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Review paper

Possibilities of early diagnosis of autism spectrum disorder, with a special attention to Asperger syndrome: A systematic literature review

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Introduction: On May 18, 2013, the American Psychiatric Association introduced new diagnostic criteria, the so-called DSM-5, in which Asperger syndrome, autism, childhood disintegrative disorder, also known as Heller's syndrome, and pervasive developmental disorders were classified as autism spectrum disorder (ASD). Based on the DSM-5 classification, Asperger syndrome can be described more specifically as ASD with specifiers, such as, for example, 'without intellectual impairment' and 'without structural language impairment.' The new classification assumes that typical symptoms, such as inflexible, stereotypical behavioral patterns do not necessarily have to appear in early childhood. The new standardizations limited falsely positive diagnoses; unfortunately, at the same time, reducing the specificity of diagnosis.

Aim: The aim of this work, based on a systematic literature review, is to discuss various diagnostic procedures conducive to timely diagnosis of ASD.

Material and methods: The source data were identified based on predefined primary medical headings: ASD, Asperger syndrome, and autism and the following keywords: diagnostic, epidemiology, genetic, prenatal, postnatal, DSM-5, and DSM-IV. The following databases were searched: PubMed, Google Scholar (searching using work titles) and UpToDate.

Results and discussion: Proper anamnesis, good medical and parental care, and the application of adequate diagnostic procedures might be conducive to a much earlier diagnosis, approximately at the age of 2. Owing to parental perceptive observation as well as genetic and imaging examinations a group of children at a higher risk might be precisely identified, consequently facilitating a quicker diagnosis.

Conclusions: Early diagnosis contributes to improved developmental outcomes.

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1. INTRODUCTION

Autism spectrum disorder (ASD) refers to a range of neurodevelopmental conditions characterized by challenged interpersonal interactions and stereotyped or restricted behavioral patterns. These include, for example, unwillingness to change the style or type of play, attachment to a particular object.[1] Diagnosis of ASD is arrived at relatively late, usually at age of school entry.[2] In 2017, it was estimated that approximately 67 million people were affected with ASD.[3] However, available epidemiological data are not consistent. The prevalence of ASD is estimated at 1%-2%, depending on the source.[4–6]

Diagnostic criteria for ASD have changed over the last years because of difficulties with its recognition and exclusion. Diagnostic criteria (DSM-IV) employed in the period of 1994–2013 distinguished autism and Asperger syndrome (AS) and were based on language delay, treating it as a differentiating criterion.[7,8] Children diagnosed with AS presented limited interests and social interactions, however displayed neither language nor adaptive delay.[9] DSM-IV text revision (DSM-TR) did not take into account the patient's medical history and diagnosis was based on the symptoms evident at the time of examination.[10]

On 18 May 2013, the American Psychiatric Association introduced new diagnostic criteria, the so-called DSM-5, in which AS, autism, childhood disintegrative disorder (CDD), also known as Heller's syndrome, and pervasive developmental disorders (PDD) were classified as ASD.[11,12]

DSM-5 was introduced to improve communication between specialists and categorized ASD into three different levels to identify severity of symptoms in the domain of social skills as well as the domain of restrictive or repetitive behaviors. This has led to changes in provided statistical data, as exemplified in Table 1. Unfortunately, epidemiological data remain inconsistent, which casts doubts as to whether this revised classification is actually better.

Based on the DSM-5 classification, AS can be described more specifically as ASD with specifiers, such as, for example, 'without intellectual impairment' and 'without structural language impairment'.[13] The new classification assumes that typical symptoms, such as inflexible, stereotypical behavioral patterns do not necessarily have to appear in early childhood. The new standardizations limited falsely positive diagnoses; unfortunately, at the same time, reducing the specificity of diagnosis.[14–16] Data presented by Maenner et al. indicate that if one compared children diagnosed with the DSM-IV-TR criteria and children who would be diagnosed according to the DSM-5 classification in this period (2006–2008), only 81.2% of children would meet both diagnostic criteria.[16] Irrespective of the data, the revised classification of AS was not welcomed by patients and resulted in their inadvertent social stigmatization.[17]

2. AIM

The aim of this work, based on a systematic literature review, is to discuss various diagnostic procedures conducive to timely diagnosis of ASD.

