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Autism spectrum disorders – epidemiology, symptoms, comorbidity and diagnosis

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Summary

In the new classification of American Psychiatric Association – DSM-5 – a category of autistic spectrum disorders (ASD) was introduced, which replaced autistic disorder, Asperger syndrome, childhood disintegrative disorder and pervasive developmental disorder not otherwise specified. ASD are defined by two basic psychopathological dimensions: communication disturbances and stereotyped behaviors, and the diagnosis is complemented with the assessment of language development and intellectual level. In successive epidemiological studies conducted in 21 century the prevalence of ASD has been rising, and currently is estimated at 1% in general population. The lifetime psychiatric comorbidity is observed in majority of patients. The most common coexisting diagnoses comprise disorders of anxiety affective spectrum, and in about 1/3 of patients attention deficit/ hyperactivity disorders could be diagnosed. Prodromal symptoms of ASD may emerge before 12 months of life, however reliability of diagnosis at such an early age is poor. Several screening instruments, based on the parental and/or healthcare professional assessments may be helpful in ASD detection. However, structured interviews and observation schedules remain the gold standard of diagnosis.

Key words: autism, autism spectrum disorders, epidemiology, diagnosis

Introduction

The diagnostic category of Autism Spectrum Disorders (ASD) has its origins in two descriptions of psychopathological syndromes published in 1940s. The first, named by Kanner the early-childhood autism, was characterized by severe communication and speech disturbances, as well as extremely stereotypic behaviors [1]. According to the suggestion of Rutter [2] and subsequent psychiatric classifications [3-5], diagnostic criteria of the disorder became more inclusive, and pertained to a growing number of patients. At the same time attempts were made to characterize those subjects more accurately, resulting in introduction of High-Functioning Autism (HFA) and Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS) diagnoses. Another source of the ASD category were Asperger's studies describing children with highly specialized, detailed interests, demonstrating simultaneously deficits in peer relationships and lack of understanding for social situations [6]. Therefore Kanner and Asperger independently described patients with autism, former low-functioning and latter high functioning subjects. Thanks to work of Lorna Wing "extremely" high-functioning subjects with autism, described by Asperger were called by his name – Asperger Syndrome (AS) [7]. Considering diagnostic difficulties associated with the presence of several, unclearly separated disorders within the category of pervasive developmental disorders, and the increasing practice of making the diagnosis of PDD-NOS, as well as diagnosing several disorders from this category in the same subject, authors of the new American psychiatric classification DSM-5 (Diagnostic and Statistical Manual of Mental Disorders – 5) decided to combine all those diagnostic categories into a single group of autism spectrum disorders [8]. According to DSM-5, presence of two core groups of symptoms: communication/

social interaction disturbances and stereotypic, repeatable behaviors, is necessary to diagnose ASD. The diagnosis is complemented by precise assessment of intellectual and linguistic abilities of the patient.

Epidemiology and clinical presentation

Despite controversies regarding the prevalence of ASD and potential causes of its increase [9], a combined analysis of published studies allows to observe several regularities. In 26 studies, mean prevalence rate of an autistic disorder (according to the DSM-IV criteria) was 21.6/10,000, and the value was negatively correlated with size of the study population [10]. Additionally, 24 studies indicated that the mean ratio of patients with the intelligence quotient (IQ) within the normal range was 32%. In each of those studies the ratio of affected males to females was higher than 1, with a mean of 4.4 [9]. The mean prevalence of Asperger's Syndrome in several dozens of studies published since 1990 was 21.3/10,000 and was lower compared to the autistic disorder. Latif and Williams [11] published a study suggesting that prevalence rate of AS may be higher than that of autistic disorder. This was caused by inclusion of people with HFA into the definition of AS. Children disintegrative disorder occurs approximately 100-times less frequently than autistic disorder, and its mean prevalence rate in 12 published studies was 1.9/10,000. Since the beginning of epidemiological studies on autism a large group of subjects with a similar dysfunctions, who had not met all the diagnostic criteria was noted. Therefore, in the beginning of the 21st century, majority of epidemiological studies have reported prevalence of a broad autism spectrum disorders. The mean ASD prevalence rate reported in those studies is 62/10,000 [10].

Current diagnostic classifications assume, that core symptoms of autism constitute three coexisting dimensions: language and communication disturbances, social functioning difficulties, and limited, stereotypical interests and behavior patterns [4, 5]. However, as mentioned above, symptoms of social deficits and communication difficulties are hard to separate. For example, people with ASD and relatively undisturbed linguistic skills demonstrate other communication-related problems (limited facial expression, no visual contact), which significantly hinder formation of social relations. For that reason, in the new American psychiatric classification- DSM-5 communication disturbances and social dysfunctions are perceived as belonging to a single psychopathological dimension. Stereotypic behaviors include several symptoms: extremely intense bizarre interests, adhesion to non-purposeful behavior schemes, motor mannerisms and focus on individual parts of complex objects [8]. Two dimensions are distinguished in the factor analysis of stereotypic behavior – repeatable motor-sensory actions and adhesion to stability (difficulties with change of schemes, rituals and unnatural affection to objects) [12]. It was also observed that stereotypical behavior may also include the dimension relatively spe-

cific for ASD – extremely intense limited interests. Considering the fact that ASD occurs in an isolated form (essential autism) or co-exists with dysmorphia, motor system dysfunctions, metabolic disorders and other chronic somatic diseases, the so called syndromic and non-syndromic ASD is distinguished, similarly to the partition of intellectual disability [13]. Heterogeneity of a clinical presentation and course (e.g. co-existence of intellectual disability, regression of development) may indicate a significant ethiopathogenetic variability of ASD. Therefore, it is probable that different genetic factors play a role in various cases of autism, which may require individualized diagnostic and therapeutic approaches.

Psychiatric comorbidity

Lifetime psychiatric comorbidity may be present in 70-100% of patients with ASD [14]. Psychopathological problems most commonly co-occurring with ASD, include: attention deficit/ hyperactivity, obsessive-compulsive, mood, and anxiety symptoms, as well as disturbances of sleep and behavior [14]. Those symptoms may cause further deterioration of functioning in ASD patients, and require a multi-dimensional treatment approach.

Anxiety disorders co-exist with ASD in 30-50% of subjects [15]. The nosologic group includes specific phobias – 30%, obsessive-compulsive disorders (OCD) – 17%, social anxiety disorder and agoraphobia – 17%, generalized anxiety disorder – 15%, persistent separation anxiety – 9%, and panic disorder – 2% [16, 17]. According to the criteria, an additional diagnosis of anxiety disorders in patients with ASD has to provide a better characteristic of symptoms present in an individual, than the diagnosis of ASD alone [17]. Diagnostic difficulties are associated with co-existence, overlap or false identification of symptoms of social anxiety and OCD in ASD subjects. Similarly to the general population, in children with ASD increased prevalence of anxiety disorders was observed with age [16, 18]. A correlation was also found between the intelligence quotient (IQ) and severity of anxiety disorders. The risk of anxiety disorders increases in the IQ interval of 70-87 [16], which may suggest, that occurrence of anxiety symptoms is dependent on relatively good development of cognitive functions.

Frequency of depressive episodes in children with ASD is estimated at 1.5-38% (including up to 10% of major depressive episodes), whereas the prevalence of bipolar disorders is estimated at 2.5-3.3% [19]. Similarly to anxiety disorders, diagnostic difficulties result from overlap of symptoms, erroneous interpretation of child's behavior and his/her communication dysfunction. Besides the typical symptoms (reduced activity, feelings of worthlessness, guilt, negative vision of the future, difficulties in decision-making, thoughts of death, reduced or irritable mood), also observations made by caregivers should be taken into account (raports of increased sadness, appearance of tearfulness, vegetative symptoms :sleep disorders, body weight changes;

loss of previously acquired skills) [20]. In order to increase objectivity of diagnosis of mood disorders co-existing with ASD, Leyfer has adapted the Kiddie Schedule for Affective Disorders and Schizophrenia for children with ASD [21].

