clinical problem in a logical and structured way. It can be used to analyse one's diagnostic processes and be used for summarising the management of a clinical situation. When used properly, a well-designed and tested Clinical Algorithm can be a useful tool in the assessment, diagnosis and management of a clinical problem. Clinical Algorithms can be a valuable tool in training juniors.

4.2 Clinical Algorithms promoting good health care

Sick neonates

Clinical Algorithms can be powerful tools in the identification of sick newborn babies at risk of neonatal mortality in the community [25].

Assessment of critically ill patients

The APACHE III (Acute Physiology And Chronic Health Evaluation) Score is used to assess the severity of illness in a patient admitted to the Intensive Care Unit within 24 hours. It is based on physiological and biochemical parameters such as pulse, mean blood pressure, temperature, and respiratory rate. The higher the score, the more seriously ill the patient is and the greater the risk of death. Margolis has commented that, although a CA is behind the score's calculation, it is not visible to the user [26].

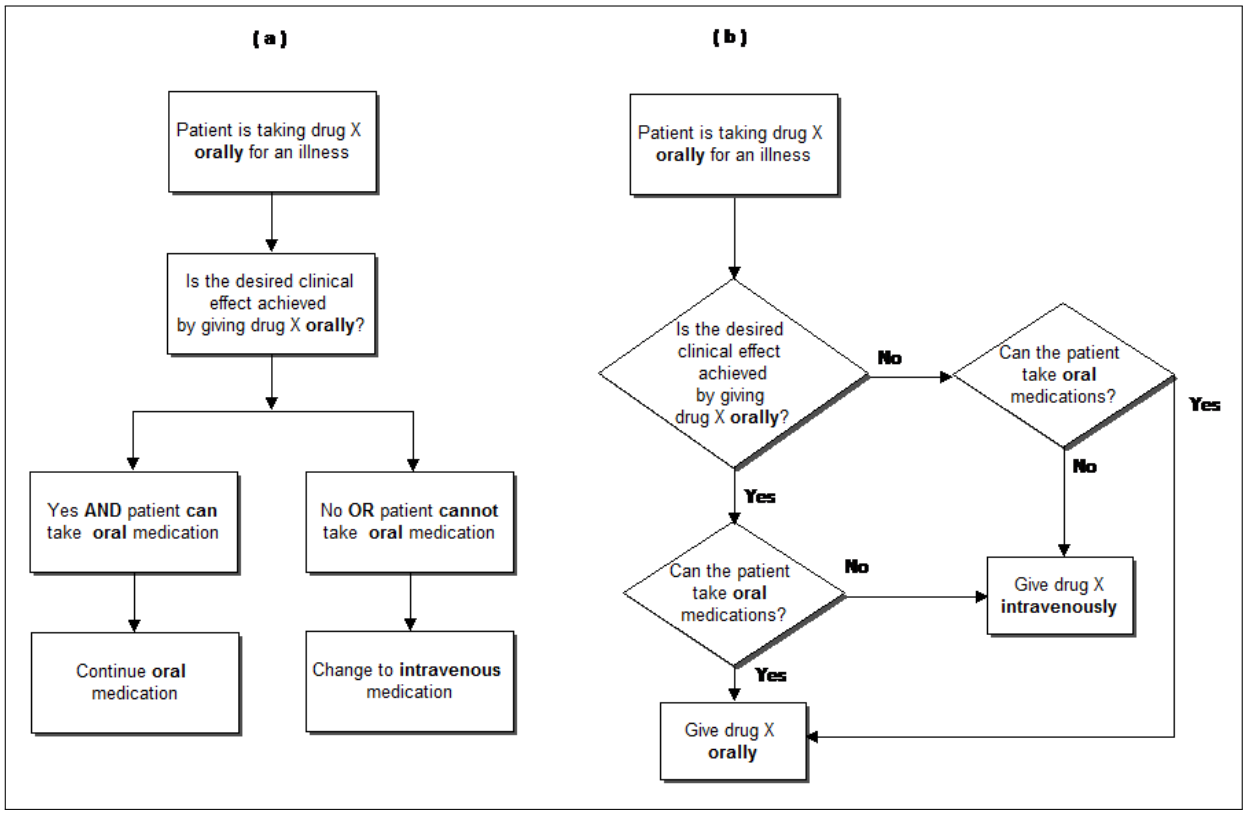

Figure 10: (a) An example of a Clinical Algorithm whose "Yes" and "No" output is combined with further logic making the decision ambiguous and more complex. (b) The correct Algorithm with disambiguation of the logic in (a). Adapted from the Figure in [9].

A web-based Apache III score calculator is available [27].

Cardiac Resuscitation

Cardiac Resuscitation Algorithms are probably the most frequently used CAs in hospital clinical practice and the UK Resuscitation Council has been refining and updating them for many years [28].

Medical Education

Undergraduates Regarding undergraduate medical education, CAs can teach paediatric decision making more effectively than prose [29] and have been useful in teaching junior doctors how to differentiate between the various types of acetabular fractures [11].

Medical Schools in the US and Hong Kong have used them in their undergraduate curricula for Cancer Education [30], and Gynaecology [31] respectively. Margolis et al., in Israel, have developed a compulsory pre-clinical course on Medical Decision Making involving the design and use of CAs [32].

Allied Health Professionals CAs have effectively contributed to the training of physicians' assistants [33, 34], A physician's assistant is an Allied Health Professional, who is trained to support a doctor in the diagnosis and treatment of patients.

Clinical Guideline Development

A Clinical Guideline is a document for guiding decisions on the Diagnosis and Management of specific clinical problems. The Post-Deployment Health Division of the US Military is one of the few health organisations that has specified standards for the design of CAs for use in its Clinical Guideline Development Programme for the diagnosis and management of post-deployment-related health conditions [35].

The CA standards used are those suggested by Margolis et al. [36]. Mozena et al. have produced an excellent book that uses a CA approach to the development of Clinical Guidelines using total knee replacement as a case example [37]. Hadorn et al. have used CAs with annotated links to the evidence-based medical literature for the diagnosis and management of female stress urinary incontinence [38] and the management of cardiac failure patients [39]. Pearson et al. [40] and Barak et al. [41] have developed a methodology for comparing competing Algorithmic Guidelines called the Clinical Algorithm Nosology.

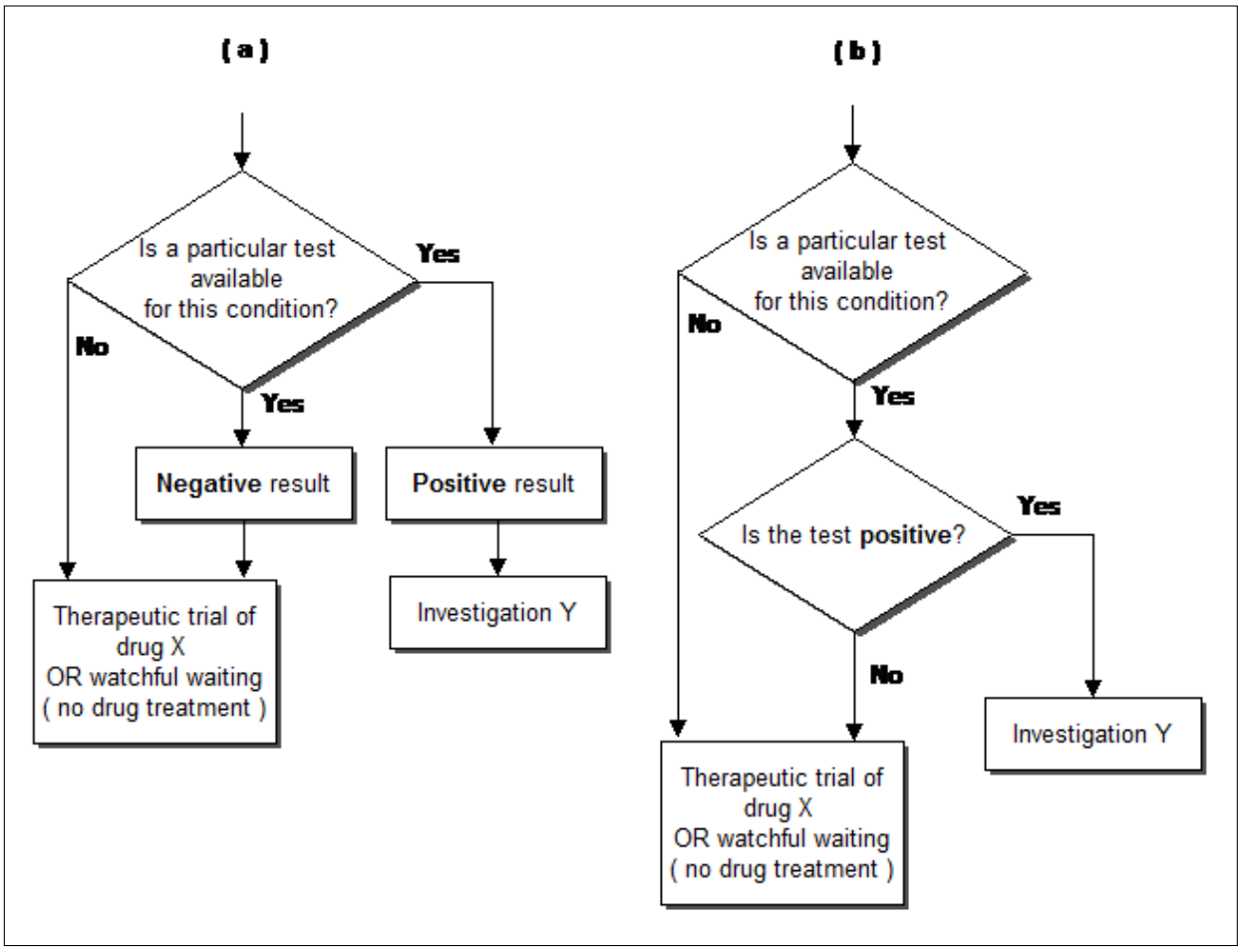

Figure 11: (a) An example of a CA with two "Yes" and one "No" options emanating from a Decision box indicating a missing stage in the logic. Adapted from the Figure in [10]. (b) shows the missing Decision box.

5 Implementation of Clinical Algorithms on Computer Systems

5.1 Historical

In 1996 Sitter et al. [42] developed a computer programme called ALGO, written in object-oriented Borland Pascal Version 7.0 for Windows, for designing and implementing CAs in Flow Chart format. The software could also measure the complexity of the Algorithm. A similar program called the Clinical Algorithm Processor (CAP) was produced by Abendroth et al. in 1989 [43, 44]. It could be used to create, edit and display CAs and was written in object-oriented Pascal for the Apple Macintosh computer.

5.2 Current

Clinical Algorithms can be readily implemented on Personal Computers using conventional programming languages such as Basic, C, Pascal, Python and Java. They can be developed for the World-Wide Web using Javascript, PHP, and MySQL. Apps can be created for the Android Smartphone using the Android Software Development Kit and the Apple Iphone, using the Objective C Development Environment.

Examples of good practice in the design of Clinical Algorithms are documented in Table 2.

6 Disadvantages of Clinical Algorithms

Common problems with the use of CAs are that they may oversimplify the clinical problem. They often represent the didactic view of a single or small consensus group of medical professionals and their structure and complexity varies greatly between authors. The more complex a CA is, the more accurate it will be but it will be more likely to compromise patient safety [58].

Medicine is still an art [59] and many clinicians are esoteric in their clinical practice so they may see the use of a CA in their medical decision-making as inflexible as they may not agree with some of the questions and cannot contribute their own relevant questions and data to the Algorithm. All of the clinical data required by the

Table 1: Examples of common errors made in Clinical Algorithms.

Description of Algorithm error	Clinical Topic	Reference
Algorithms that wander all over the page with no obvious Start or End point.	Classification of Acetabular fractures; Psychotherapy with Latino clients; Care pathway for Primary Biliary Cirrhosis.	[11] Figure 4 [12] Figure 1 [13] Figure 2
An Algorithm that spreads horizontally across the page instead of top-down.	Diagnosing Syncope in clinical practice (See also the example on Figure 6)	[7] Figure 1
Example of a Comment box accompanying an Algorithm containing data that should be included in the Algorithm.	American and British Guideline for Prevention of Falls in Older Persons	[14] Figure 1
An Algorithm where decisions are made before it formally starts.	Management of spontaneous Pneumothorax	[15] Figure 2
An Algorithm that re-starts after a Stop Box	Management of Dyspepsia	[10] Figure
A Decision box containing complex ambiguous logic.	Management of spontaneous Pneumothorax Evidence-based Algorithms for falls and Syncope.	[15] Figure 2 [16] Figure 2
A Decision box with only a "Yes" option without a "No" option.	Post-partum management of Hypertension; Diagnosis and Management of Retropharyngeal Abscess.	[17] Figure [18] Figure
A Decision box with two "Yes" options and one "No" option.	Management of Dyspepsia (See also the example on Figure 11)	[10] Figure
A Decision box with two "No" options and one "Yes" option.	Treatment and prognosis of Epidural Spinal Cord Compression; Emergency Department evaluation of sudden, severe headache.	[19] Figure 4 [20] Figure
A Decision box with a question as a response.	Pain control with Opioid drugs in a patient dying in hospital; The re-designed Opioid Algorithm	[21] Figure [22] Figure
A Decision box with "Yes" and "No" responses plus additional statements that complicate the decision	Management of moderate and severe Alcohol Withdrawal Syndromes (See also the example on Figure 10)	[9] Figure
Overlapping parametric data in a Decision box creating an ambiguous selection.	Management of Thrombocytopaenia (See also the example on Figure 9)	[8] Figure
Unusable Algorithms consisting of poorly organised collections of ambiguous logic.	Pain control with Opioid drugs in a patient dying in hospital; Diagnosis and Management of Retropharyngeal Abscess Clinical management of stable Ischaemic Heart Disease	[21] Figure [18] Figure [23] Figure 1
An Algorithm which contains a serious decision error that could result in patient harm.	Clinical management of women and young girls treated with anti-epileptic drugs	[24] Figure 2

Algorithm may not be available to the clinician so it will fail at the point where the input of such data is required. Computer-based Algorithms are slower to use than paper-base ones because of the tedious way the logic works [60]. The use of computer-based CAs in the consulting room may lead to patient complaints; the patient may feel they are competing with the computer for the personal attention of the doctor. Margolis, an Israeli Emeritus Professor of Medical Education who has made the largest contribution to research on the subject of Clinical Algorithms, has defended major objections to CAs, namely that they restrict a physician's thinking and turn him / her into a robot who does not think [61]. He defended this by stating that a CA can be written for any area of medical decision making that can be standardised leading to medical practice that could be taught more effectively, monitored more accurately, understood better, and utilise resources more efficiently.

Poor Algorithm design as illustrated by the examples in this Paper [Table 1] can pose a major safety risk to patients. Patients may be misdiagnosed, receive the wrong treatment, not be treated at all, or receive treatment they do not require. All these outcomes can be avoided if the simple logical rules of Algorithm design are followed. When the Barcelona Liver Group formulated its Hepatocellular Carcinoma Staging System in the form of a CA [62], they made no provision for a patient with three hepatic nodules less than 3 cm in diameter in their logic. Therefore a clinician who has a patient with this clinical status will have to resort to another cancer staging system that accommodates it such as the well-established TNM (Tumour, Nodes, Metastases) classification [63].

In an attempt to empower patients with managing their own health problems using CAs to reduce their level of health care consumption, it was noticed that patients using CAs actually increased their frequency of medical consultations [64].

There is no substitute for the clinical acumen and experience of a medical professional and Algorithms that are widely available on the internet can be inappropri-

Table 2: Examples of good practice in the design of Clinical Algorithms.

Description of Clinical Algorithm	Year	Reference
Diagnosis of dysphagia	1970	[45] Figure p. 381
Fever of unknown origin in family practice	1977	[46] Figures 1–4
Management of complete heart block in patients receiving pre-hospital care from paramedics	1983	[47] Figure p. 149
Diagnosis of headache	1984	[48] Figure p.1282–1283
Urinary Incontinence in the Elderly female: Prediction in diagnosis and outcome of management	1984	[49] Figure p. 231
Urological management of patients with spinal cord damage	1986	[50] Charts 1–8
Transvaginal repair of enterocele – (a protrusion of the small bowel and peritoneum into the vaginal canal)	1993	[51]
Management of facial nerve palsy and how it affects the eye	1998	[52]
Clinical Practice Guideline: Early Detection of Developmental dysplasias of the Hip	2000	[53] Figure 1
Management of falls and syncope presenting to acute medical services	2008	[16] Figures 1 and 2
Thyroid Disease Diagnostic Algorithms	2008	[54] Figures 1 and 3
Rome Foundation Clinical Algorithm Project For functional gastrointestinal disorders involving the oesophagus, stomach, duodenum, gall bladder, large bowel and rectum	2010	[55]
Breast Cancer Diagnostic Algorithms for Primary Care Providers	2011	[56] whole publication
When and how to treat patients who refuse treatment	2014	[57] Figure 1

ately used by patients with little medical knowledge and understanding seeking a self-diagnosis. What CAs will never be able to do is listen to the patient, explain things and offer reassurance, sensitivity and compassion [61].

7 Proposed International Standards for Clinical Algorithms

Flow Charts and Algorithms were originally developed in the domain of Mechanical Engineering and as medical professionals are not engineers the number of different symbols used in CAs should be kept to a minimum to avoid confusion and errors.

In 1992 Margolis et al. [36] suggested a standard for Clinical Algorithms on behalf of the Society for Medical Decision Making using a few different shaped symbols (predominantly the ones shown in Figure 7). In 1993 we proposed a similar standard for CAs based on the BSI (British Standards Institute) Standard no: 4058 [65]. Khalil et al. has suggested alignment of CA design with ISO (International Standards Organisation) Standard no: 5807 which uses three basic symbols for terminator, decision and process [66]. He has also introduced more symbols such as boxes for "Message to network", "Message from network" and "Program modification" that may only serve to confuse the user.

8 Software for drawing Clinical Algorithms

Flow Charts can be drawn using the two popular word processors, Microsoft Word – available in versions from Office 97 onwards [67] and the Open Source program, Apache OpenOffice Writer version 3.3 [68]. Diagram Designer is a an excellent easy-to-use, freeware program dedicated to Flow Chart drawing [69]. Charts can be saved in a proprietary file format or exported to the GIF / JPG image format for incorporation into documents and presentations.

9 Novel Ideas for Clinical Algorithms

A CA will fail if the user does not have all the data it requires so an Algorithm inventory could be useful particularly with more complex Algorithms to avoid this problem. A "Do not know" option could be an additional output of a "Yes/No" Decision box as shown in Figure 9 a although multiple selections of this option in a CA would seriously question the usefulness of its final output. A "Why?" option could be linked to Decision and Process boxes allowing the user to learn more about the decision or process if desired.

10 Conclusion

This Paper describes in detail the correct way to depict Clinical Algorithms as Flow Charts. It should now be obvious that the most safe and efficient way of producing a Clinical Algorithm is by way of a detailed and accurate Flow Chart. In the later part of this Paper examples of existing, published Clinical Algorithms are given, together with constructive criticism. Table 3 summarises the main learning points from this article and the Paper concludes that there are positive advantages in accurate and comprehensive Clinical Algorithms.

Table 3: The main learning points from this paper.

Key Learning Points from this Paper
An Algorithm has only one clearly defined Start point and one or more clearly defined End / Stop points.
Processes and Statements are displayed in rectangular boxes.
Decisions are displayed in diamond-shaped or hexagonal boxes (The two different types should not be mixed in the same Algorithm.)
Data flow in the Algorithm is vertical top -> down.
Consider the different Data Entity Types in the Algorithm.
Solid lines terminated with arrows indicate the direction of data flow in the Algorithm and should interconnect all symbols in it.
Decision logic should be kept simple by using one question per Decision box Avoiding using the Boolean operators AND and OR in the question.
BUT is not a Boolean operator and should be replaced by AND.
EITHER is not a Boolean operator and should be omitted.
The use of a combination of AND / OR in a Decision box is contradictory and is not correct Boolean logic.
With temporal Algorithms (i.e. now and in 1 month), consider using more than one Algorithm to clarify the logic.
Do not alter the symbols in Algorithms when copying them from published sources.
Consider putting data normally placed in footnotes below the Algorithm actually in it.
If a Clinical Algorithm can be coded using a standard prescriptive programming language such as C, Pascal, Java, or Python, the logic does not need modification.

Acknowledgements

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References

[1] Tu, SW Johnson PD, Musen MA. A Typology for Modeling Processes in Clinical Guidelines and Protocols Proc AMIA Symp. 2002 : 1181. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2244214/pdf/procamiasymp00001-1222.pdf (accessed November 2014).

[2] Sailors RM. A Proposed Classification Scheme for Multi-step Clinical Care Algorithms Proc AMIA Symp. 2001 : 1015. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2243581/pdf/procamiasymp00002-1054.pdf (accessed November 2014).

[3] Feinstein AR. An analysis of diagnostic reasoning. 3. The construction of clinical algorithms. Yale J Biol Med. 1974 Mar;47(1):5-32.

[4] Dickstein K, Cohen-Solal A, Filippatos G et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2000.: Eur J Heart Fail. 2008 Oct;10(10):933-89. doi: 10.1016/j.ejheart.2008.08.005.

[5] Sadler C. Pitfalls in the use of clinical algorithms. Orthop Clin North Am. 1986 Oct;17(4):545-7.

[6] Oudejans I, Mosterd A, Zuithoff N et al. Applicability of current diagnostic algorithms in geriatric patients suspected of new, slow onset heart failure. Age Ageing. 2012 May;41(3):309-16. doi: 10.1093/ageing/afr181.

[7] Ammirati F, Colivicchi F, Santini M. Diagnosing syncope in clinical practice. Implementation of a simplified diagnostic algorithm in a multicentre prospective trial - the OESIL 2 study (Osservatorio Epidemiologico della Sincope nel Lazio) Eur Heart J. 2000 Jun;21(11):935-40

[8] Thachil J, Fitzmaurice D. Thrombocytopenia in an adult. BMJ. 2013 Jun 10;346:f3407. doi: 10.1136/bmj.f3407.

[9] Hoffman RS, Weinhouse GL Management of moderate and severe alcohol withdrawal syndromes www.uptodate.com Sep 2013 (accessed November 2014).

[10] AgrĂ©us L, Talley N. Challenges in managing dyspepsia in general practice. BMJ. 1997 Nov 15;315(7118):1284-8.

[11] Ly TV, Stover MD, Sims SH et al. The use of an algorithm for classifying acetabular fractures: a role for resident education? Clin Orthop Relat Res. 2011 Aug;469(8):2371-6.

[12] Manoleas P, Garcia B. Clinical algorithms as a tool for psychotherapy with Latino clients. Am J Orthopsychiatry. 2003 Apr;73(2):154-66.

[13] Jones DE, Sutcliffe K, Pairman J et al. An integrated care pathway improves quality of life in Primary Biliary Cirrhosis. QJM. 2008 Jul;101(7):535-43. doi: 10.1093/qjmed/hcn043.

[14] Panel on Prevention of Falls in Older Persons, American Geriatrics Society and British Geriatrics Society. Summary of the Updated American Geriatrics Society/British Geriatrics Society clinical practice guideline for prevention of falls in older persons. J Am Geriatr Soc. 2011 Jan;59(1):148-57. doi: 10.1111/j.1532-5415.2010.03234.x.

[15] MacDuff A, Arnold A, Harvey J. BTS Pleural Disease Guideline Group. Management of spontaneous pneumothorax: British Thoracic Society Pleural Disease Guideline 2010. Thorax. 2010 Aug;65 Suppl 2:ii18-31. doi: 10.1136/thx.2010.136986.

[16] Parry SW, Frearson R, Steen N et al. Evidence-based algorithms and the management of falls and syncope presenting to acute medical services. Clin Med. 2008 Apr;8(2):157-62.

[17] Bramham K, Nelson-Piercy C, Brown MJ et al. Postpartum management of hypertension. BMJ. 2013 Feb 25;346:f894. doi: 10.1136/bmj.f894.

[18] BMJ Best Practice – Diagnosis and Management of Pharyngeal abscess http://bestpractice.bmj.com/best-practice/monograph/599/diagnosis/step-by-step.html (accessed November 2014).

[19] Schiff D,Brown P, Shaffrey ME et al. Treatment and prognosis of neoplastic epidural spinal cord compression, including cauda equina syndrome www.uptodate.com Mar 2014 (accessed November 2014)

[20] Breen DP, Duncan CW, Pope AE et al. Emergency department evaluation of sudden, severe headache. QJM. 2008 Jun;101(6):435-43. doi: 10.1093/qjmed/hcn036.

[21] Sleeman KE, Collis E. Caring for a dying patient in hospital. BMJ. 2013 Apr 17;346:f2174. doi: 10.1136/bmj.f2174.

[22] Colman A, Athey R, Richards B Flawed logic, duplicate and missing data make the opioid algorithm in Figure 2 unusable. British Medical Journal [eLetter] 02 July 2014. http://www.bmj.com/content/346/bmj.f2174/rr/759689 (accessed November 2014)

[23] Wilson J.F. Stable Ischemic Heart Disease Ann Intern Med. 2014;160(1). doi:10.7326/0003-4819-160-1-201401070 01001

[24] Epilepsy Expert Group. Clinical management algorithm for women and girls with epilepsy treated with antiepileptic drugs. Progress in Neurology and Psychiatry 2013; 17 (suppl. 1).

[25] Kamath-Rayne BD, MacGuire ER, McClure EM et al. Clinical algorithms for the identification of sick newborns in community-based settings. Acta Paediatr. 2012 Apr;101(4):344-51. doi: 10.1111/j.1651-2227.2011.02540.x.

[26] Margolis CZ Clinical algorithms in sepsis trials. Theor Surg 1994, 9: 43 – 44.

[27] Quesgen Inc. APACHE III web-based calculator http://www.quesgen.com/ApacheIII.php (accessed November 2014).

[28] UK Rescuscitation Council http://www.resus.org.uk/pages/als.pdf (accessed November 2014).

[29] Margolis CZ, Cook CD, Barak N et al. Clinical algorithms teach pediatric decisionmaking more effectively than prose. Med Care. 1989 Jun; 27(6):576-92.

[30] Ambrose RF, Brown S Jr, Wirtschafter DD et al. Construction of clinical algorithms for educational programs. J Cancer Educ. 1989; 4(3):161-6.

[31] Neale EJ, Chang AM. Clinical algorithms. Med Teach. 1991;13(4):317-22.

[32] Margolis CZ, Barnoon S, Barak N. A required course in decision-making for preclinical medical students. J Med Educ. 1982 Mar;57(3):184-90.

[33] Charles G, Stimson DH, Maurier MD et al. Physician's assistants and clinical algorithms in health care delivery. A case study. Ann Intern Med. 1974 Dec;81(6):733-9.

[34] Sox HC Jr, Sox HC, Tompkins RK The Training of Physician's Assistants – The Use of a Clinical Algorithm System for Patient Care, Audit of Performance and Education N Engl J Med 1973, 288: 818-824.

[35] PD Health – US Military Post-Deployment Health Gateway http://www.pdhealth.mil/guidelines/introduction.asp (accessed November 2014)

[36] Margolis C Z, Sokol N, Susskind O et al. Proposal for clinical algorithm standards. Society for Medical Decision Making Committee on Standardization of Clinical Algorithms. Med Decis Making. 1992 Apr-Jun;12(2):149-54.

[37] Mozena JP, Emerick CE, Black SC. Clinical Guideline Development – An Algorithmic Approach. Aspen Publishers, Inc., Gaithersburg, Maryland, 1996.

[38] Hadorn DC, McCormick K, Diokno A. An annotated algorithm approach to clinical guideline development. JAMA. 1992 Jun 24;267(24):3311- 4.

[39] Hadorn, DC. Use of algorithms in clinical guideline development in Clinical Practice Guideline Development: Methodology Perspectives. AHCPR Pub. No. 95-0009, pp 93 – 104, 2Rockville, MD, Jan. 1995.

[40] Pearson SD, Margolis CZ, Davis S et al. The clinical algorithm nosology: a method for comparing algorithmic guidelines. Med Decis Making. 1992 Apr-Jun;12(2):123-31.

[41] Barak N, Margolis CZ, Gottlieb LK. Text-to-algorithm conversion to facilitate comparison of competing clinical guidelines. Med Decis Making. 1998 Jul-Sep;18(3):304-10.

[42] Sitter H, Prunte H, Lorenz W. A New Version of the Programme ALGO for Clinical Algorithms.. Studies in Health Technology and Informatics. Vol 34: Medical Informatics Europe '96, pub. IOS Press

[43] Abendroth TW, Greenes RA. A Clinical Algorithm Processor: Enabling Flow Charts to Organize a Variety of Physician Tasks. Proc Annu Symp Comput Appl Med Care. Nov 8, 1989 : 983–984. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2245689/ (accessed November 2014).

[44] Abendroth TW, Greenes RA, Joyce EA. Investigations in the Use of Clinical Algorithms to Organize Medical Knowledge. Proc Annu Symp Comput Appl Med Care. Nov 9, 1988 : 90–95. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2245198/ (accessed November 2014).

[45] Edwards DA. Flow charts, diagnostic keys, and algorithms in the diagnosis of dysphagia. Scott Med J. 1970 Oct;15(10):378-85.

[46] Vickery DM, Quinnell RK. Fever of unknown origin. An algorithmic approach. JAMA. 1977 Nov 14;238(20):2183-8.

[47] Cayten CG, Oler J, Staroscik R et al. Clinical algorithms for prehospital cardiac care. Med Care. 1983 Feb;21(2):147-56.

[48] Jamieson M. Headache. Br Med J (Clin Res Ed). 1984 Apr 28;288(6426):1281-3.

[49] Eastwood HD, Warrell R. Urinary incontinence in the elderly female: prediction in diagnosis and outcome of management. Age Ageing. 1984 Jul;13(4):230-4.

[50] Gardner BP, Parsons KF, Machin DG et al. The urological management of spinal cord damaged patients: a clinical algorithm. Paraplegia. 1986 Jun;24(3):138-47.

[51] Raz S, Nitti VW, Bregg KJ Transvaginal repair of enterocele. J Urol. 1993, Apr;149(4):724-30.

[52] Sadiq SA, Downes RN. A clinical algorithm for the management of facial nerve palsy from an oculoplastic perspective. Eye (Lond). 1998;12 (Pt 2):219-23.

[53] Committee on Quality Improvement, Subcommittee on Developmental Dysplasia of the Hip. Clinical Practice Guideline: Early Detection of Developmental Dysplasia of the Hip. Pediatrics 2000; 105; 896. http://pediatrics.aappublications.org/content/105/4/896.full.html (accessed November 2014).

[54] Murgić J, Salopek D, Prpić M et al. Clinical guidelines development and usage: a critical insight and literature review: thyroid disease diagnostic algorithms. Coll Antropol. 2008 Dec;32(4):1283-90.

[55] Rome Foundation Clinical Algorithms Project http://www.romecriteria.org/education/clin_algor_project.cfm (accessed November 2014).

[56] California Department of Public Health, Cancer Detection Section, Breast Expert Workgroup, Fourth Edition, June 2011 Breast Cancer Screening Algorithms for Primary Care Providers https://qap.sdsu.edu/screening/breastcancer/bda/pdf/BDA_4thEdition_bw.pdf (accessed November 2014).

[57] Humphreys RA, Lepper R, Nicholson TRJ When and how to treat patients who refuse treatment. BMJ 2014; 348 doi: http://dx.doi.org/10.1136/bmj.g2043 (accessed November 2014).

[58] Mukabatsinda C, Nguyen J, Bisig et al. Is increasing complexity of algorithms the price for higher accuracy? Virtual comparison of three algorithms for tertiary level management of chronic cough in people living with HIV in a low-income country. BMC Med Inform Decis Mak. 2012 Jan 19;12:2. doi: 10.1186/1472-6947-12-2.

[59] Komaroff AL. Algorithms and the "art' of medicine. Am J Public Health. 1982 Jan;72(1):10-2.

[60] Margolis CZ, Warshawsky SS, Goldman L et al. Computerized algorithms and pediatricians' management of common problems in a community clinic. Acad Med. 1992 Apr;67(4):282-4.

[61] Margolis CZ. Uses of clinical algorithms. JAMA. 1983 Feb 4;249(5):627-32.

[62] Llovet JM, Fuster J, Bruix J; Barcelona-ClĂnic Liver Cancer Group. The Barcelona approach: diagnosis, staging, and treatment of hepatocellular carcinoma. Liver Transpl. 2004 Feb;10(2 Suppl 1):S115-20.

[63] Jain, D. Liver and intrahepatic bile ducts – tumor - TNM staging of hepatocellular carcinoma. PathologyOutlines.com, Inc. http://www.pathologyoutlines.com/topic /livertumorstaging.html (accessed November 2014).

[64] Berg AO, LoGerfo JP. Potential effect of self-care algorithms on the number of physician visits. N Engl J Med. 1979 Mar 8;300(10):535-7.

[65] Colman A, Richards B. Management of pneumothorax. Clinical algorithms should be standardized. BMJ. 1993 Aug 14;307(6901):443. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1678411/ (accessed November 2014)

[66] Khalil PN, Kleespies A, Angele MK et al. The formal requirements of algorithms and their implications in clinical medicine and quality management. Langenbecks Arch Surg. 2011 Jan;396(1):31-40.

[67] How to draw a flow chart in OpenOffice Writer. https://wiki.openoffice.org/wiki/Documentation/OOoAuthors_User_Manual/Draw_Guide/Drawing_a_flow_diagram (accessed November 2014).

[68] How to draw a flow chart in Microsoft Word 2007, 2010 and 2013. http://www.breezetree.com/articles/how-to-flowchart-in-word.htm (accessed November 2014).

[69] Vinther M. Diagram Designer 1.27.1 http://logicnet.dk/DiagramDesigner/ (accessed November 2014).

International Aspects of Education and Training in Telemedicine

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Abstract

Health care is based on patient data. The doctor or nurse / medical assistant are able by education, training, knowledge and experience to interpret patient data needed for diagnosis and treatment. Health care is dependent on a good education with respect to the management of data, information and knowledge. International activities point to ways to achieve a good level of education. These include criteria for curriculum development and accreditation, quality of information systems, further experience with a comprehensive training concept in England and the 10X10 approach in the United States.

Keywords

Education, training, health informatics, medical informatics, EFMI working group, EuroRec quality criteria, IMIA recommendations, IMIA accreditation

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1 Introduction

In health care many disciplines work together. Telemedicine is an ever-evolving way of local, regional, national and international cooperation. All work on the same basis: information about the patient. A good practice of information management can for example demonstrate high-quality health care. The European Federation for Medical Informatics (EFMI) has set up working groups (WGs) for this purpose, e.g. WG EHR for electronic health records (EHRs), but also the interdisciplinary NURSIE for Nursing Informatics and HIME (Health Information Management in Europe) for the management of health information.

Education and training take place on a national level. Reasons for this lie in the language and the subsequent application of knowledge stated in that language. Even in science education it is difficult to find a curriculum in the English language in countries such as Germany. However, renowned publications are mostly written in the English language and therefore knowledge of that language is essential. Even though German is an official language in Europe, English is essential for most international projects and international cooperation, particularly in telemedicine.

For the economy, a good education and training of the staff, especially management, is important. The need to develop programs by institutions that offer good quality professional education is crucial for small and medium enterprises including schools, colleges and universities. This requirement could present an important development area for telemedicine complemented by local activities.

2 International Initiatives and Opportunities

The European Union (EU) was quick to promote the mobility of students, lecturers and the cooperation of universities. The ERASMUS program was launched in 1987

and all 28 EU countries and five other European countries are involved in it today. In Athens, a concept for an ERASMUS funded program was launched together with a number of colleagues from European universities and research institutions under the direction of John Mantas with courses taught only by academic staff. It generated connections that are still in use today. Here are a few projects in which course material was developed and used in the field; the EU projects Nightingale and Telenurse include health care informatics supported by international participation and the EU project, IT Eductra, produced examples of training materials.

The ERASMUS program and other programs such as the Lifelong Learning GRUNDVIGT have been available since 2014 under the name ERASMUS+. In particular adult and vocational education is of paramount importance [1].

The European Centre for Medical Informatics, Statistics and Epidemiology (EuroMISE Centre) [2] was founded on 12 April 1994 as a joint facility of the Charles University in Prague and the Academy of Sciences of the Czech Republic. This was only possible through the support of the European project with the acronym EuroMISE with the coordinator GSF-Research Centre and the engagement of other universities and research organisations from Germany, The Netherlands, France, United Kingdom, Belgium, Greece, Ireland and the Czech Republic. The concept was "Teach the Teachers" with participants from Central and Eastern Europe. 14-day courses were conducted especially for colleagues of non-EU countries. The EuroMISE centre has been successfully managed for 20 years by Jana Zvarova as a common working platform for research, development, teaching and project work. One result of this work is also EJBI (European Journal for Biomedical Informatics) [3]. Many volumes or single contributions can be downloaded free of charge from this open access journal.

The European Institute for Electronic Health Records EuroRec [4], founded as an institute in 2003, has set itself the goal of supporting high quality design, implementation and adaptation of existing medical information systems (EHR systems). In several EU projects, both the structures of the EuroRec Institute as well as quality criteria for EHR systems were developed.

EuroRec was registered in France and now has its "office" in Ghent, near Brussels, which is ideal with close proximity to the European institutions. In EuroRec projects and other activities almost all 16 national ProRec centres are involved. The national centres usually undertake their own activities and/or participate in national or regional activities.

A focus in recent years has been the QREC project with 26 partners, which developed quality criteria for EHR systems for use in the development, evaluation, and certification of systems. There are more than 1,000 criteria, which are a narrative description of properties of the system and come from many sources, such as from the American and Canadian certification, manuals of European systems and other publications. The source is indicated for all criteria, which are grouped and indexed according to usage and they are also suitable for training [5].

What facilities are interested in international cooperation? Maybe you can stimulate interest in the possibilities of promotion of telemedicine and create structures that are successful in attracting funding through publications and conferences like Telemed-Berlin. Of course, the issues are important and perhaps the comparison of national policies for education and training with the aim of harmonising or even acquiring the policies is a topic that is worthy of support.

3 Organisations, Associations, Institutions, and Federations

Many organisations have training and education goals in their statutes, which they frequently achieve by means of conferences, workshops, tutorials, seminars and courses. Additionally individuals, groups of members are often responsible for the organisation of training and education events and there are many examples of this. The TELEMED-Berlin conference was founded as a working and training event 25 years ago. It also includes individual and joint national activities of BVMI (Berufsverband Medizinischer Informatiker, professional association for medical informaticians), DVMD (Deutscher Verband Medizinischer Dokumentare, German Health Information Management Association) and GMDS (Deutsche Gesellschaft fĂĽr Medizinische Informatik, Biometrie und Epidemiologie) e.g. the Congress and Academy of the conhIT fair organised annually in Berlin by the health IT industry. The following few international examples should provide guidance as to the potential opportunities for education and training in telemedicine.

IFHIMA (International Federation of Health Information Management Associations) [6] represents the interests of national member associations globally. This includes joint working with international organisations; IFHIMA is a non-profit organisation in official relations with the World Health Organization (WHO) as a recognised non-governmental organisation (NGO) and works collaboratively with WHO and other international organisations such as IMIA (International Medical Informatics Association). IFHIMA provides education modules in basic health records practice which are available to download free of charge from the IFHIMA website by practitioners working in the field of medical/health records and HIM (Health Information Management). The single modules (Table 1) have been regularly reviewed and revised. The modules provide freely available learning materials for practitioners studying for the "Institute of Health Records and Information Management (IHRIM) Overseas Certificate".

As part of the wider programme of work to professionalise and develop specialists in informatics, NHS informatics workforce development colleagues in Eng-

Table 1: Training modules IFHIMA (http://ifhima.org/learning.centre/).

Health Records Management	The Health Record Patient Identification, Registration & the Master Patient Index Record Identification Systems, Filing and Retention of Health Records Hospital Health Record Computer Applications
Healthcare Statistics	Disease & Procedure Classification and Indexing ICD 9 and ICD 10 Coding exercises and study notes
Planning & Managing a Health Records Department	Administration and Management of the Health Record Department Planning a Health Record Department

land and Wales have worked together to develop a Career Framework for the Health Informatics profession i.e. the Health Informatics Career Framework (HICF) https://www.hicf.org.uk/ The framework covers the full range of health informatics practitioners from apprentices up to directors in the seven disciplines of Health Informatics:

- Knowledge Management
- Information Management
- Information and Communication Technology
- Health Records and Patient Administration
- Clinical Informatics
- Health Informatics Education and Training
- Project and Programme Management

The aim of the HICF is to describe the profession in the same way that clinical and other professions in health and care are described and to establish career pathways and development opportunities. The HICF was first launched in 2008 and subsequently updated in 2009 and 2011. The HICF is not only designed to help individuals plan their own careers, but also to help managers with team and individual staff development; and to support workforce planning. The HICF has been developed for use across the UK and its content is also equally applicable to individuals providing services to the NHS and other health and care organizations as well as those actually employed in those organizations. Individual practitioners can progress through the levels of the framework, or across and among the disciplines, by developing their skills and competence through learning and development. The content of the HICF helps to identify common and transferable skills to help individual practitioners to plan and progress in their careers and it also helps managers to develop their workforce. It supports the selection of specific training measures and provides an annual overview of personal development with a plan for further training and development options.

IFHIMA and AHIMA (American Health Information Management Association) have launched the GWHC (Global Healthcare Workforce Council) initiative with the support of the US Department of Commerce. The aim is "to establish a global health information management curriculum and competency standards that provide a framework for healthcare and education systems worldwide to enable them to build a workforce strategy".

AHIMA is the largest national member association of IFHIMA and offers the 71,000+ members comprehensive education and training services. These include online courses, webinars, virtual laboratories, books and a "Career & Student Centre". In discussion fora diverse topics are talked over that are highly relevant to HIM practice and usually affect US-American educational issues.

AMIA (American Medical Informatics Association) is a professional society and member of IMIA with a complex structure. It has set itself the objective of transforming healthcare through science, education and practice in health informatics and biomedical informatics. In an analysis of a strategy [7], it was found that, in respect of training and education for health information management:

- the profession continues to grow and will become more important, especially in the non-academic field;
- new and new types of education and training will be required;
- there will be a large demand for informatics training for other professions.

In this context, the continuation of the 10X10 program, which has set a goal to train 10,000 people within 10 years in applied medical informatics, will be crucial. The former AMIA President, Don Detmer, put it this way [8]:
"We must invest not only in technology, but also in the education, training, and healthcare professionals who have knowledge and skills beyond clinical training. Every hospital, clinic, and health care organization will need professionals versed in informatics to assist with implementation, use, and success of health IT systems." - Don E. Detmer, MD, MA, Past President AMIA

Many universities, for example, Kansas [9], will participate in the program and the curriculum will include:

- Basics in medical informatics;
- Medical decision support;
- Informatics in public health;

- Current topics in medical informatics including successful examples.

4 International Standards for Education and Curricula

In 1999 IMIA (International Medical Informatics Association, Working Group Health and Medical Informatics Education) developed Recommendations on Education in Health and Medical Informatics (HMI) and the recommendations were revised in 2010 [10].

The objectives of these recommendations are to assist in the establishment of courses, course tracks and complete programs in HMI. The recommendations focus on the education and training requirements for employees in health care and they include the acquisition of knowledge and skills in information processing, information and communication technology. The requirements are described in a three-dimensional table. The dimensions are:

1. Health professionals (doctors, nurses, informaticians, health information managersâ);

2. Type of specialisation in health and medical informatics (ICT users, medical informaticians);

3. Educational level (Bachelor, Master).

Learning outcomes are defined in terms of knowledge and practical skills for health care and health professionals in the role of both users and specialists.

5 IMIA Accreditation

Normally evaluation of curricula and the success of the respective institutions are carried out at a national level. Also international colleagues are involved as experts in rare cases. International recognition to stimulate the mobility of students and therefore the involvement of international experts is desirable. Accordingly, IMIA now offers the possibility of accreditation. A proposal for a pilot phase for the IMIA Accreditation of HMI (health and medical informatics) curricula was accepted during the IMIA General Assembly in 2011. The development of criteria was carried out in the years 2010 and 2011 under the direction of Arie Hasman [11]. A checklist was then developed, which is used during site visits. On the basis of this checklist an accreditation report is written that has to be accepted by the Accreditation Committee of the IMIA Board. For each accreditation, an international site visit team of three colleagues is formed. The program that wishes to be accredited has to write a self-assessment report. The site visit team uses this report together with interviews with all stakeholders to assess the program. Bachelor's and/or Master's degree programs at the Universities of Kuopio / Finland, Taipei / Taiwan and Göttingen and the Instituto Professional DuocUC, Santiago de Chile, Chile have been accredited for 5 years.

6 Conclusion

This paper presents a wide range of opportunities for education and training in telemedicine and partly with the help of telemedicine. Completeness is not desired because this cannot be provided in a short overview. Rather, this article spotlights examples that can be referred to as beacons. Therefore, this contribution is perhaps a start for a discussion of another commitment in the ongoing education and training for a better healthcare through the application of medical informatics and medical/health information management systems and processes.

References

[1] Erasmus program: http://en.wikipedia.org/wiki/Erasmus_Programme, Last access: December 14, 2014

[2] EuroMISE Centre: http://www.euromise.cz, Last access: December 14, 2014

[3] European Journal for Biomedical Informatics (EJBI): www.ejbi.org, Last access: December 14, 2014

[4] EuroRec Institute: http://www.eurorec.org/ , Last access: December 14, 2014

[5] EuroRec-QREC Project: http://www.eurorec.org/RD/pastProject_Q-REC.cfm, Last access: December 14, 2014

[6] IFHIMA: www.IFHIMA.org, Last access: December 14, 2014

[7] AMIA: www.AMIA.org, Last access: December 14, 2014

[8] AMIA 10X10 training courses: http://www.amia.org/education/10x10-courses

[9] University of Kansas Course description: http://www.amia.org/education/10x10-courses/10x10-kansas/course-description, Last access: December 14, 2014

[10] Mantas J, Ammenwerth E, Demiris G, et al. Recommendations of the International Medical Informatics Association (IMIA) on Education in Biomedical and Health Informatics. First Revision. Methods Inf Med. 2010 Jan 7;49(2):105-120, reprinted in EJBI 2011, 7(2): 3-18, http://www.ejbi.org/img/ejbi/2011/2/Mantas_en.pdf Last access: December 14, 2014

[11] Hasman, A., Mantas, J. IMIA Accreditation of Health Informatics Programs. Health. Inform. Res., Sep 2013, 19(3). 154-161

Electronic Health Record in Dentistry

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Abstract

Structured representation of information in electronic health record is important for reuse of information in medical decision support, statistical analysis of data, interoperability issues and automatic speech recognition. The article presents the importance of the user interface, the interactive DentCross component that serves to the development of lifetime electronic oral health record.

Keywords

Electronic health record, dental medicine, oral health

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1 Introduction

The main role of the e-health is to provide an easy transmission and communication of information in healthcare in forms of data or knowledge [1]. During the 58th World Health Assembly held in Geneva in May 2005, the Ministers of Health of the 192 member states of the United Nations approved the so called e-health Resolution [2] that officially recognizes the added value of the information and communication technologies for health purposes. E-health technologies have opened the doorway to a new type of medical services where healthcare professionals are able to utilize them fully for prevention and management of diseases, lifelong learning and communication with colleagues and patients. Moreover, education and use of e-health technologies can help to change a passive attitude of patients to their diseases towards a proactive attitude of informed citizens for managing their own health. E-health concept has been the main topic of many books, papers in journals and presentations at conferences, e.g. [3, 4, 5, 6], and discussed in [7] in a broader e3-health concept. The e3-health concept states that there are also economic and environmental aspects of healthcare. Even the electronic health record contains economic information. It contains information on subject's (patient's) behavior, information about the prescribed treatment (which itself is an economic process bearing its costs and a potential for revenue in the form of improving subject's health). Also, the treatment contains information the prescribing physician had to take into account because the treatment reflects not only the desired change of the patient's health but also information on patient's adherence to the therapy, cost constraints and availability of treatment options. Environmental aspects are included not only in patient's anamnesis (e.g. living environment, type of work, social status) but also in social, legal and healthcare system environment of the country. New information and communication technologies make possible to describe in a structured and unique way patient's state, given procedures and the use of structured information for statistics and examination of quality of healthcare services. We will discuss in more detail the problem of a structured electronic healthcare documentation and electronic health record (EHR) in dentistry.

2 Electronic Oral Health Record

Many different definitions of electronic health record exist nowadays. International standard ISO/DTR 20514:2004 defines the electronic health record (EHR) as a repository of information regarding the health of a subject of care in computer processible form, stored and transmitted securely, and accessible by multiple authorized users. Its primary purpose is the support of continuing, efficient and integrated healthcare. Therefore EHR contains all patient medical information from multiple sources, which is retrospective, concurrent and prospective. In addition, EHRs may contain data about medical referrals, medical treatments, medications and their applications, demographic information and other non-clinical administrative information. Main goals of electronic health record are supporting continuing, efficient and high quality integrated healthcare by sharing patient health information among authorized users.

In the ideal situation, the information in EHR is continuously updated and current. Terms commonly used

in describing the EHR include interactive user interfaces and structured data entries [8, 9], interoperability [10] and standards [11, 12], real-time and point-of-care usage [13], privacy enhancing techniques improving security aspects [14, 15, 16], semantic interoperability by ontology based approaches [17, 18] or decision support systems [19]. The EHR allows collection of data for other reasons than for direct patient care, such as quality improvement, outcome reporting, resource management, and public health communicable disease surveillance.

New requirements to collect data in healthcare are based on an electronic health record, where information is stored in a structured form. Data entry into the EHR systems during examination of a patient should be supported by user-friendly interfaces. In dentistry, the part of EHR focused on oral health information is called electronic oral health record (EOHR), see [20]. In advanced healthcare environment dental clinics can connect oral health information to hospital EHR [21]. It means that past medical history, laboratory tests, can be retrieved from the hospital EHR.

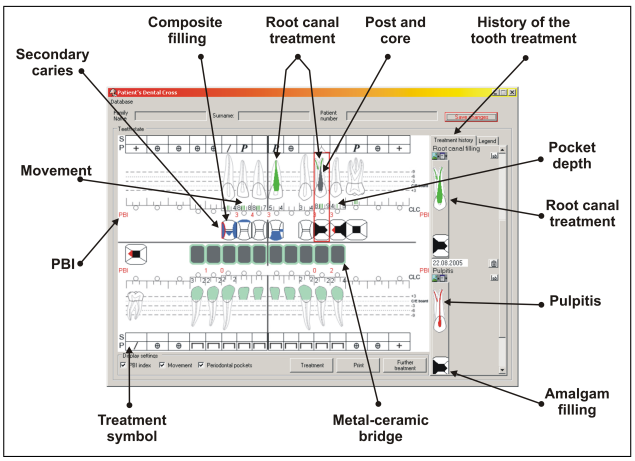

Figure 1: DentCross component.

We have developed a fully interactive graphical component called DentCross to store in EOHR information about dentice of adults [22]. A dentist can choose about 60 different actions, treatment procedures or tooth parameters that are displayed graphically and in a well-organized manner. Further the DentCross component can be supported by automatic speech recognition and connected with the structured electronic health record [23, 24]. The synergy of the voice control and the graphical representation of data make hand-busy activities in the dental practice easier, quicker and more comfortable [25]. This can result in a better quality of data stored in a structured form in EOHR. Moreover, structured information in EOHRs can highly support decision-making processes and telemedical applications. Since 2005 oral health data have been collected (using interactive DentCross component as the interface) in the University Hospital in Prague-Motol. There is dental knowledge incorporated in EOHR for both gathering data as well as their classification (Figure 1).

3 Voice Controlled Dent Cross Interface

The first version of the interactive software component Dent Cross was developed in 2005 for the permanent dentition [26]. The dentist may use different kinds of representation diagnosis or treatment. It also includes a treatment plan and progress of individual visitors step by step with graphical representations of changes in dentition.

Nowadays software solution working with an interactive component Lifetime DentCross includes the option of entering data not only for permanent, but for a mixed deciduous teeth. For these situations the ontology model of dental medicine was extended. The user interface for dentistry is based on a new software version of the interactive component Lifetime Dent Cross [27].

Each existing tooth is described using the basic anatomical structures – crown root suspension system of the tooth and complementary information about teething. User interface is dominated by its own graphic dental cross. In addition to the basic data needed for patient identification (name, surname, personal identification number) will also find controls for working with the user interface. They are chosen so that the user can easily enter into the history of treatment, treatment plan and eventually tooth can also use other forms for detailed periodontal examination, such as recording the presence of tartar, a record depth of periodontal pockets, gingival condition and looseness of the PBI (papilla bleeding index). In Figure 2, we demonstrate a record of a comprehensive examination.

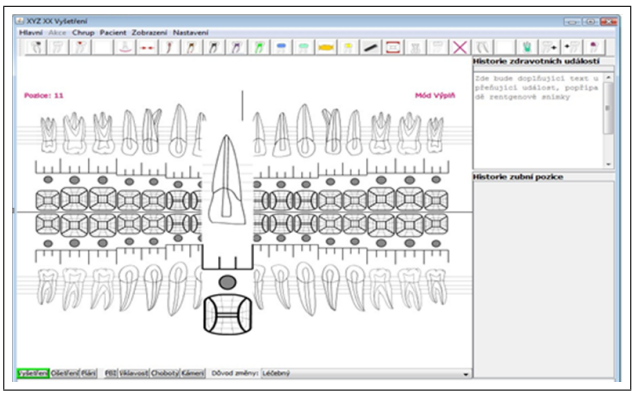

Figure 2: Example of the Lifetime DentCross component.

In [28] the comparison of three methods for time-consuming data entry in dentistry was performed: dental registration in the WHO card and electronic oral health record (EOHR) controlled by keyboard or voice.

All three methods were used in 126 patients. First, patients were examined by standard techniques (communication between doctor and nurse) and the data reported to WHO card. The same person carried out all data entry into the EHR using a keyboard or voice control. The difference in time-consuming examination of records using EHR-operated keyboard or voice was not significant. In

clinical practice, it is required to find ways to avoid the manual operation of the dental EHR using a keyboard, mouse or touch screen. Therefore, there was added an automatic recognition (ASR) to allow the dentist use the software without having to touch. This eliminates the need for a second person making the entry to your computer or redundant hygienic procedures (washing hands, changing gloves, etc.)

4 Conclusions

Necessity of using a human voice to control computer or other devices arose in typical hands-busy environments such as surgery or dentistry. The problems with data storage into the EHR during an examination of a patient led us to further research in the area of the automatic speech recognition in the dental practice. The synergy of the voice control and graphical representation of the dental arch makes hand-busy activities in the dental practice easier, quicker and more comfortable. The use of an interactive DentCross component for recording oral health information was applied also in forensic dentistry [29].

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References

[1] J. Zvárová, A. Veselý, I. Vajda, I.. ”Data, Information and Knowledge”. In Data Mining and Medical Knowledge Management: Cases and Applications P. Berka, J. Rauch., D. Zighed Eds., IGI Global, New York, 2009, pp. 1-36.

[2] J. C. Healy ”The WHO eHealth resolution – eHealth for all by 2015?”. Methods Inf Med, 46, 2007, pp. 2-5.

[3] I. Iakovidis, P. Wilson, J.C. Healy Eds. eHealth: Current Situation and Examples of Implemented and Beneficial eHealth Applications. Amsterdam: Health Technology and Informatics 100, IOS Press, 2004.

[4] G. Demiris, Ed. eHealth: Current Static and Future Trends. Amsterdam: Health Technology and Informatics 106, IOS Press, 2004.

[5] B. Blobel, P. Pharow, M. Nerlich,. Eds., eHealth: Combining Health Telematics, Telemedicine, Biomedical Engineering and Bioinformatics to the Edge. Global Experts Summit Textbook. Amsterdam: Health Technology and Informatics 134, IOS Press, 2004.

[6] S. K. Andersen, G. O. Klein, S. Schulz, J. Aarts, M. C. Mazzoleni, Eds. eHealth Beyond the Horizon – Get IT There. Proceedings of MIE2008. Health Technology and Informatics 136, IOS Press, Amsterdam, 2008.

[7] J.Zvárová, K. Zvára, ”e3Health: Three Main Features of Modern Healthcare”. In E-Health Systems Quality and Reliability: Models and Standards, A. Moumtzoglou, A. Kastania, Eds., IGI Global, New York, 2010, pp.18-27.

[8] A. M. van Ginneken, H. Stqam, E. van Mulligen M. de Wilde, R. van Mastrigt, J. H. van Bemmel. ”ORCA: the versatile CPR”, Methods Inf Med. 38, 1999, pp. 332-338.

[9] A. M. van Ginneken ”The computerized patient record: balancing effort and benefit”, Int J Med Inf 65, 2002, pp. 97-11.

[10] A. Bakker ”Access to EHR and access control at a moment in the past: A discussion of the need and an exploration of the consequences”. Int J Med Inform 73, 2004, pp. 267-270.

[11] D. Kalra ”Electronic Health Record Standards” Methods Inf Medicine 45, Suppl 1, 2006, pp. 136-144.

[12] B. Blobel ”Advanced EHR Architecture – Promises or Reality”, Methods Inf Med 1, 2006, pp. 95-101.

[13] E. Reuss, M. Menoyi, M. Buchi, J. Koller, H. Krueger ”Information access at the point of care: what can we learn for designing a mobile CPR system?”. Int J Med Inform 73, 2004, pp. 365-369.

[14] E. H. Kluge ”Informed consent and the security of the electronic health record (EHR): some policy considerations”. Int J Med Inform 73, 2004, pp. 229-234.

[15] P. Pharow, B. Blobel ”Electronic signatures for long lasting storage purposes in electronic archives”. Int J Med Inform 74, 2005,279-287.

[16] U. Sax, I. Kohane, K. D. Mandl. âžWireless technology infrastructures for authentication of patients. PKI that rings”. J Am Med Inform Assoc 2005, pp. 263-268.

[17] Z. Min, D. Baofen, M. Weeber, A. M. van Gineken ”Mapping Open SDE domain models to SNOMED CT”. Methods Inf Med 1, 2006, pp. 4-9.

[18] C. Friedman, I. Shagina, Y. Lussier, G. Hripcsak ”Automated encoding of clinical documents based on natural language processing”. J Am Med Inform Assoc 11, 2004, pp. 392-402.

[19] A. Hasman, B. Blobel, J. Zvárová Eds. Data and Knowledge for Medical Decision Support, IOS Press, Amsterdam, 2013.

[20] W.D. Heid, J. Chasteen, A.W. Forrey ”The electronic oral health record”, J Contemp Dent Pract 3, 2002, pp. 43â“54.

[21] S.Suebnukarn, P. Rittipakorn, B.Thongyoi, K. Boonpitak, M. Wongsapai, P Pakdeesan, âžUsability assessment of an electronic health record in a comprehensive dental clinic”, SpringerPlus 2:220, 2013, pp.1-8.

[22] J. Špidlen, M. Pieš, Z. Teuberová, M. Nagy, P. Hanzlíček, J.Zvárová, T. Dostálová ”MUDRLite – an electronic health record applied to dentistry by the usage of a dental-cross component” EMBECÂ´05, IFMBE Proceeding 2005, pp. 1077-1081.

[23] J. Zvárová, P. Hanzlíček, M. Nagy, P. Přečková, K. Zvára, L. Seidl ”Biomedical Informatics Research for Individualized Life-Long Shared Healthcare”, Biocybernetis and Biomedical Engineering, 29, pp. 31-41.

[24] T. Dostálová, M. Seydlová, J. Zvárová, P. Hanzlíček, M. Nagy ”Computer-Supported Treatment of Patients with the TMF Parafunction”, in. eHealth: Combining Health Telematics, Telemedicine, Biomedical Engineering and Bioinformatics to the Edge B. Blobel, P. Pharow, J. Zvarova, D. Polez Eds. Berlin: CEHR Conference Proceedings 2007, pp. 171-178.

[25] J. Špidlen, P. Hanzlíček, A. Říha, J. Zvárová ”Flexible Information Storage in MUDRII EHR”. Int J Med Inform 75, 2006 pp. 201-208.

[26] P. Hanzlíček, J. Špidlen, H. Heroutová, M. Nagy ”User Interface of MUDR Electronic Health Record”. In R. Baud R. at al. Eds. Int J Med Inform 74, 2005, pp.221-227.

[27] K. Zvára, L. Seidl., V. Kašpar. (2009), "Lifetime Dental Cross" (version 1.1, computer program, EuroMISE LTD), proprietary licence, unpublished.

[28] K.Chleborad,, K. Zvara Jr. T. Dostalova, K. Zvara, R. Hippmann, R. Ivancakova, Z. Trmal, J. Psutka "Evaluation of voice-based data entry to an electronic health record system for dentistry", Biocybernetics and biomedical engineering 33, 2013 , pp.204/210,

[29] J. Zvárová, T. Dostálová, P. Hanzlíček, Z. Teuberová, M. Nagy, M. Pieš, et al. "Electronic health record for forensic dentistry". Methods Inf. Med., 47, 2008, pp. 8â"13.

International Joint Meeting EuroMISE 2015 (IJM EuroMISE 2015)

16.–18. June 2015, in Prague, The Czech Republic

EuroMISE Mentor Association is the main organizer of the IJM EuroMISE 2015 (Garant: Jana Zvárová, The Czech Republic) that covers the following events.

1 International Conference

BIG DATA CHALLENGES FOR PERSONALISED MEDICINE

Wednesday, June 17th 2015, Garant: Pirkko Nykänen, Finland

Call for papers will be opened at the beginning of March 2015

2 International symposium

INFORMATION – BASED PREVENTION IN HEALTHCARE

Tuesday, June 16th 2015, Garant: Milan Tuček, The Czech Republic

Call for papers will be opened at the beginning of March 2015

3 Mentoring course

BIG DATA – ANALYSIS AND MODELLING CHALLENGES

Tuesday, June 16th 2015 (half day) Garant: Pirkko Nykänen, Finland

The challenges of big data in health informatics are not only in capturing and storing information but also in providing the methods and tools to analyze and manage big data. Many questions need to be solved with big data to be able to improve research and exploit research outputs to improve health both at a public health level and at personalized medicine level.

One of the most significant obstacles in personalized medicine is the translation of scientific discoveries into effective clinical outcomes that relate to the individual. A critical factor in the successful translation is the access, management, and analysis of integrated patient data, within and across different functional domains. Currently most clinical and basic research data are stored in disparate and separate systems, and it is often difficult for clinicians and researchers to access and share these data. Furthermore, inefficient workflow management in clinics and research laboratories has created many obstacles for clinical decision-making and assessment of outcomes. We need to open our perspectives from closed disconnected data silos which will restrict the analysis and utilization of big data.

The power of big data is that it can provide individualized evidence leading to the development of truly personalized medicine. Big data can also provide the means for decision support across all aspects of health care, e.g. for

assessing safety and efficacy of drugs, for health technology assessments and for improving prevention, diagnosis and treatment. To achieve these we need advanced statistical methods and tools to analyze and manage big data, to retrieve and analyze data using data text mining and semantic tools, to retrieve information through population-based data mining, to develop patient-oriented tools for data sharing and patient empowerment and to promote collaboration between research, clinics and industry.

The challenges of big data include: Standards for consolidating, characterizing, validating and processing of data; ontologies for knowledge and relationships between knowledge entities such as genes, drugs, diseases, symptoms, patients and treatments; integration of various data sources and information systems and integration of environmental data with individual genomic measurements; and open access – availability, readability and usability of big data. In all these, we need to take into account the security and privacy requirements for personal health data which means that data users should be accountable for the custodianship of personal medical information. This will be a challenge with big data as we are dealing with both regulated and non-regulated healthcare environments and with reuse of data, secondary use of health data. Big data offers a challenge for biomedical informatics today - to connect molecular and cellular biology to the clinical world thus allowing us to consider individual variations and not simply population averages.

4 Mentoring course

INTRODUCTION TO TECHNOLOGY ACCEPTANCE

Thursday, June 18th, 2015 (half day) Garant: Arie Hasman, The Netherlands

Underutilization of information systems is still a problem nowadays. Therefore it is important to obtain insight in why these systems are not successful in order to be able to design better systems. In the past user satisfaction with information systems was used as a proxy for system success. The idea was that the more satisfied users are about a system, the more they will use it. Several questionnaires were developed to measure user satisfaction. However, user satisfaction appeared not to be a good predictor of system's success. In this introduction it is explained why that was the case.

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Obsah

Holistické elektronické zdravotnictví založené na informacích

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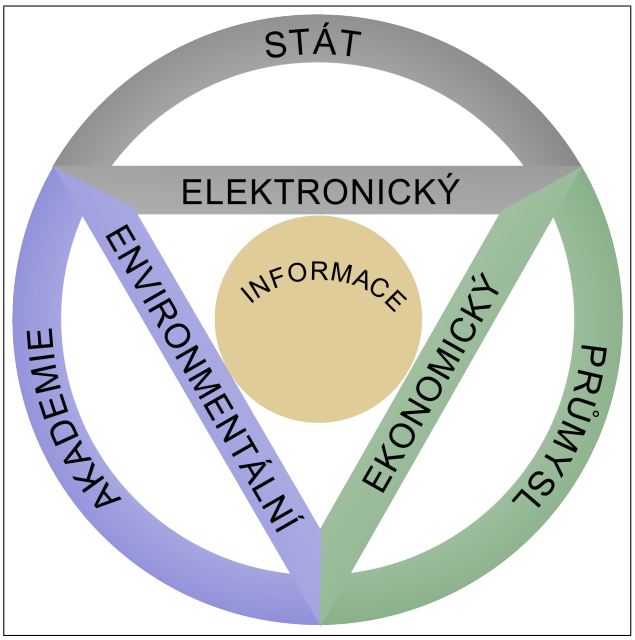
Abstrakt

Článek ukazuje důležitý vývoj medicínské informatiky od jejího vzniku do současnosti s uvedením příkladů. Jsou popsány různé výklady slova „informatika“ stejně jako vztah oborů biomedicínská informatika, zdravotní informatika, zdravotnická informatika k oboru medicínská informatika. Uvedené prolínající se obory tvoří jeden ze základů pro biomedicínu a zdravotnictví. Hrají rovněž významnou roli v novém konceptu holistického elektronického zdravotnictví založeného na informacích.



Obrázek 1: Holistické elektronické zdravotnictví založené na informacích.