3. MATERIAL AND METHODS

The research question was: 'What is the current knowledge concerning preliminary diagnosis of ASD?' The source data were identified based on predefined primary medical headings: ASD, AS, and autism. Then, the results were limited by searching for phrases with the conjunction 'and' added to the above headings and the following keywords: diagnostic, epidemiology, genetic, prenatal, postnatal, DSM-5, and DSM-IV. Only original works in English published in 1990–2020 were included in the study. The following databases were searched: PubMed, Google Scholar (searching using work titles) and UpToDate. The obtained results were limited by removing duplicates. Finally, 76 original papers were included for the analysis. The search results reflect current knowledge as of 18 July 2020. Detailed search results are provided in the Table 2. The review was carried out according to the principles determined by Arksey and O'Malley (2005) with the application of a five-stage data selection method.[18]

Table 1. Differences in recognized cases indicative of problematic systematization of diagnostic procedures.

Continent	DSM-IV			DSM-5		
	Percentage	Year*	Source	Percentage	Year*	Source
Europe	0.70%–5.58%	2005	Williams JG et al.[19]	1%–2%	2018	Isaksson J et al.[20]
	0.68% [a]	2011	Parner ET et al.[21]	0.18% [b]	2019	Simashkova N et al.[22]
South Asia	1.89%	2012	Duchan E, Patel DR et al.[23]	0.09%–1.07%	2017	Perera H et al.[24] Al-Mendalawi M[25]
	–	–	–	0.09% [c]	2016	Al-Mendalawi M[25]
	–	–	–	3% [d]	2019	Hunter DJ, Reddy KS[26]
USA	0.76%	2010	Kim JY et al.[27]	2.5%	2016	Piskorz-Ogórek K et al.[6]
Australia	0.5%	2007	Hansen SN et al.[28]	–	–	–
Africa	lack of precise data[29]					

Comments: * year of calculation from the quoted study; [a] e.g. Denmark; [b] e.g. Russia; [c] India; [d] Bangladesh.

4. DISCUSSION

4.1. Prenatal

Comparing data from the Finnish Hospital Discharge Register (FHDR; employed to identify children with ASD), the Finnish Medical Birth Register (FMBR; employed to assess the mother's health status) and the Finnish Population Register Center (FPRC; data used to identify fathers, siblings and control groups), Jokiranta-Olkoniemi et al. revealed that the risk of AS is greater in younger siblings if an older child is also diagnosed with this disorder.[30] In Sweden, based on the study carried out in 2014 and including the population of 2049 899 children (born between 1982 and 2007) it was evidenced that the inheritance of ASD depends on the degree of kinship and ranges from 2.6% (cousins) to 59% in the case of monozygotic twins, with evidently more cases among the male sex (male to female ratio 2.6).[31,32] Moreover, a number of commonly known genetic disorders have been reported to be more frequently associated with ASD. These include, among others, fragile X syndrome (FXS), tuberous sclerosis complex (TSC), Rett syndrome (RTT), neurofibromatosis type I (NF-1), in which the prevalence of ASD is estimated to be 10%, and Turner syndrome (TS) with the prevalence of ASD assessed at 5%.[33]

Such statistical data indicate the feasibility of prenatal diagnostic testing. However, many inconsistencies and ambiguities can be noticed in available literature.