Sleep disturbances are present in 40-83% of patients with ASD. Most common symptoms include difficulties falling asleep, nighttime waking and early morning waking [22]. Polysomnography usually reveals REM phase disorganization, reduced length of the REM sleep and lack of muscle relaxation [23, 24]. Children with ASD who experience poor sleep are overactive during the day, have more obsessive-compulsive symptoms and more ritual activities. Studies indicate also that endophenotype of sleep may be correlated with child's behavior: the prolonged waking time at night is associated with daytime overactivity, and sleep fragmentation is related to an increased number of stereotypic behaviors [23, 25].

Diagnostic criteria of ADHD are met approximately by 30% of children with ASD, and another 25% demonstrate subclinical symptoms of the disorder [26]. Contrary to the new DSM-5 classification, previous diagnostic systems barred simultaneous diagnosis of ADHD and ASD, in that case perceiving hyperkinetic disorders as a consequence of developmental and cognitive disorders characteristic for ASD [26]. Co-existing ADHD symptoms are associated with more severe problems with verbal working memory, executive dysfunctions, disturbances of organization and planning skills, externalizing behaviors and more disabling core symptoms of ASD [26, 27]. Studies indicate the co-occurrence of ADHD may warrant a modification of pharmacotherapeutic approach [26].

It is estimated that tics occur in 22% of the whole population of ASD patients. In half of cases the co-existing symptoms meet the criteria of Tourette Syndrome, and in other half of cases – criteria of chronic motor tics [28]. Differentiation between motor tics and stereotypic movements may be challenging. Prevalence of tics seem to increase in high-functioning patients with ASD. In a study of school-children with diagnosis of AS/HFA, tics co-existed in 26% of them [29]. In another study of children meeting the criteria of autism it was demonstrated that 4.3% of them meet simultaneously the criteria of Tourette Syndrome [30]. Co-existence of Tourette Syndrome may be associated with lower intensity of ASD symptoms, although there is currently no sufficient evidence supporting this hypothesis [30].

For many years autism was regarded an early form of schizophrenia. Only in the beginning of 1970s those were distinguished as separate diseases. Interestingly, occurrence of psychotic disorders among patients meeting the criteria of ASD is relatively rare [21]. There have not been many studies so far that would look for correlations between psychotic and ASD symptoms. On the other hand, a great emphasis is placed on diagnostic difficulties – a differentiation between psychotic symptoms and those being a result of ASD. On various occasions they may cause a false diagnosis of schizophrenia, therefore leading to its overdiagnosis in that group of patients [31].

According to the DSM-IV classification, a simultaneous diagnosis of schizophrenia and ASD is justified only if autistic symptoms clearly precede development of psychotic ones. Otherwise a diagnosis of early childhood schizophrenia has to be made. Retrospective studies based on history taken from parents indicate that approximately half of patients with confirmed schizophrenia had met the criteria of ASD at the earlier stage of their life [32].

Prodromal symptoms of ASD in the first and second year of life

Prodromal symptoms of ASD and their predictive value for the risk of the disease are intensively searched for. According to the diagnostic criteria [4, 5], those diagnostic markers should be predominantly associated with the social communication deficits (building relationships, and verbal and non-verbal forms of communication), as well as with the restricted range of activity, behaviors and interests.

The analysis of early development in children who developed autism in later life indicates that some behavior patterns suggesting the risk of ASD may be observed during the first year of life (see Table 1). Diagnostic value of that warning signals has not been confirmed, although combined occurrence of several markers probably indicates an increased risk of ASD. Many pre-diagnostic indexes analyzed in relation to an early childhood are associated with inability to create a joint attention, predictive value of which in relation to the further social development and communication has been relatively well understood [33]. This skill, impaired in children with ASD seems to predate verbal communication and has a key role in further development of social interactions.