Klíčová slova

Medicínská informatika, biomedicínská informatika, zdravotní informatika, zdravotnická informatika, elektronické zdravotnictví

Význam deficitu cerebrálního folátu pro rozvoj a léčbu poruch autistického spektra

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Abstrakt

Autismus resp. poruchy autistického spektra (PAS) představují vážné celoživotní neurobehaviorální postižení, výrazně komplikující integraci jedince do běžného života. Etiologie PAS je ve většině případů neznámá, pravděpodobně komplexní z různých příčin, které se mohou vyskytovat současně. Deficit cerebrálního folátu (Cerebral Folate Deficiency – CFD) je neurodegenerativní onemocnění charakterizované sníženou likvorovou koncentrací metabolicky aktivních folátů při současně většinou normálních sérových hladinách. Zatímco vážný CFD je zjevný pro své motorické a senzorické příznaky, mírný CFD může hrát roli pro rozvoj samostatných behaviorálních postižení včetně PAS bez zjevného tělesného postižení. CFD je různě závažný, většinou částečně, výjimečně zcela, kompenzovatelný syndrom, u něhož byly publikovány i případy pozitivního vlivu léčby na jádrové příznaky PAS (narušení komunikace, sociální interakce, neschopnost abstrakce, stereotypní chování), běžně označované jako neléčitelné. Výjimečně byly publikovány i případy plného zotavení ze symptomů PAS při CFD. Ačkoliv byl CFD popsán již v roce 2002, první větší studie zaměřená na sledování efektu léčby CFD na jádrové symptomy idiopatických PAS byla publikována teprve v roce 2013. Cílem tohoto review bylo shrnout dostupné informace o koincidenci CFD a PAS, popsat význam deplece folátů pro vývoj a funkci centrálního nervového systému (CNS) a poukázat na potenciální vztahy k dalším patologickým nálezům u PAS. Dalším cílem bylo zmapovat nejčastější příčiny CFD, kvantifikovat koincidenci CFD a PAS a zhodnotit účinnost dosud testované léčby, opět se zaměřením na zlepšení jádrových symptomů PAS. Další výzkum v této oblasti by mohl perspektivně přinést nové terapeutické možnosti idiopatického autismu.

Klíčová slova

Autismus, deficit cerebrálního folátu, folát, protilátky folátových receptorů, EHR

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Úvod

Poruchy autistického spektra (PAS) zahrnují skupinu pervazivních vývojových poruch charakterizovaných narušením komunikace, reciproké sociální interakce a nedostatečností v oblasti představivosti se sklony ke stereotypnímu chování. PAS je celoživotní postižení s nejistou prognózou, většina pacientů dnes není schopna samostatné společenské integrace. Odhadovaná prevalence se pohybuje v různých populacích v rozmezí od $0,1$ do $1,5\%$. a představuje tak výrazné socioekonomické zatížení. PAS je neurobehaviorální postižení ve většině případů neznámé etiologie [1]. Výzkum je kromě genetických příčin v poslední době rozšiřován i o další oblasti jako jsou epigenetické změny, exogenní intoxikace, autoimunita etc. Toto review shrnuje dostupné informace o koincidenci PAS a deficitu cerebrálního folátu (Cerebral Folate Deficiency – CFD). CFD je syndrom charakterizovaný sníženou koncentrací 5-MTHF (5-methyltetrahydrofolátu) v likvoru při současně normálních hladinách 5-MTHF v séru či erytrocytech. Symptomy CFD a jejich závažnost jsou velmi variabilní. Z některých publikovaných prací vyplývá, že CFD může přispívat k rozvoji a progresi PAS a že kompenzace CFD může potlačovat základní symptomy PAS [2, 3, 4, 5, 6, 7].

Význam transportu a utilizace folátů pro CNS

Transport folátů začíná v proximálním ileu [8], kde jsou foláty hydrolyzovány na své monoglutamátové formy, absorbovány, chemicky redukovány a konvertovány především na 5-MTHF. Iniciální redukce probíhá v enterocy-

tech, případně v játrech, ale příslušný enzym DHFR (Dihydrofolát reduktáza) je přítomen ve všech tkáních.

Intracelulární transport zajišťují 3 typy receptorů: RFC (Reduced Folate Carrier) a PCFT (Proton-coupled Folate Transporter) pracující na principech Na^+ antiportu [9] resp. H^+ synportu [10]. Třetí typ receptoru FOLR1 (Folate Receptor 1 – též FR-α) je založen na endocytóze, je ATP-dependentní a jako jediný zajišťuje výrazně rozdílnou koncentraci folátů mezi intra- a extracelulárním prostorem [11]. FOLR1 je exprimován především v membránách buněk plexus choroideus, placentární tkáně, štítné žlázy, proximálních tubulů ledvin a dalších tkání, kde zajišťuje aktivní jednosměrný transport folátů [12]. Fyziologická koncentrace folátů v likvoru je ve srovnání se systémovým oběhem zhruba 3x vyšší [13].

Intracelulární retence folátů je zajištěna polyglutaminací enzymem FPGS (Folypolyglutamát syntáza). Transport folátů do mitochondrií je pak zajišťován dalším specifickým transportérem SLC25A32 [14]. Polyglutamátové formy folátů nemohou být transportovány přes membrány, ale jsou vhodným substrátem pro metabolickou utilizaci. Katalytická aktivita enzymů folátových drah a FPGS jsou vzájemně spjaty a ovlivňují se negativní zpětnou vazbou bránící nadměrné intracelulární retenci folátů [15].

Folát se ve svých 9 chemických formách účastní více než stovky metabolických reakcí. Foláty jsou kofaktory syntézy purinů a pyrimidinů, prekurzorů DNA a mRNA a jsou nezbytné pro dělení a růst buněk [16].

Genová exprese je výrazně ovlivněna methylací jednotlivých úseků DNA i nosného chromatinu. Substrátem methylace je S-adenosylmethionin (SAM), produkt regenerace homocysteinu na methionin, která je závislá na folátu [17].

SAM je také nezbytný pro konverzi serotoninu na melatonin, který se podílí na řízení spánkového cyklu. Abnormality v hladinách melatoninu byly u PAS pozorovány v 9 studiích [18].

Při nedostatku folátu organismus regeneruje SAM pomocí alternativní metabolické dráhy a spotřebovává tak cholin, který je podmíněně esenciální pro vývoj CNS [19]. Deplece cholinu vede ke snížení syntézy lipoproteinů, k narušení stability myelinových membrán, k demyelinizaci a atrofii CNS [20]. Cholin je také přímou součástí molekul sfingomyelinu, jeho nedostatek tedy může narušovat i samotnou syntézu myelinu. Cholin je prekurzorem acetylcholinu a lze tedy očekávat narušení jeho syntézy [19]. K depleci cholinu může synergicky přispívat i vyhraněný jídelníček, častý u PAS, s následnou malnutricí [21]. Folát je také kofaktorem v metabolické dráze regenerace cholin - glycin, konkrétně v konverzi dimethylglycin - sarcosin. Katalýza probíhá i bez folátového kofaktoru, výsledné produkty jsou však jiné a vzniká toxický formaldehyd [22].

Folát je nezbytný pro syntézu serinu. Serin neprochází hematoencefalickou bariérou a po jejím formování je vyvíjející se plod závislý na lokální syntéze v CNS [23]. Serin má prokázaný trofický efekt na nervovou tkáň [24]. Inhibice utilizace serinu v CNS je spojována se zvýšenou apoptózou neuronů [25]. Kromě folátu je i L-serin nezbytný pro syntézu myelinu a fosfolipidů, tedy i k formování dendritů a růstu axonálních spojení. Phospatidyl-L-serin, metabolit serinu, je činný v řízení apoptózy a v synaptickém pruningu (eliminaci nadbytečných nervových spojení během vývoje a zrání mozku) v raném postnatálním období. D-Serin a glycin, další metabolity serinu, fungují i jako inhibiční neurotransmitery, mají neuromodulační efekt a vystupují jako signální molekuly ovlivňující růst a vývoj mozku a maturaci synapsí [23].

Snížená likvorová hladina 5-MTHF je spojována s poruchou regenerace tetrahydrobiopterinu (BH4) [26]. BH4 je nezbytným kofaktorem syntézy serotoninu, dopaminu a oxidu dusnatého (NO). Narušení serotoninergních i dopaminergních drah je spojováno s patofyziologií PAS a může ovlivnit nejen samotný synaptický přenos, ale i dříve popsanou syntézu koncových produktů (melatonin), nebo hromadění prekurzorů (serotonin) [27]. NO je silným lokálním vazodilatanciem. Několik studií nalezlo lokální poruchy perfúze částí CNS u pacientů s PAS [28, 29, 30]. Při nedostatku BH4 je 5-MTHF alternativním kofaktorem syntézy NO.

Snížení syntézy NO vede k produkci superoxidů a oxidativnímu poškození tkání [31]. Oxidativní poškození membrán buněk i jejich kompartmentů včetně mitochondrií může být způsobeno i samotnou deplecí SAM na podkladě nedostatku 5-MTHF. Volné radikály tak mohou nejen narušovat lipoproteiny v buněčných membránách a přispívat k poruchám růstu a formování axonů, dendritů a synaptických spojení, ale také přímo narušovat integritu vnitřních membrán mitochondrií a výrazně tak ovlivnit produkci ATP. Snížení syntézy ATP může vést k poruchám dělení, růstu i synaptického pruningu, stejně jako k funkčnímu narušení synaptické aktivity a v neposlední řadě i k dalšímu snížení ATP-dependentního importu folátů do CNS. Zvýšený oxidativní stres nebo narušení produkce ATP u pacientů s PAS byl popsán ve 3 kontrolovaných studiích a 9 kazuistikách [32].

Nelze také pominout, že mutace v genech pro proteiny folátových katalytických enzymů či transportních receptorů mohou výrazně přispívat k narušení folátového metabolismu. Příkladem mohou být popsané případy PAS či podobných neurobehaviorálních onemocnění u mutací genů *MTHFR* (Methlytetrahydrofolát reduktáza) [33], *DHFR* [34] a *FOLR1* [35]. Kromě genetických změn je třeba vzít v úvahu i epigenetické změny ve smyslu atypické methylace DNA či změny struktury histonů, publikované v souvislosti s PAS [36]. Deplece 5-MTHF v CNS je zřejmě v přímé souvislosti s hypo- i hypermethylací genů spojovaných s PAS, např.: *AFF, GABRB3, MECP2, NLGN3, NRXN1, SLC6A4, UBE3A* [37], *OXTR* [38], *SHANK3* [39]. Nedostatek folátu v kritickém období prenatálního a raného postnatálního vývoje tak může přispívat k narušení exprese těchto genů a tím k rozvoji PAS.

Cíle

Našim cílem bylo kvantifikovat koincidenci PAS u publikovaných případů CFD od roku 2002, kdy bylo one-

mocnění poprvé systematicky popsáno až do dnešního dne (říjen 2014). Druhým cílem bylo kvantitativní zhodnocení účinnosti léčby CFD se zvláštním zaměřením na zlepšení v jádrových symptomech PAS.

Metody

K vyhledávání publikací jsme využili veřejné rozhraní databáze Americké národní lékařské knihovny - PubMed. Vyhledali jsme publikace odpovídající heslu „Cerebral Folate Deficiency“ a z nalezené množiny vybrali klinické studie a kazuistiky. Typ studie nebyl, pro poměrně malý počet zdrojů, rozlišován. Z každé nalezené publikace byl získán počet pacientů, klinický obraz, diagnóza či popis PAS, příbuzné neurobehaviorální symptomy, etiologie, terapeutický postup a výsledek léčby se speciálním zaměřením na hodnocení účinku na symptomy PAS. Částečné symptomy typické pro PAS (poruchy komunikace, narušení sociální interakce, ...) případně podobné, nebyly do hodnocení konkomitance PAS u CFD započítávány, pokud nebyla PAS ve studii přímo diagnostikována či popsána v širší škále symptomů. Vzájemně odlišné struktury jednotlivých studií a šíře záběru tohoto review znemožnily provedení hlubší statistické analýzy. Z toho důvodu byly tedy nálezy hodnoceny pouze výčtem.

Výsledky

Klinický obraz CFD

Ramaekers et al. v roce 2002 popsali CFD u 5 pacientů jako progresivní onemocnění s normálním vývojem do 4. – 6. měsíce věku a následnou manifestací dráždivosti, progresivní mikrocefalie, psychomotorické retardace, cerebelární ataxie a poruchy hybnosti dolních končetin. Ve 3 letech věku se často manifestovala epilepsie a po 6. roce věku byly u části pacientů zjištěny poruchy zraku. Autoři nalezli výrazně sníženou koncentraci 5-MTHF v likvoru a normální sérovou koncentraci u 5 případů [40].

Stejní autoři v roce 2004 publikovali dalších 20 případů. U některých pacientů byla, kromě již uvedených symptomů, popsána spastická paraplegie, ztráta sluchu a patologické nálezy na MRI mozku (frontotemporální atrofie s periventrikulární a subkortikální demyelinizací a atrofie cerebella). Protože autoři nenalezli mutace v genu pro receptor FOLR1, ale přesto potvrdili jeho nefunkčnost, vyslovili hypotézu o možném epigenetickém poškození či jeho blokování jinou sloučeninou včetně autoprotilátek (Folate Receptor Auto Antibody – FRAA) [41].

V obou studiích byla testována symptomatická léčba vysokými dávkami 5-formyltetrahydroflátu (5-FTHF), která účinně potlačila neurologické symptomy. Došlo k vymizení záchvatů, k normalizaci EEG, ke zlepšení rovnováhy i koordinace úmyslných pohybů, stejně jako ke snížení hyperexcitability a impulzivního jednání. U pacientů rovněž došlo ke zlepšení kognitivních funkcí, u žádného pacienta však nebyla pozorována plná úprava stavu.

Klinický obraz CFD se v dalších studiích ukázal jako značně variabilní, jeho etiologie heterogenní a bez jednoznačné korelace mezi hladinou likvorového 5-MTHF a klinickými symptomy, jejich druhem, počtem a mírou vyjádření [40, 41].

Koincidence syndromu CFD s dalšími nálezy včetně PAS

V již uvedené studii [41] byla PAS, dle ADOS (Autism Diagnostic Observation Schedule), diagnostikována u 7 z 20 pacientů s CFD. Roční terapie 5-FTHF vedla k normalizaci likvorových hladin 5-MTHF a pterinů u 18 pacientů. Autoři také vytvořili první terapeutický protokol založený na suplementaci vysokými dávkami 5-FTHF.

Ramaekers et al. v roce 2003 publikoval CFD bez prokázané etiologie u 4 pacientek s Rettovým syndromem. Léčba 5-FTHF měla částečně příznivý vliv [42].

Moretti et al. v roce 2005 publikoval kazuistiku 6-leté dívky s CFD s vývojovým opožděním, psychomotorickým regresem, záchvaty, mentální retardací a autistickými příznaky. Terapie 5-FTHF vedla ke zlepšení motorických dovedností [43].

Hansen et al. v roce 2005 publikoval kazuistiku dívky s idiopatickým progresivním neurologickým onemocněním manifestovaným ve 3 letech věku a refrakterním k léčbě. K prohlubujícímu se vývojovému opoždění se později přidaly problémy s rovnováhou, spasticita a ataxie ve věku 12 let. V tomto věku autoři prokázali i výrazný CFD. Po zahájení terapie 5-FTHF došlo během 1 týdne k velmi výraznému motorickému i kognitivnímu zlepšení s následnou stagnací po jednom roce léčby, kdy musela být terapeutická dávka 5-FTHF zdvojnásobena na 30 mg/denně [44].

Ramaekers et al. v roce 2005 publikoval studii srovnávající likvorové hladiny 5-MTHF a sérové hladiny FRAA na souboru 28 dětí s klinicky diagnostikovaným CFD. 25 z 28 pacientů bylo FRAA pozitivních, na rozdíl od srovnatelné zdravé kontrolní skupiny, kde nebyl pozitivní ani jeden test. U 4 FRAA pozitivních pacientů byla diagnostikována PAS (dle ADOS). Všichni FRAA pozitivní pacienti byli léčení 5-FTHF. U 2 nejmladších autistických pacientů (2 a 3 roky) zaznamenali výrazné zlepšení neurologických i autistických symptomů, u 2 starších (12 a 15 let) byla léčba mnohem méně úspěšná a autistické symptomy neustoupily. U 1 dalšího pacienta s autistickými příznaky došlo léčbou k plnému vymizení symptomů [2].

Ormazabal et al. v roce 2006 měřila likvorové hladiny neurotransmiterů, pterinů a 5-MTHF u 283 pediatrických pacientů s neurologickým postižením neznámé etiologie. U 15% případů našli výrazně sníženou likvorovou hladinu 5-MTHF [45]. Ve stejném roce tatáž skupina autorů publikovala studii dalších 165 pacientů s těžkou epileptickou encefalopatií, poruchami hybnosti, Rettovým syndromem nebo mitochondriálním onemocněním. V této skupině nalezli mírný až hluboký CFD v 74% případů [13].