The aryl-hydrocarbon receptor nuclear translocator (2ARNT2) gene (15q25.1), presented in the central nervous system and kidneys, conditions, among others, a normal development of the brain and the spinal cord during embryonic development and shortly after birth. It codes the transcription factor responsible for neurodevelopmental processes.[34–38] Genetic variant rs17225178 in the ARNT2 gene modifies transcription factor binding sites and genomic regions that regulate the chromatin state.[39] It has been evidenced that the mutation in the ARNT2 gene leads to the development of ASD, and single nucleotide polymorphism (SNP) of the ARNT2 receptor is associated with the development of AS and autistic traits.[39] This gene can be isolated from fetal blood (sensitivity – 98%, specificity – 96%).[34–38]

In 2014, Durdiaková et al. formulated a hypothesis that people with ASD exhibit a missense mutation in the SLC25A12 gene.[40] As a result, impaired efflux of aspartate from neuronal mitochondria prevents normal myelin formation.[41] A genetic test can be performed using placental tissues (sensitivity and specificity for single nucleotides exceeds 99%).[42] In 2019, Sharma et al. published a study that compared the process of myelinization in rats from the FAST group, i.e., susceptible to the development of epilepsy, ASD and ADHD, and in rats from the SLOW group, i.e., resistant to epilepsy. It was evidenced that the process of myelinization was delayed in FAST rats.[43,44] This study may suggest that patients susceptible to epilepsy, who also exhibit impaired myelinization (e.g., as a result of SLC25A12 mutation) are predisposed to the development of ASD. Epileptic seizures (irrespective of family history) of unknown

Table 2. Result of database search.

Primary medical headings	Additional keyword	Number of results found in database	
		PubMed	Google Scholar
ASD	–	840	10 900
	diagnostic	65	108
	epidemiology	0	6
	incidence	31	0
	postnatal	1	7
	prenatal	1	27
	genetic	24	105
	etiology	9	10
	DSM-IV	10	6
	DSM-5	9	35
Asperger syndrome	–	42	3520
	diagnostic	6	4
	epidemiology	0	7
	incidence	0	0
	postnatal	0	0
	prenatal	0	0
	genetic	1	15
	etiology	0	3
	DSM-IV	3	4
	DSM-5	1	7
Autism	–	1306	82 800
	diagnostic	107	1090
	epidemiology	1	149
	incidence	13	0
	postnatal	2	54
	prenatal	6	419
	genetic	48	1280
	etiology	16	248
	DSM-IV	36	106
	DSM-5	10	280

etiology may appear as early as in the second month of age.[45] Consequently, such a child may be immediately qualified as having a greater risk of ASD.

Oblak et al. evidenced a reduced density of gamma-aminobutyric acid (GABA) B receptors in the cingulate cortex (responsible for emotion formation and processing, learning to act and understanding the outcomes of activity) and in the fusiform gyrus in patients with ASD. Anomalies appear in the prenatal or early neonatal period.[46,47] Reduced GABAB1/GABAB2 receptor subunits of GABAB are also predisposing factors to epilepsy which is frequently associated with ASD.[48] Currently used antiepileptic drugs, e.g., benzodiazepines, are not GABAB receptor agonists, which may indicate the necessity to modify therapeutic schemes.[47,49,50] The earlier the medication or behavioral treatment is intro-

duced, depending on the patient's predispositions, the better the prognosis.[51]

Hobbs et al. (2007) published a study carried out with 80 patients and concluded that an increased head circumference in relation to the fetal body parameters may be a predisposing factor for the development of ASD in the future.[52] Fetal ultrasound may identify such anomalies already in the 18th week of gestation.[53,54] In order to verify that hypothesis, Whitehouse et al. (2011) repeated that study with a group of 14 children.[55] The obtained results contradicted the ones from 2007. However, owing to the small study group of 2011, the hypothesis formulated in 2007 requires further verification.

