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AUTISM IN REVIEW

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ABSTRACT • Autism spectrum disorders are a group of neurodevelopmental disorders characterized by impaired verbal and/or nonverbal communication in addition to repetitive stereotypical behaviors. We present a review article on this topic. Criteria for diagnosis are defined by the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM 5). Abnormalities at the level of synapses, including newly described genetic perturbations, have been implicated in the pathogenesis of autism. Non-invasive modalities like Diffusion Tensor Magnetic Resonance Imaging have identified white matter tract involvement in the brains of autistic individuals. Early and intensive intervention impact prognosis. Risperidone and aripiprazole are FDA approved for irritability in autism although no known medication relieves core symptoms of social and communication impairment. Fluoxetine is used to decrease anxiety in autistic patients.

Keywords : autism, synapse, early lintervention, applied behavior analysis (ABA), selective serotonin reuptake inhibitors (SSRI)

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RÉSUMÉ • Les troubles du spectre autistique représentent un groupe de troubles neurodéveloppementaux caractérisés par un déficit au niveau de la communication verbale et/ou non-verbale accompagné de comportements répétitifs et stéréotypés. Nous présentons une revue de synthèse sur l'autisme. Les critères diagnostiques sont définis par le Manuel diagnostique des troubles mentaux (DSM 5). Des anomalies des synapses au niveau des perturbations génétiques sont impliquées dans la pathogénèse de l'autisme. L'intervention précoce et intensive améliore le pronostic. Des techniques d'imagerie non invasives telles que la résonance magnétique par tenseur de diffusion (DTMRI) ont détecté des différences dans l'organisation des tractus de substance blanche chez des individus souffrant d'autisme. La risperidone et l'aripiprazole sont approuvés par l'administration américaine des produits alimentaires et médicamenteux (FDA) pour le traitement de l'irritabilité. Fluoxetine est connu pour son action anxiolitique chez les patients autistes. Cependant, il n'existe pas encore de traitement médicamenteux reconnu pouvant agir sur les signes majeurs de l'autisme que sont le déficit des capacités sociales et de communication.

INTRODUCTION

Autism spectrum disorder (ASD) is a clinically distinct neurodevelopmental disorder with increasing prevalence. Recent data in the United States estimates that 1/68 children received the diagnosis of autism [1]. This disorder is characterized by abnormal social interaction with self-focus, impaired connectivity, organization and synaptogenesis [2-4]. The neuropathological and genetic bases of ASD are beginning to unfold.

Diagnosis of autism

Autistic children may avoid eye contact, repeat actions like turning around themselves and use the parent's hand instead of pointing to indicate an object they want [1]. They may not relate to other children or adults, so that if they enter a room where children are on one side and toys on the other side, they would disregard other children. They may not respond when called by name and may not play pretend games like feeding a doll. They lack joint attention, meaning that they may not look when you point to a flying airplane. They are very rigid and adhere to routines, so they have difficulty adapting to changes and can have temper tantrums. Expressing and understanding feelings is impaired, and their reaction to the way things taste, look, smell, feel, or sound is unusual. Many autistic children have language delays and echolalia, echoing words or phrases instead of using normal language. They may be fascinated by spinning objects like the washing machine or may turn toy cars upside down and spin the wheels. Many children lose skills or words they had acquired at an earlier age [1].

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM 5) [5] classified these symptoms into two domains: the *social communication* and *interaction* domain, which includes deficits in verbal and nonverbal communication, and the *repetitive behavior* domain. In order to formally diagnose ASD, children should meet at least three symptoms in the domain of social communication and interaction, and two symptoms in the repetitive behavior domain (Table I). The symptoms must be present from early childhood and usually limit daily functioning [5]. Learning in a regular school without additional educational support may be impaired and even routine care like haircuts, dental work, eating and sleeping become problematic. These symptoms must not be

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TABLE I DSM 5 CRITERIA FOR DIAGNOSIS OF AUTISM

Social communication and interaction domain	Repetitive and restrictive behavior domain
1. Deficits in social emotional reciprocity	**1. Stereotyped or repetitive speech, motor movements, or use of objects**
Abnormal social approach	Simple motor stereotypies
Failure of normal back and forth conversation	Echolalia
Reduced sharing of interests, emotions, affect and response	Repetitive use of objects
Total lack of initiation of social interaction	Idiosyncratic phrases
2. Deficits in nonverbal communicative behaviors	**2. Excessive adherence to routines, ritualized patterns of behavior**
Poorly integrated verbal and nonverbal communication	Excessive resistance to change such as motoric rituals
Abnormalities in eye contact and body-language	Insistence on same route or food
Deficits in understanding and use of nonverbal communication	Repetitive questioning or extreme distress at small changes
Total lack of facial expression or gestures	
3. Deficits in developing and maintaining relationships	**3. Highly restricted, fixated interests that are abnormal in intensity or focus**
Difficulty making friends	Strong attachment to and/or preoccupation with unusual objects
Apparent absence of interest in people	Excessively circumscribed or presevative interests
Difficulties adjusting behavior to suit different situations	**4. Hyper- or hypo-reactivity to sensory input**
	Unusual interest in sensory aspects of environment
	Apparent indifference to pain/heat/cold
	Adverse response to specific sounds or textures
	Excessive smelling or touching of objects
	Fascination with lights or spinning objects

Content adapted from DSM 5 [5]

accounted for by general developmental delays. Therefore, if severe gross motor or fine motor delays are present, other diagnoses should be considered. Furthermore, physicians are encouraged to address and consider specifiers such as verbal and cognitive abilities, association with known medical conditions, environmental risk factors or genetic conditions such as Fragile X or prenatal valproate exposure [5]. Severity level should also be addressed (Table II).

According to DSM 5, as compared to the previous DSM 4, Asperger disorder, childhood disintegrative disorder, pervasive developmental disorder not otherwise specified (PDD-NOS) are all included under the autism spectrum disorders (ASD) umbrella. Rett syndrome is now considered as a separate disorder (Table III).

Comorbid intellectual impairment, developmental coordination disorder, structural language disorder, anxiety disorders and/or depressive disorders, attention deficit hyperactivity disorder and other psychiatric disorders may coexist with autism [5]. Epilepsy, sleep problems and gastrointestinal problems are well described comorbidities [5].

As for formal diagnostic assessments, the Autism Diagnostic Interview Revised (ADI-R) and the Autism Diagnostic Observation schedule (ADOS) constitute gold standards [6]. ADI-R is a semi-structured interview for caregivers of suspected cases of autism [6], whereas ADOS involves observation of social behavior, communication and play by an ADOS certified therapist [7].

According to the American Academy of Pediatrics Council of Children with Disabilities, all patients with autism spectrum disorder should undergo a physical and a neurological examination, an audiogram and a tympanogram. If metabolic disease is suspected, then and only then is a metabolic workup requested. Brain MRI is recommended if tuberous sclerosis is suspected or the neurological examination reveals abnormalities. If a history of seizures exists, an electroencephalogram (EEG) should be performed. Testing for fragile X in boys is recommended in case of family history of cognitive impairment. In a female with regression, MECP2 gene testing must be undertaken to rule out Rett syndrome [8].

Currently, it is recommended to perform comparative genomic hybridization (CGH) microarray studies to determine gene microduplications or microdeletions associated with autism [9].

RISK FACTORS

Many environmental, biological and genetic risk factors have been associated with autism. Maternal intake of valproic acid and thalidomide during pregnancy is associated with a higher risk for autism [10,11].

Perinatal stress and prematurity are also associated with a higher incidence of autism [12].

Research on environmental pollutants implies but does not prove an association with increased prevalence of autism [13,14].

Increased parental age might constitute one risk factor [15], although this has come under scrutiny as a cause. A definit risk factor is having an older sibling with ASD [16].

TABLE II SEVERITY LEVELS FOR AUTISM

Severity Level	Level 3	*Level 2*	Level 1
Support required by the child	Very substantial	*Substantial*	Required
Verbal communication skills deficits	Severe	*Marked*	Noticeable when no support in place
Nonverbal communication skills deficits	Severe	*Marked*	Noticeable when no support in place
Impairments in social functioning	Severe	*Apparent even with supports in place*	Decreased interest in social interaction
Initiation of social interaction	Very limited	*Limited*	Difficult, odd or unsuccessful
Response to social overtures from others	Minimal	*Reduced*	Atypical or unsuccessful
Inflexibilty of behavior	Present	*Present*	Interferes with functioning
Coping with change	Extremely difficult	*Difficult*	Problems of organization and planning
Restricted /repetitive behaviors	Markedly affect function	*Interfere with function*	
Changing focus or action	Causes great distress	*Difficult/Causes distress*	Difficult

Content adapted from DSM 5 [5]

In a study of 86 Lebanese children with autism, it was concluded that there was a significant association between autism and advanced parental age, maternal unhappiness during pregnancy, living close to industrial zones and previous childhood infection [17].

Genetics and autism spectrum disorders

There is a 90% concordance rate in monozygotic twins for ASD [18].

Chromosomal microarray analysis is a leading genetic tool used to uncover genetic aberrations in children with developmental and behavioral abnormalities. Comparative genomic hybridization (CGH) and single nucleotide polymorphisms (SNP) microarrays are two techniques that detect copy number variants (CNV) including microduplications and microdeletions. Five to ten percent of children with autism carry disease-causing CNVs with a higher frequency in more severe phenotypes [9]. Among the common CNVs detected in autistic children are deletions and duplications of chromosome 16p11.2, maternal duplications of the Prader-Willi/Angelman region, and duplications of the Williams syndrome critical region 7q11.23.

Autistic features are described in a number of known genetic syndromes. Common characteristics of autism susceptibility genes include those involved in early neurological development, neuronal migration and synaptogenesis [19-21].

Autistic features have been reported in 30-50% of children with Fragile X syndrome, in 50% of children with CHARGE syndrome, 6-7 % of children with Down syndrome and in a number of children with tuberous sclerosis [22].

Newly described autism susceptibility genes include the neurolignins, neurexins (including CNTNAP 2), human serotonin transporter and human oxytocin receptor genes [19] as well as many others. MECP2 gene mutations that cause Rett syndrome result in disruption of GABAergic neurons [23].

Epigenetic mechanisms such as genomic imprinting and DNA methylation that affect gene expression without a change in DNA sequence have also been implicated. Epigenetic modifications of autism genes might provide the link between environmental factors and genetic predisposition [24].

TABLE III COMPARISON BETWEEN DSM 4 & DSM 5 ASD DIAGNOSES

DSM 4	DSM 5 ASD
Subdiagnoses as • Autistic disorder • Asperger syndrome • Pervasive developmental disorder not otherwise specified • Childhood disintegrative disorder • Rett disorder	The diagnosis is autism spectrum disorder (ASD; no subdiagnoses) [e.g. Asperger is included under ASD] Rett syndrome as a separate disorder
Symptoms dvided into three areas: 1. Social reciprocity 2. Communicative intent 3. Restrictive and repetitive behavior	Symptoms divided into two domains: 1. Social communication/interaction 2. Restricted and repetitive behavior

Content adapted from DSM 5 [5] and DSM 4 TR [40]

Autism and the synapse

In 2003, Zoghbi and colleagues proposed that autism and Rett syndrome are both due to synaptic anomalies [20]. The human brain is governed by a balance between excitation and inhibition. Synaptic integration, the input and output of neurotransmitters, is significantly affected by the dynamics of these excitation-inhibition regulation mechanisms, thus affecting neural circuitry, neuronal plasticity and long-term potentiation [25]. The assumption of excitation-inhibition imbalance in ASDs is supported by the fact that at least 30% of ASD patients also have epilepsy [26].

SCREENING FOR AUTISM

Pediatricians play a crucial role in screening for autism spectrum disorders. It is of utmost importance to address parental concerns. The American Academy of Pediatrics recommends developmental screening at every well child visit. For children younger than 24 months, the Infant/Toddler Checklist from the Communication and Symbolic Behavior Scales Developmental Profile may be used [22,27]. The Modified Checklist for Autism in Toddlers (M-CHAT) is a very useful parental questionnaire for children older than 18 months [22,28] and has been validated in many languages including Arabic, English and French. As soon as the child is found to be at risk, he/she should be immediately referred to a pediatric neurologist, child psychiatrist and a special education/early intervention program [22].

DIFFUSION TENSOR IMAGING

Diffusion tensor imaging (DTI) is an MRI technique that provides detailed information on white matter microstructure.

Using DTI, white matter regions involving frontal, prefrontal, superior, middle and inferior temporal regions and the corpus callosum were affected in some autistic patients [29,30].

Furthermore, age differences were found, possibly related to the timing of white matter disruption [29].

Ameis *et al*. compared nineteen children and adolescents with ASD to sixteen age and IQ matched controls. Prominent diffusion measure differences in ASD children, but not adolescents, were found using DTI. Also, disruption in tracts integrating frontal, temporal, and occipital structures involved in socio-emotional processing were found in tract-specific analysis of ASD children [30].

MANAGEMENT

Early intervention

When the diagnosis is made, parents are urged to start early intervention. This consists of applied behavioral analysis (ABA), speech therapy, occupational therapy, psychomotor therapy and special education. Toddlers should be placed in a regular day care to increase interaction with neurotypic normal children.

Early intervention in autistic patients between the ages of 18 to 48 months has a major positive effect on outcome. This results from neural plasticity still present at this young age [31].

Based on experimental psychology research, ABA intervention is applied to teach new skills, to promote adaptive behaviors and to reduce interfering maladaptive behaviors [32].

Positive effects in favor for ABA are noted for adaptive behavior, IQ outcome, expressive language, receptive language and daily communication skills [31]. Intensive behavioral treatment started between ages 4 and 7 years was effective in decreasing aberrant behaviors and social problems [33]. Other strategies used include structured teaching (TEACCH method), developmental models and relationship-focused early intervention model [32].

Speech therapy produces gains in communication skills [32]. It is more effective when the speech therapist collaborates with family, peers, teachers and special educators. It is advised to limit the use of one language at home and at school. Occupational therapy promotes self-care skills, organization, attention and play skills [32]. Sensory integration remediates deficits in neurological processing of sensory information, thereby improving adaptation of the child to the environment [32].

Pharmacotherapy for autism

Many drugs have been tried in autism to alleviate symptoms. