

AUTISM – DISORDER OF EARLY BRAIN DEVELOPMENT EARLY DIAGNOSTICS OF AUTISM – THE COMMON MULTIDISCIPLINARY GOAL.

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Abstract: *Due to its high prevalence (60-70 in 10 000 born children) autism (also known as pervasive development disorders) belongs to the most frequently occurring neurodevelopmental disorders. The group includes disorders with extremely heterogeneous clinical phenotypes of multiple complex cognitive-behavioral deficits with developmental specificities that are manifested during childhood by the age of 6 at the latest. The diagnostic process as well as subsequent care of the child and its family members are conducted by a multidisciplinary team of specialists, embracing physicians, university graduates with non-medical education as well as parents, relatives and the lay public in general. With regard to physicians, the pediatric, pediatric neurologist, pediatric psychiatrist, ophthalmologist and otorhinolaryngologist are involved. The role of the pediatric neurologist is to participate in early diagnosing of a disorder, make the differential diagnostics and conduct therapy of the related neurological co-morbidities, mainly represented by epilepsy.*

Keywords: *autism, pervasive developmental disorders, neurodevelopmental disorders, pediatric neurologist, early diagnostics, epilepsy*

Introduction

The “autistic spectrum“ (i.e. autism spectrum disorders - ASD, abbreviated as “autism”, derived from the Greek word “autos“), now also termed “pervasive neurodevelopmental disorders“ - PDD, or “autisms“ are currently classified as disorders of the developing brain (i.e. neurodevelopmental disorders - NDD). The group includes disorders with extremely heterogeneous clinical phenotypes of multiple complex cognitive-behavioral deficits with developmental specificities that are manifested during childhood by the age of 6 at the latest. There are three dominant groups of clinical symptoms: deficits in social capabilities and interactions, deficits in verbal and non-verbal reciprocal communication and a limited stereotyped repertory of activities and interests. As a result, the

disorder completely and deeply changes the cognitive-behavioral phenotype as well as development of affected children (Rapin and Tuchman; 2006). Within the spectrum of autistic children boys are affected more frequently, roughly at a ratio of 2-4 boys to 1 girl, and if a mental handicap is not present at the same time, such as in the case of Asperger's syndrome, the rate is higher (Fombonne; 2005). If, however, autism occurs in girls, its nature is more serious (Hirtz et al; 2006). Autism without an intellect impact and with good social functionality is known as "high-functioning" (De Mayer; 1981).

As there is still no unique or specific diagnostic biological marker known, the ASD diagnostics (except for the Rett syndrome) is established at the level of a clinical cognitive-behavioral syndrome (phenomenological classification). In the Czech Republic this is based on the diagnostic criteria of the International Health Organization, MKN-10th. revision (WHO; 1992, MKN-10; 1992) and in the U.S.A. on Revision IV of the Diagnostic and Statistic Mental Disease Manual (DSM-IV; 1994).

Epidemiology of autism

Autism has now become a widespread social problem and surely is not a rare illness. The incidence of children with autism (specifically I mean the complete spectrum of the pervasive developmental disorders = "autisms") is on the rise. Up until the 1980s the prevalence reported was 1 autistic child in 40 000, but according to more recent information it has risen to 1 in 150 children (Rapin and Tuchman; 2008, Baird; 2006). The mentioned increase in prevalence, called "epidemic of autism" by some, probably does not indicate any actual increase. The seeming is apparently caused mainly by the increase of interest among the professional public and an improved awareness among both professionals and laymen, but also by broadening of the diagnostic criteria and greater availability of diagnostics. There was not even the serious suspicion confirmed that the increase of autism incidence might be causally connected with vaccination (Fombonne et al; 2006), including, too, the case of autistic regression in toddlers (Woo et al; 2007).

The role of pediatric neurologist within the multidisciplinary diagnostic and therapeutic management of autism.

Although a child with autism frequently appears healthy at first sight, the disorder affecting them is in fact serious and "pervasive", with profound individual and social impacts both in childhood and adulthood (Anagnostou and Schevell; 2006). Within recent decades it was parents, family members and other laymen, who together with pedagogical and social workers, speech therapists and professionals in many medical as well as non-medical fields have pointed to it and, by joined forces, have achieved a significant broadening of awareness concerning autism among both professional and lay public. Physicians, further university-educated specialists and laymen now take part in the care of autistic children in the Czech and Slovak republics. Children with autism are placed in state and non-state schools with special pedagogical guidance after the diagnostic process completion, and social support is also enhanced by numerous parent organizations.

In the modern management of autism an important role in the multidisciplinary team belongs to the pediatric neurologist. The benefit of the specialism is particularly significant with regard to differential diagnostics of the broader context of “symptomatic or syndromic“ autism, and further in its early diagnostics in the therapy of autistic children with associated epilepsy or EEG epileptiform abnormality and further neurological symptoms or associated disorders. They involve sleep disorders, quite frequent in autistic children and causing them considerable difficulties (Malow et al; 2006). In recent years, neurologists have also given great attention to the intensive stereotypes that represent a core symptom in autism and maintain the view that they should be considered and treated as movement disorders which have much in common with tics. A recent study has called attention to the association of tics and Tourett syndrome in some children with autism (Canitano and Vivanti; 2007).

In the diagnostics and care of autistic children mainly the pediatrician, psychiatrist, pediatric neurologist, geneticist, biochemist, otorhinolaryngologist, psychologist and educator from among the medical and university-educated specialists are involved in the long term. Most recently also the potential contribution of the immunologist has been discussed, as some literary information dealing with the immunological problems in relation to autism indicates that specific serum antibodies exist in mothers of children with autism, which identify prenatally expressed brain antigens (Zimmerman et al; 2007). Whether immunology plays a role in autism, mainly in autistic regression, and how important is positive family anamnesis of immunological disorders, however, still remains unclear (Singer et al; 2006).

The pediatric neurologist also has early diagnostics of autism in his hands

The pediatric neurologist is very frequently one of the first child-health specialists to be consulted on health problems of children with autism. Parents with a handicapped child typically seek his help for problems with speech development, atypical psychomotor development, frequently because of psychomotor retardation or central hypotonia (Ošlejšková et al; 2007a), and further for behaviour disorders, sleep disorders, atypical movement disorders and manifestations or epileptic and non-epileptic seizures. If the parent brings the child to our clinic for specialized examination, we carry out the complete neurological and psychological diagnostics and differential diagnostics, as the Pediatric Neurology Clinic at the Faculty of Medicine of MU and the University Hospital, Brno, serves as a “Diagnostic centre for children with pervasive developmental disorders“. Our experience shows, however, that children with autism are referred for examination at our centre late, even in the cases where parents repeatedly called the attention of physicians, teachers and other professionals to “something wrong“ happening. For most disorders of the autistic spectrum the diagnosis can realistically be established as early as 36 months of age and for Asperger’s syndrome at about 72 months (Allen; 1988; Baier; 2000, Kurita; 1985, Trillingsgaard; 2005) while identification of early warning signals is already possible within the first year of life (Maestro; 2005, Zwaigenbaum; 2005, Baghdadli et al.; 2003, Charman; 2003). The reliability of early diagnostics is high,

namely 88% in a work by American authors who evaluated its reliability 7 years later, i.e. at the age of 9 of the children who had a disorder of the autistic spectrum diagnosed already at the age of 2 (Turner; 2006). At our clinic we have completed, in collaboration with the students of the 5th. year of the Faculty of Medicine at Masaryk University, a study focusing on identification of the time delay between the first symptoms of autistic disorder as noticed by parents and making the diagnosis. Another aim of the study was to establish the number of contacts with professionals (physicians, teachers, speech therapists), when parents described some odd traits in their child's behaviour, and still the child was not sent to a specialized centre. Retrospectively, we assessed 204 children (59 girls and 145 boys; 126 children (39 girls and 87 boys) with child autism (CHA), 57 (17 girls and 40 boys) with atypical autism (AA) and 21 children (3 girls and 18 boys) with Asperger's syndrome (AS). Firstly, the data on the ages of first symptoms was traced back in records for 201 children, the resulting mean age being 29.7 months (a range of 0-72, median 30 +- 17.0) and the mean age of establishing a diagnosis for 204 children was 81.5 months (a range of 13-276, median 69. +-45.). The mean time delay of establishing a diagnosis for 201 children amounted to 51.3 months (a range of 0-246, median 39 +- 40,9). The length of delay until establishment of diagnosis is the shortest in patients with AA (mean time of 44.4 months = 3 years and 8 months), longer in patients with CHA (49.5 months = 4 years and 2 months) and the longest in patients with AS (80.8 months = 6 years and 9 months). Statistically relevant was the difference in the lengths of time to establishing diagnosis between the patients with CHA and AS ($P = 0.023$) and the patients with AA and AS ($P = 0.019$). We managed to determine the average number of visits made to physicians and other specialists before referral to a specialized centre for establishing diagnosis for 133 children, equalling 2.4 (a range of 1-5, median 2+-0,9) (Ošlejšková et al; 2007b). Based on the study results we realized the continued need, despite all the diagnostic achievements, to call attention to the early symptoms of autism and recommend that complaints by parents are not underestimated as they very often intuitively uncover the disorder in its early stage. Putting the accent on early symptoms and possibility of identifying the disorder we have published two guidance articles for practical purposes (Ošlejšková; 2008a, Ošlejšková; 2008b). Early interventions and plasticity of the child brain give some hope that with a very early diagnosis there is some chance to positively affect in part the weight and scope of the core symptoms (Dawson and Zahnil; 2003, Howlin; 2003).

The main clinical initial manifestations of autisms in very young children, important for early diagnostics

The most frequent identifiable clinical manifestation of autism in the social sphere during the first months of life and early childhood is the stagnation of the common mother-child interaction, i.e. emotionally positive and generally "happy" response when cuddled, with accompanying laughter when teased. To the contrary, a child tends to keep to themselves and impresses their surroundings as living in their own world. They are withdrawn, distant, social smile is missing, they do not wave back bye-bye. A child does not calm down when mother takes them in her arms crying and soothes them, which is

the commonest response in healthy children as well as those with mental retardation. A child does not make mutual empathic eye contact, although it is capable of "eye contact". When looking at us, we sometimes get the feeling as if they gazed through us into the distance. They are typically characterized as quiet, obedient to passive and unassuming. At about two years of age they may be very self-reliant, prefer self help and may even learn some skills sooner than other children of the same age. Winning their "shared attention" is difficult, i.e. we are not able to direct the child's attention toward things that we are pointing out and showing to them. "Declarative pointing" is missing completely, which means that the child does not make us give attention to things around them that catch their interest. They do not show them to us and do not demand our thoughts about them or our interest in them. Their games do not include imitation because they are not able to play "at something" (such as the symbolic game to impersonate a family – the dad and mummy game, the school game). On the other hand, they prefer some activities which they very enjoy and do them with speed and dexterity, tirelessly over and over again, for example arranging building blocks in lines based on colour, turning on water, turning the light on and off, closing the litter-bin lid. They greatly enjoy playing with mechanical toys, parts of household things and items of "everyday use of rather technical character", such as washing machines with a rotating drum, radio sets, grinders or alarm-clocks. Autistic children clearly prefer them to the softness of teddy bears and other cuddly toys, i.e. to "soft" toys. Children frequently make unusual and atypical movements and take to motor stereotypes. They walk on tiptoes, shake or twist their arms without emotional context, make tap sounds. They rarely cry, sometimes are even described as "tearless", and may create an impression of not feeling pain. On the other hand, they are rather attracted to "sound-making" toys. Autistic children very much like to listen to simple tunes time and time again, which has a calming effect on them. In the development of speech we can observe a wide range of deviations. The most frequent in this age category, however, is the retardation of speech development and absence of babble. In approx. 30 % of cases regression of speech is observed. Speech regression typically occurs from 1.5 to 3 years of age, the time when children are typically placed in kindergartens and the regression is then erroneously attributed to adaptation to the new environment of the social facility or is considered as its unhappy consequence. The regression often involves only a very small number of meaningfully used words. The child stops using them, but at the same time there is no effort made to develop some kind of substitute communication e.g. with gestures or facial expressions, as is usual with completely deaf children without autism. Other autistic children seem to not understand or hear because they do not react to instructions, but mainly when called by their names. The family even sometimes suspect they are deaf. Here the syndrome of verbal auditory agnosia may even be involved and such children are usually non-speaking whole their lives. Autistic children may have a very good mechanical memory. In some speaking autistic children we can observe inexhaustible pleasure in memorizing rhymes, fairy tales and long stories that they remember with incredible ease and sometimes are even mentioned as prodigies in this connection. Even after the second year of life immediate or delayed echolalia persists. The children often with great skill incorporate into their speech complete parts of texts they have memorized from TV commercials, videos or radio, the so-called "scripts". They have difficulty with pronouns or words that change

the meaning according to context. They confuse pronouns and very often talk about themselves in other than the 1st, usually the 3rd. person, or they use their names to refer to themselves.

Differential diagnostic contribution of the pediatric neurologist

Autism represents a complex multidisciplinary area of problems primarily relating to childhood, but at the same time involving a lifelong disorder, as in certain form it lasts until adulthood (Howlin et al.; 2004, Anagnostou and Schevell; 2006). Specialists engaged in its diagnosing know that a number of other disorders may occur alongside autism. Up to 70 % of these patients are stated to have mental retardation with IQ 70 and lower, further frequently occurring problems include associated motive disorders, vision and hearing disorders, speech problems untypical of autism, sleep problems and other gastrointestinal and internal, neurological and psychiatric comorbidities. It is essential to understand, however, that autism itself can only be part of a broader clinical picture of an etiopathogenetically identifiable disorder or illness. And that is where one of the important roles of the child neurologist rests. Based on his knowledge, neurological and diagnostic paraclinical examinations he can recognize the broader context of this “syndromic (symptomatic) autism“. This terminology used by Coleman is easily comprehensible to a neurologist. The idiopathic autism, by contrast, is one where a dominant genetic share is expected and the disorder is isolated (Coleman; 2005). To summarize in other words, the clinical behaviorally cognitive syndrome of autism may be part of another illness that can be etiologically diagnosed. This may include monogenically determined diseases or chromosomal aberrations (Angelman syndrome, Prader-Willi syndrome, Rett syndrome, Down syndrome, fragile X syndrome, Williams – Beuren syndrome, Tuberous Sclerosis Complex, Sotos syndrome and others) or hereditary disorders of metabolism, which can be diagnosed at enzyme or metabolite levels (such as Smith-Lemli-Opitz syndrome, mitochondrial disorders, *adenylosuccinate* lyase deficiency and the like). Autism can also be one of the effects of prenatal infectious diseases such as rubeola, cytomegalovirus, herpes simplex virus and others. Modern imaging methods (CT and MRI of the brain) may detect focal structural lesions in the CNS of the frontal or temporal lobes or the cerebellum (Amaral et al; 2008). In recent decades the brain structure of autistic people has been studied post mortem (Autism Tissue Program, USA). The brains of autistic people are somewhat larger and frequently testify to disorders of neuronal migration, which may in turn cause development of epilepsy. With regard to differential diagnostics established by the pediatric neurologist a subgroup of “*autistic children with regression*“ is of interest. Regression can be observed in about one third of children with autism, taking the place of their originally normal development. During early childhood, regression or stagnation of speech, communication and game appears. Regression takes place early, typically between the 18th. and 24th. months and is not progressive. Usually a stabilized period of different lengths follows and may last for months or even years. After that some amount of improvement takes place, however not recovery. The pediatric neurologist always considers Rett syndrome

and searches for genetic or rare neurometabolic disorders, but the specific cause of regression often remains unknown (Caronna et al; 2008).

Management of epilepsy therapy in autistic children

There is a high level of coexistence of epilepsy and/or epileptiform specific abnormality in EEG with autism, in literature specified as a very broad range of 5-38.3 % (Wrong; 1993, Tuchman; 2002, Kelley and Moshe; 2006, Canitano; 2007, Hara; 2007). In our cohort it amounted to 44 % (Ošlejšková et al; 2008a). About one third of children with autism will have epileptic seizures in adulthood (Volkmar and Nelson; 1990). Incidence of epileptic seizures is distributed bimodally. The first peak is recorded at an age of about 5 years and the other one then during adolescence (Tuchman and Rapin; 2002). Incidence of cases with epileptic seizures rises in children with mental retardation.

At present it is not recommended to only therapeutically influence with antiepileptics the subclinical epileptiform discharges, but it is also appropriate to carefully treat the clinically manifest epileptic seizures and at the same time reliably monitor and record the behaviorally cognitive and emotional outcome of the child. Full compensation of epileptic seizures is important and especially regarding the mentioned atypical cases it may, too, have the general positive influence on the autistic and further cognitive manifestations. At the same time, it is necessary to readily and flexibly respond to behavioral and cognitive expressions and any negative responses in a child's mood and behaviour, which during the therapy with antiepileptics cannot be fully ruled out in children with autism (Matson and Dempsey; 2008, Peake et al; 2006, Canitano; 2007, Kagan Kushnir et al; 2005). Further detailed observations are necessary. The complexity of the problems in question is even enhanced by the fact that autism with epilepsy distinctly presents a multidisciplinary field and such cases can only be evaluated correctly by the creatively collaborating pediatric neurologist, psychologist, psychiatrist and pediatricist.

Conclusion

Autism represents a very frequent and serious disorder of early brain development and falls in the group of neurodevelopmental disorders. The management of diagnostics of "autisms" requires a day-to-day close multidisciplinary cooperation of many university-educated professionals (both physicians and non-physicians) with parents and the lay public. The role of the pediatric neurologist on the multidisciplinary team is irreplaceable. He mainly participates in early diagnostics of autism, differential diagnostics of symptomatic autism, in the therapy of epileptic seizures in autistic children and of further associated neurological disorders such as sleep disorders. Despite the whole significant progress in medical research achieved during the last decades, pervasive development disorders continue to present a serious individual, social and medical problem. In many respects we are able to help children with autism and their families, but in its core symptoms, the disorder unfortunately continues to be untreatable.

AUTISMUS – PORUCHA ČASNÉHO VÝVOJE MOZKU

Abstrakt: Autismus (alias pervazivní vývojové poruchy) patří díky své vysoké prevalenci (60-70 / 10 000 narozených dětí) mezi nejčastější neurovývojové vady. Skupinu tvoří poruchy s extrémně heterogenním klinickým fenotypem mnohočetných komplexních kognitivně behaviorálních deficitů s developmentálními specifiky, které se manifestují v průběhu dětství nejpozději do 6ti let věku. Diagnostický proces i následnou péči o dítě a jeho rodinu realizuje multidisciplinární tým odborníků, kam patří lékaři, vysokoškolsky vzdělaní nelékaři, ale i rodiče, příslušníci rodin a další laická veřejnost. Z lékařů je to pediatr, dětský neurolog, dětský psychiatr, oční lékař a otorinolaryngolog. Úkolem dětského neurologa je podílet se na včasné diagnostice poruchy, realizovat diferenciální diagnostiku a řídit terapii přidružených neurologických komorbidit, což je především epilepsie.

Klíčová slova: autismus, pervazivní vývojové poruchy, neurovývojové vady, dětský neurolog, včasná diagnostika, epilepsie