Table 1. **Early behavioral signals useful in diagnosis of autism in a 1-y.o. child (Pisula, 2012) [52]**

Behavioral indexes indicating the increased risk of ASD	Development stage when the difficulties may be manifested
Untypical visual contact	1st half of the 1st year of life
No, or significantly limited, interest in social stimuli (including human face), ignoring them, short glances on people	1st half of the 1st year of life
No ability to alternating participation in interactions, limited abilities of initiating and maintaining contact	1st half of the 1st year of life
No appropriate reaction to messages directed to the child	1st half of the 1st year of life
No emotional tuning to emotions expressed by other person; no adaptation of facial expression to a situation; untypical facial expression	1st half of the 1st year of life
No smile in social situations, no other forms of expressing joy in contact	1st half of the 1st year of life
No reaction, or delayed reaction to own name	8-10 months (or earlier)

table continued on the next page

No pointing out in order to direct another person's attention to an object interesting for a child	8-12 months
Reduced anticipation reaction	2nd half of the 1st year of life
Eyes do not follow a person, or a toy, or something observed by a parent	2nd half of the 1st year of life
No complex social behavior combining look, facial expression, voice tone and gesture	2nd half of the 1st year of life
A child may seem "excluded" from its surrounding. Does not seem to hear what is going on about him/her	1st half of the 1st year of life
Reduced vocalization and twitter, especially during an interaction with another person	1 year
No demand to be lifted or hugged	1 year
Untypical, delayed and non-harmonic motor development	1 year
No understanding of gesture of social significance (e.g. waving goodbye)	Break of the 1st and the 2nd year of life

In the 2nd year of life, atypical behavior is manifested more clearly and may be present in all diagnostic dimensions of autism. In the field of social relationships warning signs include: lack of shared interests, a limited ability to read emotions in facial expression (or using such information in the regulation of behavior), limited expression of feelings and lack of attachment behaviors, as well as largely limited interest in other children. Dimension of communication dysfunctions comprise atypical, often delayed development of speech, repeating words without understanding, absence of drive to communicate and lack of symbolic play, which requires creation of mental representation of objects. Moreover, in some children a regression of development, at first associated usually with communication skills may occur. In the field of limited behavior, interest and activity patterns, signals suggesting an increased risk of ASD include: atypical play patterns involving organizing and schematic arrangement of objects; playing with elements of toys without using them as a functional whole; stereotypical motor patterns: spinning, rocking, hand flapping; insistence on schemes and routines; excess interest in some forms of activity and their persistent repetition; increased sensitivity to some stimuli and limited – for the child's age – interest in the surrounding world.

The most commonly confirmed early symptoms of ASD occurring in the 1st and 2nd year of life comprise: lack of behavior reflecting child's readiness to establish social relations (no reaction to name, limited visual contact, atypical facial expression in social situations, no emotional interplay, a low interest in social stimuli and poor vocalization), as well as limited imitation skills, attachment behaviors and difficulties in the creation of joint attention [34, 35]. Those early markers are used to construct ASD screening tools.

Tools used for screening and assessment of the risk for ASD

Screening for autism takes into account information from caregivers and clinical observation. There are many screening tools for ASD in children below the age of 3 years, and only some are presented below.

The most popular screening tool is CHAT (*The Checklist for Autism in Toddlers*) [36]. It is designed for examination of 18-months-old children during routine pediatric assessment visits, although it may also be used with older children, even 24- or 36-months-olds. The tool consists of two parts: 9 questions to parents and 5 short clinical observations. CHAT has a coherent and well documented scientific basis [37]. Sensitivity of the tool is rather low (0.18–0.38), but the estimated specificity is very high (0.98–1) [38, 39]. CHAT is a tool recommended by the National Autistic Society for pediatricians in the United Kingdom.