Other, less frequent, cytogenetic abnormalities include: egs. 16p11.2, dup7q11.23, 22q11.2, 1q21.1, 15q13.3, dup17p12, 3q37-q38, egs. PTCHD1/PTCHD1AS, NRXN1, SHANK1, SHANK2, SHANK3, NLGN3, NLGN4x, NRXN3, CNTNAP2, DPP6.[33] Microdeletion at 16p11.2 is most often associated with ASD of an early onset (accounting for approximately 1% of cases).[56] It is a predisposing factor for speech impairment, a typical dysfunction in children with ASD. A genetic test using fetal blood can be performed presently only in the Unites States.[34]

The association of the rs4141463 allele of 20p12.1 with ASD was also reported. The study was carried out with a small study population hence it has not been extensively discussed here.[45]

4.2. Postnatal – noticeable by parents

The first ASD symptoms generally appear between 6th and 12th months of age.[57] These include: lack of initiation of joint attention and disturbed sleep. In a healthy infant born on term, after 36 h following birth, the EEG pattern should reflect a normal sleep and wake cycle and the dominance of the so-called active sleep (the state equivalent to REM sleep in adults).[58,59] Children with ASD exhibit circadian rhythm sleep disorders characterized by insomnia, waking up during the sleep cycle at night or waking up very early in the morning.[60]

Before the 15th month of age also other, subjective symptoms appear, including: poor eye contact, poor response to one's name, impaired gestures.[61,62] Children with ASD find it difficult to recognize emotions based on facial expressions and do not identify emotions expressed by the type of gaze.[63,64] This is associated with the impaired activity of oxytocin (OXT) in the amygdala, resulting from genetic polymorphisms of OXT receptors.[65,66] Normally, OXT reduces anxiety associated with interpersonal interactions and facilitates the development of attachment and closeness.[67]

4.3. Postnatal – detectable in diagnostic and screening tests

Magnetic resonance imaging (MRI) performed in children with ASD reveals a significantly increased bulk volume of the amygdala as compared to healthy controls.[68] Based on a series of conducted studies, Mosconi et al. reported that 2–4-year-old children with ASD have unproportionally enlarged right amygdala volumes as compared to total tissue volume (TTV) of the brain. Interestingly, left amygdala volumes increased proportionally to the TTV.[69] It was hypothesized that the enlargement of the amygdala occurs already before the 2nd year of age (the earliest age of diagnosis).[69,70] The presence of anomalies already evident in the 2nd year of age suggests that diagnosis might be arrived at earlier.

Goji et al. proposed proton magnetic resonance spectroscopy (H-MRS) as one of the possible diagnostic tests.[71] They proved that levels of N-acetylaspartate (NAA) in the anterior cingulate cortex were significantly decreased in children with AS compared to controls.[71]

Modified checklist for autism in toddlers, revised form (M-CHAT-RF) is the 2-stage screener that allows one to assign children to ASD risk groups, consequently reducing the number of children needing the follow-up, which facilitates earlier diagnosis.[72] Preliminary screening based on obtaining from parents answers to 20 questions allows one to identify children in risk groups at this stage. In the next stage (involving only patients from risk groups) parents answer 20 follow-up questions asked by a nurse (the original M-CHAT test consists of 23 questions).[72,73] The questions aim at identifying standard symptoms characteristic for a child with autism, for example, lack of interest in peers, lack of response to one's name or auditory sensitivity. The next stage involves clinical observation and assessment of the patient's status by a pediatrician. Patients, who are qualified to be in a risk group by specialists, are referred to further diagnostic tests to be conducted by a developmental pediatrician and clinical psychologist.[72]

Parent's Observations of Social Interaction (POSI) is a 7-item screening tool that allows one to qualify children aged 16-30 months of age to a high risk group (sensitivity 94%).[74] The diagnostic process consists of 5 M-CHAT-RF items and 2 DSM items. Presently, Floating Hospital for Children in Boston is authorized to perform the testing.

5. CONCLUSIONS

(1) Presently available literature data indicate that a preliminary diagnosis of ASD may be considered approximately in the 26th month of age.
(2) Timely diagnosis before the age of 2 years would facilitate the beginning of therapy in the period when the child's neurodevelopment is most intensive and would consequently improve longterm prognosis.
(3) The suggested associations between epilepsy and ASD indicate that children with early epileptic episodes might be predisposed to develop ASD.
(4) This hypothesis requires confirmation statistically obtained in further studies.

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