Pineda et al. v roce 2006 publikovala kazuistiku Kearns-Sayre Syndromu (KSS). KSS je způsoben delecemi v mitochondriálním genomu s následnou poruchou

dýchacího řetězce, tvorby ATP a manifestuje se progresivním neurologickým i svalovým poškozením. Na podkladě deplece ATP dochází, mimo jiné, k narušení ATP-dependentního transportu folátů receptory FOLR1 a k následnému CFD. Po terapii vysokými dávkami 5-FTHF došlo ke zlepšení chůze a postupně také k obnově myelinizace. Ani dlouhodobá léčba však nepřinesla ústup areflexie a cerebelárních symptomů [46].

Ramaekers et al. v roce 2007 publikoval studii 25 pacientů s nízkofunkčním autismem. Hladiny sérového folátu byly v normě, ale u 23 z 25 pacientů byla nalezena snížená likvorová koncentrace 5-MTHF. 19 z těchto 23 bylo pozitivní na FRAA. Roční terapie 5-FTHF vedla k normalizaci likvorové hladiny 5-MTHF a k částečné nebo úplné úpravě klinického obrazu [47].

Ramaekers et al. v roce 2007 publikoval srovnávací studii obsahu likvoru u 33 pacientek s Rettovým syndromem. CFD byl nalezen u 14 z nich a 6 z této skupiny bylo FRAA pozitivních. Ve skupině bez CFD byly FRAA pozitivní pouze 2 pacientky [48].

Mercimek-Mahmutoglu et al. v roce 2007 publikovala atypický případ H-ABC syndromu (Hypomyelination with Atrophy of the Basal Ganglia and Cerebellum) s konkomitantním CFD a normálními likvorovými hladinami neurotransmiterů. H-ABC syndrom je komplex vývojových vad CNS viditelných na MRI, pohybových poruch a mentální retardace různé tíže. Etiologie H-ABC není známa. V publikovaném případě přinesla terapie pomocí 5-FTHF a levodopa / carbidopa ústup opiostonických a okulogyrických záchvatů. Po vysazení levodopa / carbidopa likvorová hladina 5-MTHF opět klesla [49].

Ramaekers et al. v roce 2008 testoval účinnost bezmléčné diety na hladinu FRAA, protože volný protein FOLR1 je součástí mléka savců a autoři ověřovali hypotézu, že organismus vytváří FRAA v imunitní odpovědi a FRAA následně mohou blokovat i membránové receptory FOLR1. Do této studie bylo zařazeno 24 dětí, přičemž 10 z nich bylo diagnostikováno jako nízkofunkční autisté dle ADOS a ADI (Autism Diagnostic Interview). Dlouhodobá terapie 5-FTHF přinesla u všech pacientů zlepšení řady neurologických symptomů. Z 10 autistických pacientů došlo u 2 případů k výraznému a u dalších 4 případů k částečnému zlepšením v oblasti pozornosti, komunikace a stereotypního chování [3].

Moretti et al. v roce 2008 publikoval 7 případů atypického CFD (psychomotorická retardace, vývojové opoždění, dyskinezie, záchvaty). Polymorfismy FOLR1 či genů pro enzymy činné ve folátových drahách nebyly prokázány. 5 ze 7 pacientů mělo diagnostikováno autismus nebo PAS (dle ADI-R a ADOS) s nejvýraznějšími projevy v oblasti citlivosti na změny, lpění na rituálech, repetitivních pohybů a fascinace senzorickými vjemy. Skupina nebyla etiologicky konzistentní. Po nasazení léčby 5-FTHF došlo u 4 ze 7 pacientů ke zlepšení jak v neurologických tak autistických symptomech [4].

Případ neúspěšné léčby u pacientky s vývojovým opožděním, epilepsií a kómatem, s CFD a nálezem FRAA publikoval Bonkowsky et al. v roce 2008. Léčba 5-FTHF neovlivnila klinický stav [50].

Hasselmann et al. v roce 2010 popsal případ Alperovy choroby (fatální neurodegenerativní prionové onemocnění) u 3,5 leté dívky s konkomitantním CFD, pravděpodobně na podkladě prokázaných FRAA. Pacientka byla léčena podáváním 5-FTHF. Přes dále progredující onemocnění měla léčba pozitivní vliv na hladinu likvorového 5-MTHF, frekvenci záchvatů a komunikační schopnosti pacientky. Postupně klesly i likvorové koncentrace některých zánětlivých mediátorů (IL-8, IFN-γ). Podpůrná léčba 5-FTHF, stejně jako v jiných, zde uvedených, případech, neovlivnila hladinu sérových FRAA. Pacientka zemřela ve věku 5,5 roku [51].

Serrano et al. v roce 2010 popsala 6 případů CFD u KSS. Byly hlášeny poruchy myelinizace bílé hmoty a mozková atrofie, stejně jako snížené likvorové hladiny 5-MTHF a elevace metabolitů serotoninu a dopaminu. Autoři uvádějí terapii 5-FTHF jako jasně prospěšnou [52].

Mangold et al. v roce 2011 publikovala svou retrospektivní studii o 103 případech CFD u pacientů z let 1999 až 2007. Klinicky diagnostikovaný autismus nachází ve zdravotních záznamech 4 pacientů s CFD, častěji s mírným než vážným deficitem likvorového 5-MTHF. Diagnóza byla jednoznačná pouze u 22 ze 103 pacientů a retrospektivní studie nedošetřovala ostatní pacienty na diagnózu PAS. Nicméně uvádí, že např. mentální retardaci mělo 84, epilepsii 53 a motorické postižení 75 pacientů s CFD. Studie také nezmiňuje terapii ani její účinnost, nicméně uvádí CFD jako poměrně častý syndrom u řady různě závažných neurologických onemocnění [53].

Dill et al. v roce 2011 publikovala případ 8-letého chlapce s LAMM syndromem (Congenital Deafness with Labyrinthine Aplasia, Microtia, and Microdontia) a CFD na podkladě homozygotní mutace *FOLR1*. MRI a MRS (spektroskopie) CNS, kromě nálezů typických pro LAMM syndrom, odhalila i poruchy myelinizace a depleci cholinu frontoparietálně i v oblasti mozkového kmene. Pacient byl odkázán na umělou plicní ventilaci (UPV). Terapie 5-FTHF rapidně zlepšila stav vědomí, rovnováhu a chůzi a zmírnila epilepsii. Pacienta bylo následně možné odpojit od UPV. Po 2 týdnech však došlo k recidivě epilepsie, která ustoupila až po nasazení pyridoxal-5-fosfátu [54].

Banka et al. v roce 2011 publikoval 3 případy pacientů s homozygotní mutací genu *DHFR*, se závažným progredujícím nálezem na CNS, gastrointestinálním traktu i oběhovém systému a s fatálními důsledky v jednom z případů. Nálezy zahrnovaly megaloblastickou anémii, hluboký CFD, frontální i cerebelární hypoplazii, dilataci mozkových komor a další strukturální patologie na MRI CNS. Krevní hladina kyseliny listové byla normální ve všech případech, nicméně likvorové koncentrace 5-MTHF i BH4 byly výrazně nízké. Terapie pomocí 5-FTHF přinesla jen malý benefit ve formě zlepšení likvorových hladin a zmírnění epilepsie. Přeživší pacienti zůstali nadále v klinicky závažném stavu [55].

Cario et al. v roce 2013 publikoval další 3 případy pacientů s homozygotními mutacemi genu *DHFR* a s mír-

nější symptomatologií. U pacientů byla zjištěna megaloblastická anémie, porucha erytropoézy a neurologické symptomy zahrnující epilepsii, oční myoklonus a vážné poruchy učení. U všech případů nalezli vážný CFD, stejně jako dobrou klinickou odpověď na terapii vysokými dávkami 5-FTHF. V publikaci je rovněž popsána rekurence symptomů při opakovaném přerušování léčby u jednoho nespolupracujícího pacienta [56].

Leuzzi et al. v roce 2012 publikoval případ CFD se silně impulzivním jednáním, autoagresivitou, poruchou hrubé motoriky a řeči, ale bez typických autistických příznaků. V 6 letech věku byla v likvoru pacienta nedetekovatelná hladina 5-MTHF. Patogenní mutace genů *MTHFR* a *FOLR1* nebyly nalezeny. Pacient byl také negativní na FRAA a příčina CFD nebyla odhalena. Po nasazení léčby 5-FTHF došlo k úpravě likvorové hladiny 5-MTHF, pacientův klinický stav se však léčbou nezlepšil [57].

Sadighi et al. v roce 2012 publikovala případ dříve zdravé 58-leté ženy s náhlou retrográdní amnézií a myoklonem. U pacientky byla zjištěna snížená koncentrace likvorového 5-MTHF i BH4 a následně u ní byla prokázána přítomnost FRAA. Půlroční terapie 5-FTHF symptomy zcela potlačila [58].

Steele et al. v roce 2012 publikovala 2 pacienty s progredující epilepsií, poruchami hybnosti, hypotonií a záchvaty neznámé etiologie s následně prokázaným CFD. U jednoho pacienta byly zjištěny i autistické rysy. Pacientům byl dlouhodobě podáván 5-FTHF. Dlouhodobá terapie postupně přinesla výrazné zlepšení epilepsie, ale i problémů s motorikou, řečí a celkových psychických schopností [5].

Ho et al. v roce 2014 publikoval případ 13-letého chlapce s mutismem, psychomotorickou retardací a katatonickou schizofrenií. MRI CNS i krevní metabolické testy byly v normě. Lumbální punkce prokázala CFD a následný krevní test odhalil elevaci FRAA. Devítiměsíční léčba 5-FTHF nepřinesla zásadní zlepšení stavu [59].

Případ CFD z deficitu MTHFR s pozdní manifestací publikoval Wang et al. v roce 2014 u 13-letého chlapce se schizofrenií. Tříměsíční léčba 5-FTHF, cobalaminem, pyridoxinem a betainem (kofaktory a intermediáty folátového metabolismu) upravila CFD a zcela potlačila klinické symptomy a pacient se vrátil do běžného života [60].

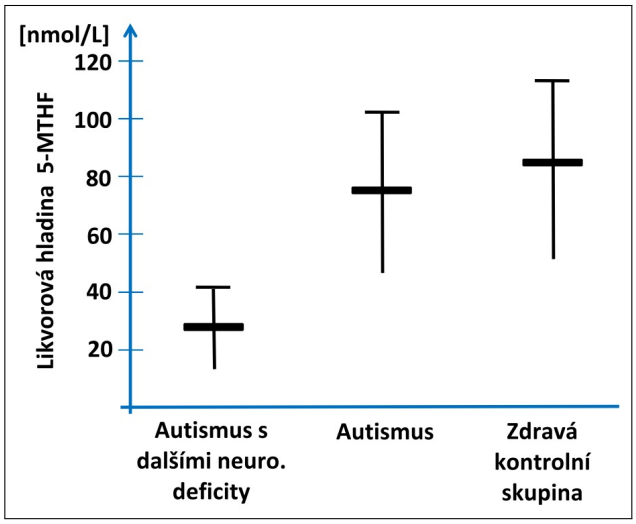
Al-Baradie et al v roce 2014 publikovala případ dvojčat s vývojovým opožděním, epilepsií a CFD. Jedno z dvojčat mělo jasné autistické symptomy. Molekulárně genetickým vyšetřením byla u obou zjištěna homozygotní mutace v genu *FOLR1*. Terapie 5-FTHF zcela potlačila epilepsii a výrazně zlepšila sociální interakci i motorické dovednosti obou pacientů [7].

Wang et al. v roce 2014 publikoval případ CFD u anemické dívky s neurologickým postižením dolních končetin, intrakraniálními kalcifikacemi, regresem mentálních schopností a poruchami spánku. Autoři nalezli nejen likvorový, ale i systémový deficit folátu a elevaci homocysteinu. Likvorová hladina 5-MTHF byla nedetekovatelná. U pacientky byla prokázána mutace genu *SLC46A1*, kódujícího folátový transportní receptor PCFT. Suplementace 5-FTHF přinesla plný ústup symptomů v 6 letech věku [61].

CFD u idiopatického dětského autismu

Všechny výše uvedené studie, ať už zaměřené na přítomnost FRAA či jiné příčiny, se zabývaly vždy CFD jako primární diagnózou a případný autismus resp. PAS uváděly pouze jako případnou komorbiditu. Publikace, které PAS při CFD neuvádí, často hovořily o jiných neurovývojových poruchách a většina z nich neobsahuje informace o diferenciálně diagnostickém vyšetření k vyloučení PAS.

Frye et al. publikoval v roce 2013 otevřenou studii účinnosti léčby jádrových symptomů PAS pomocí aplikace 5-FTHF u 93 pacientů s idiopatickým autismem. Převažoval nález mírného CFD bez typické klinické manifestace. Převažující příčinou byla dle autorů přítomnost FRAA, které byly detekovány u 75% pacientů. Známé příčiny PAS byly u pacientů vyloučeny, resp. pacienti se známou genetickou poruchou nebyli do studie záměrně zařazeni. Po 4-měsíční terapii vysokými dávkami 5-FTHF (2 mg/kg/den) došlo ke střednímu až výraznému zlepšení u třetiny pacientů, především v receptivní a expresivní složce řeči, pozornosti a stereotypním chování. Studie je zatím první svého druhu a má své limity a omezení. Všichni pacienti sice byli klinicky diagnostikováni jako PAS před zahájením studie, ale outcome byl hodnocen pouze rodiči pacientů dle Clinical Global Impression Scale. Studie nebyla slepá a kontrolovaná placebem. Kontrolní skupinu tvořila část dětí čekající na zahájení terapie [6].



Obrázek 1: Srovnání likvorových hladin 5-MTHF mezi 3 skupinami. Vytvořeno podle [19]

Ramaekers et al. v roce 2013 ve svém review porovnával likvorové koncentrace 5-MTHF z dříve publikovaných případů CFD. Autoři ukazují, že míra snížení likvorového 5-MTHF významně koreluje se závažností postižení. Výrazně nižší hladiny 5-MTHF v likvoru jsou spojovány s těžším neurologickým deficitem, kdy primární diagnóza je opřena o nález typického CFD. Naopak u primární di-

agnózy idiopatického autismu resp. PAS je snížení likvorového 5-MTHF mírnější, dokonce v rozsahu normálních hodnot (1). Autoři také potvrzují negativní korelaci hladin 5-MTHF v likvoru s hladinami FRAA v séru [19]. Studie zpracovávala některá data ze zde již uvedených studií, v nichž byla popsána účinnost léčby 5-FTHF na neurologické i autistické symptomy.

Tabulka 1: Shrnutí nálezů PAS u CFD a účinnosti léčby 5-FTHF.

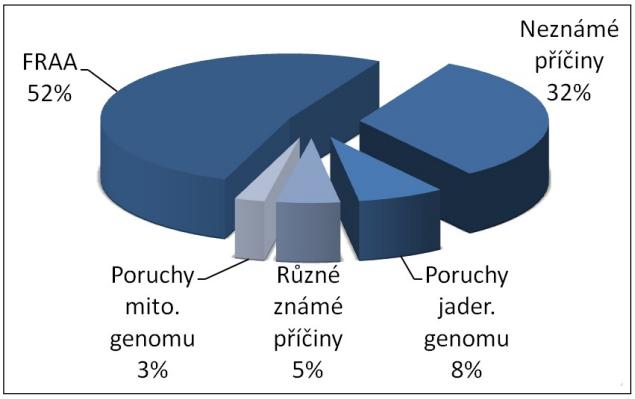
Počet pacientů		*Účinnost léčby*		*Etiologie*	*Ref.*
Celkem	*PAS*	*ND*	*PAS*		
5	n/a	5	n/a	n/a	[40]
20	7	n/a	n/a	n/a	[41]
1	1	1	0	n/a	[43]
1	n/a	1	n/a	n/a	[44]
28	4	18	2	FRAA	[2]
4	n/a	4	n/a	Rett	[45]
1	n/a	1	n/a	KSS	[46]
25	25	n/a	n/a	FRAA	[47]
14	n/a	n/a	n/a	FRAA	[48]
1	n/a	0	n/a	n/a	[49]
24	10	n/a	6	FRAA	[3]
7	5	4	4	různá	[4]
1	n/a	0	n/a	n/a	[50]
1	0	0	n/a	Alper	[51]
6	n/a	n/a	n/a	KSS	[52]
103	4	68	n/a	různá	[53]
1	0	n/a	n/a	FOLR1	[54]
3	0	2	0	DHFR	[55]
3	2	n/a	n/a	DHFR	[56]
1	0	0	0	n/a	[57]
1	1	0	0	FRAA	[58]
2	1	2	1	n/a	[5]
1	0	n/a	n/a	FRAA	[59]
1	n/a	1	n/a	MTHFR	[60]
2	1	2	1	FOLR1	[7]
1	0	1	0	SLC46A1	[61]
93	93	93	31	FRAA	[6]
351	**154**	**203**	**45**	**CELKEM**	

Závěry

Nalezli jsme celkem 351 publikovaných případů CFD v letech 2002 – 2014 (1). S ohledem na skladbu autorů nelze vyloučit, že určitá, menší část případů, byla publikována opakovaně. PAS byla popsána u 44% pacientů, řada studií však neuvádí, zda byli pacienti cíleně podrobeni diferenciálně diagnostickému vyšetření na PAS. Navíc, u velmi těžkých případů CFD, nebylo diagnostické vyšetření PAS prakticky možné. Řada z uvedených studií uvádí v anamnéze pacientů poruchy sociální interakce a komunikace. Je možné, že celkový podíl pacientů s PAS byl tedy vyšší než 44%. Variabilní pozitivní účinek na jádrové symptomy PAS (komunikace, sociální interakce, ...) byl hlášen u 29% pacientů s PAS a CFD. U většiny pacientů byl aplikován 5-FTHT v monoterapii, kombinovaná léčba byla použita ojediněle [54],[60].

Terapie pomocí 5-FTHF je primárně symptomatická. Především u těžších neurologických deficitů dochází k částečné úpravě stavu v poměrně krátké době, nicméně část případů vykazuje další postupné zlepšení při dlouhodobém podávání. Efekt je možné vysvětlit širokou metabolickou rolí folátů zahrnující význam jak pro funkci (syntéza neurotransmiterů, hormonů, metabolismus aminokyselin, ...), tak pro strukturu (syntéza sfingomyelinů, protektivní antioxidační účinek, methylace DNA, ...) CNS. Podávání 5-FTHT neovlivňuje hladiny FRAA. Nežádoucí účinky léčby jsou hodnoceny většinou jako méně časté a mírné – poruchy spánku, zvýšení hyperaktivity [6]. U pacientů s epilepsií může léčba v některých případech zvyšovat incidenci záchvatů [60]. U pacientů léčených Risperidonem se podáním 5-FTHF může opětovně zvyšovat agresivita [6]. U některých sdružených genetických poruch bylo léčbu pro silný proepileptický efekt nutno doplnit o další medikaci (pyridoxal-5-fosfát, ...). Komplexní studie léčby mírného CFD na symptomy PAS, kontrolovaná placebem, hodnotící účinnost a bezpečnost léčby 5-FTHT nebo 5-MTHF, zatím nebyla publikována. Stejně tak chybí dlouhodobá studie vlivu různých společně či po sobě působících subklinických nox narušujících folátový metabolismus lokálně v CNS během kritických období prenatálního a raného postnatálního vývoje.

Nejčastější publikovanou příčinou CFD je přítomnost FRAA, druhou největší skupinu tvoří CFD neznámé etiologie. Minoritní zbytek tvoří většinou genetické poruchy (2). Výrazně zvýšené titry FRAA rezultují v typický obraz CFD, nicméně významnost mírně zvýšených hladin FRAA v patofyziologii PAS zatím není přesně známa, i když řada pacientů na léčbu reagovala pozitivně (1).



Obrázek 2: Základní etiologická skladba CFD.

Diskuze

Narušení folátového a na folátu závislého metabolismu lokalizovaného pouze v CNS je u PAS poměrně těžce diagnostikovatelné. Jedinou dostupnou a zcela spolehlivou metodou je lumbální punkce s vyšetřením hladiny 5-MTHF v likvoru, která není u pacientů s PAS pro svou in-

vazivitu běžně indikována. Méně invazivní metody, jako je MR spektroskopie nemá dnes potřebnou rozlišovací schopnost v řádech nmol/l. Vyšetření FRAA je dostupné pouze v několika málo laboratořích na světě. Nelze tedy vyloučit, že mírný CFD u PAS dlouhodobě uniká pozornosti v diagnostice i terapii a že může přispívat ke vzniku a rozvoji idiopatické PAS. Tyto poruchy jsou částečně či ojediněle zcela kompenzovatelné. Přestože první nálezy PAS u CFD byly identifikovány před 10 lety a prevalence PAS se odhaduje na $0,1\breve{}1,5\%$, nalezli jsme jen několik desítek publikovaných případů (1).

Prevalence mírného CFD u PAS zatím není dostatečně zmapována, stejně jako podíl jednotlivých příčin. Důvodem je velmi malá testovaná populace (celkem 351 publikovaných případů). Ani účinek léčby mírného CFD na symptomy zatím nebyl dostatečně prozkoumán a zdokumentován. Publikované výsledky však jasně ukazují na nutnost dalšího výzkumu v této oblasti především proto, že PAS je v současné době považován za neléčitelnou celoživotní poruchu většinou neznámé etiologie s vysokým socioekonomickým dopadem. U pacientů s PAS a zároveň prokázaným CFD bylo opakovaně popsáno zlepšení neurologických symptomů i symptomů typických pro PAS. Řada publikací ukazuje na negativní korelaci mezi věkem pacienta a účinností léčby. Včasná intervence se tedy zdá být zásadní.

Potenciální význam folátového metabolismu dokresluje také fakt, že byly publikovány studie terapie PAS založené na podávání látek, jejichž syntéza či hladina je na folátech přímo či nepřímo závislá nebo je folátem regulována, případně fungují jako kofaktory ve folátových drahách (2).

Tabulka 2: Další experimentální terapie PAS založené na podávání látek metabolicky související s folátem.

Látka	*Publikace*	*Zdroj*
melatonin	18 klinických studií	[18]
tetrahydrobiopterin	4 klinické studie	[62]
cobalamin	1 klinická studie	[63]
pyridoxin	3 studie	[64]
cholin	1 animal studie	[65]
antioxidanty	4 klinické studie	[62]
SSRI	9 studií	[66]

Velká část etiologie CFD (32%), význam mírného CFD pro rozvoj PAS a souvislost s dalšími potenciálními noxami, jako je oxidativní stres, exogenní intoxikace, infekce a další, směřují k nutnosti dalšího výzkumu epigenetických vlivů. Předpokládáme, že etiologie PAS může být významně spojena se synergistickým působením více epigenetických vlivů, které se společně manifestují jako neurobehaviorální syndrom, ale samostatně představují subklinické, nemanifestní noxy. Výzkum uvedené hypotézy je zcela na místě. Případné potvrzení by výrazně ovlivnilo klinický výzkum farmakoterapie PAS dle pravidel medicíny založené na důkazech. Heterogenní příčiny, které se mohou vyskytovat současně a vzájemně se synergisticky posilovat, pokud nejsou zkoumány všechny najednou, prakticky znemožňují správně vybrat testovací skupinu. Smíšená testovací skupina složená z více vzájemně nerozlišených fenotypů PAS, by ovlivnila výsledek každé studie náhodným způsobem a mezi výsledky studií by byly vždy výrazné rozdíly. Postupně by bylo možné identifikovat pouze dominantní příčiny, jak se tomu zdá být u závažného CFD na podkladě FRAA.

Naopak, pokud by bylo možné identifikovat a klasifikovat jednotlivé, samostatně nevýznamné, ale společně manifestní noxy, výrazně by to přispělo k identifikaci nových etiologií PAS a ke klasifikaci příslušných fenotypů. Identifikace a klasifikace mnoha příčin, patologií a jejich vzájemných souvislostí napříč specializacemi interní medicíny, neurologie, genetiky a psychiatrie si však zřejmě vyžaduje specifický přístup k zachycení problematiky a potřebu strukturovaného modelování informací a znalostí s využitím aparátu ontologií a formálních jazyků. Užitných aplikací takového širšího informačního modelu je celá řada: standardizace vyšetřovacích panelů, interdisciplinární podpora rozhodování v diagnostice, základ pro screening fragilní populace rodičů i dětí s vyšším rizikem rozvoje PAS, sběr dat pro vzájemně srovnatelný výzkum, interoperabilní profilový elektronický zdravotní záznam pro výměnu dat a další.

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Reference

[1] Z. Sedlacek and M. Havlovicova, "Detsky autismus,"in Detsky autismus, 1st ed., M. Hrdlicka and V. Komárek, Eds. Praha: Portál s.r.o., 2004, pp. 130–137.

[2] V. T. Ramaekers, S. P. Rothenberg, J. M. Sequeira, T. Opladen, N. Blau, E. V Quadros, and J. Selhub, "Autoantibodies to folate receptors in the cerebral folate deficiency syndrome.,"N. Engl. J. Med., vol. 352, no. 19, pp. 1985–1991, May 2005.

[3] V. T. Ramaekers, J. M. Sequeira, N. Blau, and E. V Quadros, "A milk-free diet downregulates folate receptor autoimmunity in cerebral folate deficiency syndrome.,"Dev. Med. Child Neurol., vol. 50, no. 5, pp. 346–52, May 2008.

[4] P. Moretti, S. U. Peters, D. Del Gaudio, T. Sahoo, K. Hyland, T. Bottiglieri, R. J. Hopkin, E. Peach, S. H. Min, D. Goldman, B. Roa, C. a Bacino, and F. Scaglia, "Brief report: autistic symptoms, developmental regression, mental retardation, epilepsy, and dyskinesias in CNS folate deficiency.,"J. Autism Dev. Disord., vol. 38, no. 6, pp. 1170–1177, Jul. 2008.

[5] S. U. Steele, S. M. Cheah, A. Veerapandiyan, W. Gallentine, E. C. Smith, and M. A. Mikati, "Electroencephalographic and seizure manifestations in two patients with folate receptor autoimmune antibody-mediated primary cerebral folate deficiency.,"Epilepsy Behav., vol. 24, no. 4, pp. 507–12, Aug. 2012.

[6] R. E. Frye, J. M. Sequeira, E. V Quadros, S. J. James, and D. A. Rossignol, "Cerebral folate receptor autoantibodies in autism spectrum disorder.,"Mol. Psychiatry, vol. 18, no. 3, pp. 369–81, Mar. 2013.

[7] R. S. Al-Baradie and M. W. Chaudhary, "Diagnosis and management of cerebral folate deficiency. A form of folinic acid-responsive seizures.,"Neurosciences (Riyadh)., vol. 19, no. 4, pp. 312–6, Oct. 2014.

[8] R. Zhao and I. D. Goldman, "Folate and thiamine transporters mediated by facilitative carriers (SLC19A1-3 and SLC46A1) and folate receptors.,"Mol. Aspects Med., vol. 34, no. 2–3, pp. 373–85, 2013.

[9] I. Ifergan, G. Jansen, and Y. G. Assaraf, "The reduced folate carrier (RFC) is cytotoxic to cells under conditions of severe folate deprivation. RFC as a double edged sword in folate homeostasis.,"J. Biol. Chem., vol. 283, no. 30, pp. 20687–95, 2008.

[10] H. Yuasa, K. Inoue, and Y. Hayashi, "Molecular and functional characteristics of proton-coupled folate transporter.,"J. Pharm. Sci., vol. 98, no. 5, pp. 1608–16, May 2009.

[11] J. B. Wollack, B. Makori, S. Ahlawat, R. Koneru, S. C. Picinich, A. Smith, I. D. Goldman, A. Qiu, P. D. Cole, J. Glod, and B. Kamen, "Characterization of folate uptake by choroid plexus epithelial cells in a rat primary culture model.,"J. Neurochem., vol. 104, no. 6, pp. 1494–503, Mar. 2008.

[12] K. Hyland, J. Shoffner, and S. J. Heales, "Cerebral folate deficiency.,"J. Inherit. Metab. Dis., vol. 33, no. 5, pp. 563–70, Oct. 2010.

[13] A. Ormazabal, A. García-Cazorla, B. Pérez-Due?as, V. Gonzalez, E. Fernández-Alvarez, M. Pineda, J. Campistol, and R. Artuch, "Determination of 5-methyltetrahydrofolate in cerebrospinal fluid of paediatric patients: reference values for a paediatric population.,"Clin. Chim. Acta., vol. 371, no. 1–2, pp. 159–162, 2006.

[14] S. A. Lawrence, S. A. Titus, J. Ferguson, A. L. Heineman, S. M. Taylor, and R. G. Moran, "Mammalian Mitochondrial and Cytosolic Folylpolyglutamate Synthetase Maintain the Subcellular Compartmentalization of Folates.,"J. Biol. Chem., Aug. 2014.

[15] K. Pietrzik, L. Bailey, and B. Shane, "Folic acid and L-5-methyltetrahydrofolate: comparison of clinical pharmacokinetics and pharmacodynamics.,"Clin. Pharmacokinet., vol. 49, no. 8, pp. 535–48, Aug. 2010.

[16] M. Serrano, B. Pérez-Due?as, J. Montoya, A. Ormazabal, and R. Artuch, "Genetic causes of cerebral folate deficiency: clinical, biochemical and therapeutic aspects.,"Drug Discov. Today, vol. 17, no. 23–24, pp. 1299–306, Dec. 2012.

[17] J. Kaluzna-Czaplińska, E. Zurawicz, M. Michalska, and J. Rynkowski, "A focus on homocysteine in autism.,"Acta Biochim. Pol., vol. 60, no. 2, pp. 137–142, 2013.

[18] D. A. Rossignol and R. E. Frye, "Melatonin in autism spectrum disorders: a systematic review and meta-analysis.,"Dev. Med. Child Neurol., vol. 53, no. 9, pp. 783–92, Sep. 2011.

[19] V. Ramaekers, J. M. Sequeira, and E. V Quadros, "Clinical recognition and aspects of the cerebral folate deficiency syndromes.,"Clin. Chem. Lab. Med., vol. 51, no. 3, pp. 497–511, Mar. 2013.

[20] A. Y. Hardan, N. J. Minshew, N. M. Melhem, S. Srihari, B. Jo, R. Bansal, M. S. Keshavan, and J. A. Stanley, "An MRI and proton spectroscopy study of the thalamus in children with autism.,"Psychiatry Res., vol. 163, no. 2, pp. 97–105, 2008.

[21] J. C. Hamlin, M. Pauly, S. Melnyk, O. Pavliv, W. Starrett, T. A. Crook, and S. J. James, "Dietary intake and plasma levels of choline and betaine in children with autism spectrum disorders.,"Autism Res. Treat., vol. 2013, p. 578429, Jan. 2013.

[22] Z. Luka, S. Pakhomova, L. V Loukachevitch, M. E. Newcomer, and C. Wagner, "Folate in demethylation: the crystal structure of the rat dimethylglycine dehydrogenase complexed with tetrahydrofolate.,"Biochem. Biophys. Res. Commun., vol. 449, no. 4, pp. 392–8, 2014.

[23] T. J. de Koning, K. Snell, M. Duran, R. Berger, B.-T. Poll-The, and R. Surtees, "L-serine in disease and development.,"Biochem. J., vol. 371, no. Pt 3, pp. 653–61, May 2003.

[24] R. Savoca, U. Ziegler, and P. Sonderegger, "Effects of L-serine on neurons in vitro.,"J. Neurosci. Methods, vol. 61, no. 1–2, pp. 159–67.

[25] S. Furuya, J. Mitoma, A. Makino, and Y. Hirabayashi, "Ceramide and its interconvertible metabolite sphingosine function as indispensable lipid factors involved in survival and dendritic differentiation of cerebellar Purkinje cells.,"J. Neurochem., vol. 71, no. 1, pp. 366–77, Jul. 1998.

[26] A. L. Miller, "The methylation, neurotransmitter, and antioxidant connections between folate and depression.,"Altern. Med. Rev., vol. 13, no. 3, pp. 216–226, 2008.

[27] C. Pagan, R. Delorme, J. Callebert, H. Goubran-Botros, F. Amsellem, X. Drouot, C. Boudebesse, K. Le Dudal, N. Ngo-Nguyen, H. Laouamri, C. Gillberg, M. Leboyer, T. Bourgeron, and J.-M. Launay, "The serotonin-N-acetylserotonin-melatonin pathway as a biomarker for autism spectrum disorders.,"Transl. Psychiatry, vol. 4, p. e479, Jan. 2014

[28] W.-H. Yang, J. Jing, L.-J. Xiu, M.-H. Cheng, X. Wang, P. Bao, and Q.-X. Wang, "Regional cerebral blood flow in children with autism spectrum disorders: a quantitative 99mTc-ECD brain SPECT study with statistical parametric mapping evaluation.,"Chin. Med. J. (Engl)., vol. 124, no. 9, pp. 1362–1366, May 2011.

[29] M. Sasaki, E. Nakagawa, K. Sugai, Y. Shimizu, A. Hattori, Y. Nonoda, and N. Sato, "Brain perfusion SPECT and EEG findings in children with autism spectrum disorders and medically intractable epilepsy.,"Brain Dev., vol. 32, no. 9, pp. 776–782, 2010.

[30] S. K. Gupta and B. V. Ratnam, "Cerebral perfusion abnormalities in children with autism and mental retardation: a segmental quantitative SPECT study.,"Indian Pediatr., vol. 46, no. 2, pp. 161–164, Feb. 2009.

[31] M. E. Hyndman, S. Verma, R. J. Rosenfeld, T. J. Anderson, and H. G. Parsons, "Interaction of 5-methyltetrahydrofolate and tetrahydrobiopterin on endothelial function.,"Am. J. Physiol. Heart Circ. Physiol., vol. 282, no. 6, pp. H2167–72, Jun. 2002.

[32] A. Ghanizadeh, M. Berk, H. Farrashbandi, A. Alavi Shoushtari, and K.-A. Villagonzalo, "Targeting the mitochondrial electron transport chain in autism, a systematic review and synthesis of a novel therapeutic approach.,"Mitochondrion, vol. 13, no. 5, pp. 515–9, Sep. 2013.

[33] D. Pu, Y. Shen, and J. Wu, "Association between MTHFR gene polymorphisms and the risk of autism spectrum disorders: a meta-analysis.,"Autism Res., vol. 6, no. 5, pp. 384–92, Oct. 2013.

[34] M. Adams, M. Lucock, J. Stuart, S. Fardell, K. Baker, and X. Ng, "Preliminary evidence for involvement of the folate gene polymorphism 19bp deletion-DHFR in occurrence of autism.,"Neurosci. Lett., vol. 422, no. 1, pp. 24–9, 2007.

[35] B. Pérez-Due?as, C. Toma, A. Ormazábal, J. Muchart, F. Sanmartí, G. Bombau, M. Serrano, A. García-Cazorla, B. Cormand, and R. Artuch, "Progressive ataxia and myoclonic epilepsy in a patient with a homozygous mutation in the FOLR1 gene.,"J. Inherit. Metab. Dis., vol. 33, no. 6, pp. 795–802, Dec. 2010.

[36] D. Siniscalco, A. Cirillo, J. J. Bradstreet, and N. Antonucci, "Epigenetic findings in autism: new perspectives for therapy.,"Int. J. Environ. Res. Public Health, vol. 10, no. 9, pp. 4261–4273, 2013.

[37] L. Thompson, M. Thompson, and A. Reid, "Functional neuroanatomy and the rationale for using EEG biofeedback for clients with Asperger's syndrome.,"Appl. Psychophysiol. Biofeedback, vol. 35, no. 1, pp. 39–61, 2010.

[38] S. Mamrut, H. Harony, R. Sood, H. Shahar-Gold, H. Gainer, Y.-J. Shi, L. Barki-Harrington, and S. Wagner, "DNA methylation of specific CpG sites in the promoter region regulates the transcription of the mouse oxytocin receptor.,"PLoS One, vol. 8, no. 2, p. e56869, Jan. 2013.

[39] L. Zhu, X. Wang, X.-L. Li, A. Towers, X. Cao, P. Wang, R. Bowman, H. Yang, J. Goldstein, Y.-J. Li, and Y.-H. Jiang, "Epigenetic dysregulation of SHANK3 in brain tissues from individuals with autism spectrum disorders.,"Hum. Mol. Genet., vol. 23, no. 6, pp. 1563–78, Mar. 2014.

[40] V. T. Ramaekers, M. Häusler, T. Opladen, G. Heimann, and N. Blau, "Psychomotor retardation, spastic paraplegia, cerebellar ataxia and dyskinesia associated with low 5-methyltetrahydrofolate in cerebrospinal fluid: a novel neurometabolic condition responding to folinic acid substitution.,"Neuropediatrics, vol. 33, no. 6, pp. 301–8, Dec. 2002.

[41] V. T. Ramaekers and N. Blau, "Cerebral folate deficiency.,"Dev. Med. Child Neurol., vol. 46, no. 12, pp. 843–51, Dec. 2004.

[42] V. T. Ramaekers, S. I. Hansen, J. Holm, T. Opladen, J. Senderek, M. Häusler, G. Heimann, B. Fowler, R. Maiwald, and N. Blau, "Reduced folate transport to the CNS in female Rett patients.,"Neurology, vol. 61, no. 4, pp. 506–15, Aug. 2003.

[43] P. Moretti, T. Sahoo, K. Hyland, T. Bottiglieri, S. Peters, D. del Gaudio, B. Roa, S. Curry, H. Zhu, R. H. Finnell, J. L. Neul, V. T. Ramaekers, N. Blau, C. A. Bacino, G. Miller, and F. Scaglia, "Cerebral folate deficiency with developmental delay, autism, and response to folinic acid.,"Neurology, vol. 64, no. 6, pp. 1088–90, Mar. 2005.

[44] F. J. Hansen and N. Blau, "Cerebral folate deficiency: life-changing supplementation with folinic acid.,"Mol. Genet. Metab., vol. 84, no. 4, pp. 371–373, Apr. 2005.

[45] A. Ormazabal, A. García Cazorla, B. Pérez Due?as, M. Pineda, A. Ruiz, E. López Laso, M. García Silva, I. Carilho, C. Barbot, B. Cormand, M. Ribases, L. Moller, E. Fernández Alvarez, J. Campistol, R. Artuch, A. Garc'ia Cazorla, and M. Garc'ia Silva, "[Usefulness of analysis of cerebrospinal fluid for the diagnosis of neurotransmitters and pterin defects and glucose and folate transport deficiencies across blood brain barrier].,"Med. Clin. (Barc)., vol. 127, no. 3, pp. 81–5, Jun. 2006.

[46] M. Pineda, A. Ormazabal, E. López-Gallardo, A. Nascimento, A. Solano, M. D. Herrero, M. A. Vilaseca, P. Briones, L. Ibá?ez, J. Montoya, and R. Artuch, "Cerebral folate deficiency and leukoencephalopathy caused by a mitochondrial DNA deletion.,"Ann. Neurol., vol. 59, no. 2, pp. 394–398, Feb. 2006.

[47] V. T. Ramaekers, N. Blau, J. M. Sequeira, M.-C. Nassogne, and E. V Quadros, "Folate receptor autoimmunity and cerebral folate deficiency in low-functioning autism with neurological deficits.,"Neuropediatrics, vol. 38, no. 6, pp. 276–81, Dec. 2007.

[48] V. T. Ramaekers, J. M. Sequeira, R. Artuch, N. Blau, T. Temudo, A. Ormazabal, M. Pineda, A. Aracil, F. Roelens, F. Laccone, and E. V Quadros, "Folate receptor autoantibodies and spinal fluid 5-methyltetrahydrofolate deficiency in Rett syndrome.,"Neuropediatrics, vol. 38, no. 4, pp. 179–83, Aug. 2007.

[49] S. Mercimek-Mahmutoglu and S. Stockler-Ipsiroglu, "Cerebral folate deficiency and folinic acid treatment in hypomyelination with atrophy of the basal ganglia and cerebellum (H-ABC) syndrome.,"Tohoku J. Exp. Med., vol. 211, no. 1, pp. 95–6; author reply 97, Jan. 2007.

[50] J. L. Bonkowsky, V. T. Ramaekers, E. V Quadros, and M. Lloyd, "Progressive encephalopathy in a child with cerebral folate deficiency syndrome.,"J. Child Neurol., vol. 23, no. 12, pp. 1460–3, Dec. 2008.

[51] O. Hasselmann, N. Blau, V. T. Ramaekers, E. V Quadros, J. M. Sequeira, and M. Weissert, "Cerebral folate deficiency and CNS inflammatory markers in Alpers disease.,"Mol. Genet. Metab., vol. 99, no. 1, pp. 58–61, Jan. 2010.

[52] M. Serrano, M. T. García-Silva, E. Martin-Hernandez, M. del M. O'Callaghan, P. Quijada, A. Martinez-Aragón, A. Ormazábal, A. Blázquez, M. A. Martín, P. Briones, E. López-Gallardo, E. Ruiz-Pesini, J. Montoya, R. Artuch, and M. Pineda, "Kearns-Sayre syndrome: cerebral folate deficiency, MRI findings and new cerebrospinal fluid biochemical features.,"Mitochondrion, vol. 10, no. 5, pp. 429–32, Aug. 2010.

[53] S. Mangold, N. Blau, T. Opladen, R. Steinfeld, B. Wessling, K. Zerres, and M. Häusler, "Cerebral folate deficiency: a neurometabolic syndrome?,"Mol. Genet. Metab., vol. 104, no. 3, pp. 369–72, Nov. 2011.

[54] P. Dill, J. Schneider, P. Weber, D. Trachsel, M. Tekin, C. Jakobs, B. Thöny, and N. Blau, "Pyridoxal phosphate-responsive seizures in a patient with cerebral folate deficiency (CFD) and congenital deafness with labyrinthine aplasia, microtia and microdontia (LAMM).,"Mol. Genet. Metab., vol. 104, no. 3, pp. 362–8, Nov. 2011.

[55] S. Banka, H. J. Blom, J. Walter, M. Aziz, J. Urquhart, C. M. Clouthier, G. I. Rice, A. P. M. de Brouwer, E. Hilton, G. Vassallo, A. Will, D. E. C. Smith, Y. M. Smulders, R. A. Wevers, R. Steinfeld, S. Heales, Y. J. Crow, J. N. Pelletier, S. Jones, and W. G. Newman, "Identification and characterization of an inborn error of metabolism caused by dihydrofolate reductase deficiency.,"Am. J. Hum. Genet., vol. 88, no. 2, pp. 216–25, Feb. 2011.

[56] H. Cario, D. E. C. Smith, H. Blom, N. Blau, H. Bode, K. Holzmann, U. Pannicke, K.-P. Hopfner, E.-M. Rump, Z. Ayric, E. Kohne, K.-M. Debatin, Y. Smulders, and K. Schwarz, "Dihydrofolate reductase deficiency due to a homozygous DHFR mutation causes megaloblastic anemia and cerebral folate deficiency leading to severe neurologic disease.,"Am. J. Hum. Genet., vol. 88, no. 2, pp. 226–31, Feb. 2011.

[57] V. Leuzzi, M. Mastrangelo, A. Celato, and C. Carducci, "A new form of cerebral folate deficiency with severe self-injurious behaviour.,"Acta Paediatr., vol. 101, no. 11, pp. e482–3, Nov. 2012.

[58] Z. Sadighi, I. J. Butler, and M. K. Koenig, "Adult-onset cerebral folate deficiency.,"Arch. Neurol., vol. 69, no. 6, pp. 778–779, 2012.

[59] A. Ho, D. Michelson, G. Aaen, and S. Ashwal, "Cerebral folate deficiency presenting as adolescent catatonic schizophrenia: a case report.,"J. Child Neurol., vol. 25, no. 7, pp. 898–900, 2010.

[60] Q. Wang, J. Liu, Y.-P. Liu, X.-Y. Li, Y.-Y. Ma, T.-F. Wu, Y. Ding, J.-Q. Song, Y.-J. Wang, and Y.-L. Yang, "[Methylenetetrahydrofolate reductase deficiency-induced schizophrenia in a school-age boy].,"Zhongguo Dang Dai Er Ke Za Zhi, vol. 16, no. 1, pp. 62–6, Jan. 2014.

[61] Q. Wang, X. Li, Y. Ding, Y. Liu, Y. Qin, and Y. Yang, "The first Chinese case report of hereditary folate malabsorption with a novel mutation on SLC46A1.,"Brain Dev., 2014.

[62] R. E. Frye and D. A. Rossignol, "Treatments for biomedical abnormalities associated with autism spectrum disorder.,"Front. Pediatr., vol. 2, p. 66, Jan. 2014.

[63] K. Bertoglio, S. Jill James, L. Deprey, N. Brule, and R. L. Hendren, "Pilot study of the effect of methyl B12 treatment on behavioral and biomarker measures in children with autism.,"J. Altern. Complement. Med., vol. 16, no. 5, pp. 555–560, May 2010.

[64] R. E. Frye, D. Rossignol, M. F. Casanova, G. L. Brown, V. Martin, S. Edelson, R. Coben, J. Lewine, J. C. Slattery, C. Lau, P. Hardy, S. H. Fatemi, T. D. Folsom, D. Macfabe, and J. B. Adams, "A Review of Traditional and Novel Treatments for Seizures in Autism Spectrum Disorder: Findings from a Systematic Review and Expert Panel.,"Front. public Heal., vol. 1, p. 31, 2013.

[65] E. A. Langley, M. Krykbaeva, J. K. Blusztajn, and T. J. Mellott, "High maternal choline consumption during pregnancy and nursing alleviates deficits in social interaction and improves anxiety-like behaviors in the BTBR T+Itpr3tf/J mouse model of autism.,"Behav. Brain Res., Oct. 2014.

[66] K. Williams, A. Brignell, M. Randall, N. Silove, and P. Hazell, "Selective serotonin reuptake inhibitors (SSRIs) for autism spectrum disorders (ASD).,"Cochrane database Syst. Rev., vol. 8, p. CD004677, Jan. 2013.

Úvod jak přijímat technologie

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Abstrakt

Článek uvádí řadu přístupů jak přijímat technologie a zajistit spokojenost uživatelů. Sama spokojenost uživatele nepředpovídá dobře přijetí a užití systému, ale je dobrým vodítkem při vytváření návrhu systému. Současné informační systémy jsou stále nedostatečně využívány. Aplikace modelů pro přijetí technologie uživatelem může poskytnout důležité poznatky pro zvýšení využití systémů. Zvlášť významné jsou modely integrující spokojenost uživatelů a přijetí technologie. Závěrem uvádíme různé uživatelské technologie podporující přijetí modelů.

Klíčová slova

Informační technologie, zdravotnictví, spokojenost uživatele, přijetí technologie, integrace

Klinické algoritmy: účel, obsah, pravidla a benefity

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Abstrakt

Článek popisuje výhody a nevýhody klinických algoritmů v grafickém formátu vývojového diagramu, jejich návrh a symboliku, aktuální využití v klinické praxi, implementaci na počítačích, software použitý při jejich tvorbě, návrhy pro mezinárodní standardy klinických algoritmů a nové návrhy pro jejich zapracování do dalších algoritmů.

V článku jsou uvedena podrobná pravidla a postupy pro kreslení vývojových diagramů. Je vysvětlen význam klinických algoritmů v medicíně a uvedeny příklady dobře navržených algoritmů.

Klíčová slova

Algoritmy, klinické algoritmy, rozhodování, vývojový diagram, medicína

Mezinárodní pohled na výuku a vzdělávání v telemedicíně

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Abstrakt

Zdravotní péče je založena na datech o pacientech. Lékař nebo zdravotní sestra (zdravotnický asistent) jsou schopni interpretovat data pacientů potřebná pro diagnostiku a léčbu s využitím výuky, vzdělávání, znalostí a zkušeností. Zdravotní péče je závislá na dobrém vzdělání s ohledem na správu dat, informace a znalosti. Mezinárodní aktivity ukazují možnosti dosažení dobré úrovně vzdělání.

K těmto možnostem patří kritéria pro návrh učebních osnov a akreditaci, kvalita informačních systémů, dále zkušenosti se srozumitelnou koncepcí vzdělávání v Anglii nebo přístup 10x10 ve Spojených státech.

Klíčová slova

Výchova, vzdělávání, zdravotní informatika, medicínská informatika, EFMI, EuroRec, IMIA, doporučení, akreditace

Elektronický zdravotní záznam v zubním lékařství

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Abstrakt

Strukturovaná reprezentace informací v elektronickém zdravotním záznamu je důležitá pro opětovné použití informací při podpoře lékařského rozhodování, statistické analýze dat, interoperabilitě a automatickém rozpoznávání řeči.

Článek prezentuje význam uživatelského rozhraní s interaktivní komponentou zubního kříže (DentCross), která slouží k vývoji celoživotního elektronického orálního zdravotního záznamu.

Klíčová slova

Elektronický zdravotní záznam, zubní lékařství, orální zdraví

Mezinárodní setkání EuroMISE 2015 (IJM EuroMISE 2015)

16.-18. června 2015, Praha, Česká republika

Hlavní pořadatel setkání IJM EuroMISE 2015: EuroMISE Mentor Association

Garant: Jana Zvárová, Česká republika

Setkání IJM 2005 sestává z následujících částí:

1 Mezinárodní konference

BIG DATA CHALLENGES FOR PERSONALISED MEDICINE

Středa, 17. června 2015, Garant: Pirkko Nykänen, Finsko

2 Mezinárodní symposium

INFORMATION – BASED PREVENTION IN HEALTHCARE

Úterý, 16. června 2015, Garant: Milan Tuček, Česká republika

3 Mentoringový kurz

BIG DATA – ANALYSIS AND MODELLING CHALLENGES

Úterý, 16. června 2015 (odpoledne) Garant: Pirkko Nykänen, Finsko

4 Mentoringový kurz

INTRODUCTION TO TECHNOLOGY ACCEPTANCE

Čtvrtek 18. června 2015 (dopoledne) Garant: Arie Hasman, Nizozemsko