A variant of CHAT is the tool called M-CHAT (*Modified-CHAT*), designed for examination of 3- to 16-months-old children [40]. The questionnaire contains 23 questions (9 taken directly from CHAT) and is filled by parents. The tool has a high sensitivity (approx. 0.85), but data on its specificity are not clear (approx. 0.43-0.95) [39]. Screening results are influenced by child's mental age, as well as by presence of any serious motor disorders or vision/hearing disorders, however this obstacle is not limited to M-CHAT [41]. The tool is one of recommended by the American Academy of Pediatrics in the USA, as a tool for screening of children aged 18-24 months.

Another modification of CHAT is Q-CHAT (*Quantitative CHecklist for Autism in Toddlers*), designed for examination of children aged 18-24 months [42]. In the questionnaire a parent assesses frequency of individual behavior or severity of a problem in a 5-point score (not a dichotomous one, as in case of M-CHAT). Early results concerning Q-CHAT appear promising [42], however the data on sensitivity and specificity are not available yet.

ESAT (*Early Screening of Autistic Traits Questionnaire*) [43] is another promising screening tool, designed for examination of children over the age of 14 months. Preliminary data regarding properties of the tool are very promising, especially in terms of sensitivity assessed at 0.88 [44]. Specificity may be significantly lower – 0.14, however requires more studies. The tool has been translated into Polish and is currently under studies.

The BISCUIT battery is designed for examination of children from 18 months to 3 years of age [45]. The test consists of 3 scales filled by diagnosing specialist, taking history from a parent, and also based on his/her own observation. Properties of the tool claimed by authors are: sensitivity 0.93, specificity 0.87. Properties of the tool have not been verified by other authors yet. A Polish language version has been developed and is currently analyzed.

Diagnostic tools

ADI-R (*Autism Diagnostic Interview-Revised*) and observation protocol ADOS (*Autism Diagnostic Observation Schedule*) [46], with a new version (ADOS-2)-supplemented with a module for diagnosis of children under 12 months of age, are a diagnostic "gold standard" in ASD.

ADI–R is a partly structuralized interview, designed for diagnosis of children over the age of 24 months, but also of adults. The test has been developed considering diagnostic criteria of ICD–10 and DSM–IV. Appropriate sensitivity and specificity parameters of ADI-R with application of new DSM-5 diagnostic criteria have been confirmed in recent studies [47]. ADI-R consists of 93 items, focusing on both behavior currently displayed by a patient, and behavior observed at particular developmental stages. A result exceeding the screening thresholds in 4 areas of diagnostic algorithms: communication, mutuality of social interactions, limited and repeated behavioral patterns and interests, and age at onset of first symptoms, indicates presence of PDD.

ADOS-2 is a standardized protocol of observation [48, 49]. It has a form of 5 modules for patients in different age groups and at various stages of linguistic development. Algorithms of the Module 1-4 allow calculation of a result that reflects presence and intensity of symptoms characteristic for ASD. In the Module T, for children aged from 12 to 30 months, there are 3 score ranges for disturbing symptoms. The algorithm provides information about how many of them are present in a particular child, simultaneously avoiding a formal classification, that may be inappropriate at that early age.

ADI-R and ADOS tools have been translated into Polish and their use in scientific research has been authorized [50, 51].

Conclusions

Autism spectrum disorders (ASD) constitute a new category in the DSM-5 classification. The class will replace autistic disorder, Asperger's syndrome and childhood disintegrative disorder and pervasive developmental disorder not otherwise specified. That change should allow a more reliable diagnosis of deficits in social interaction/communication and stereotypical behavior, occurring since early stages of development. Frequency of the ASD diagnoses may increase, which possibly results from a change in diagnostic practice, greater awareness of clinicians, including GPs, and improvement of screening and diagnostic tools detecting early symptoms of autism. However, results of epidemiological studies do not preclude an actual increase in the prevalence of ASD. It was proposed that social dysfunctions and communication disturbances may constitute elements of the same psychopathological dimension of ASD, whereas the repeatable motor-sensory schemes and the insistence on stability may be distinct aspects of stereotyped behavior. The new view of autism spectrum disorders

may facilitate studies on their etiopathogenesis and biological markers, as well as facilitate introduction of effective therapeutic approaches.

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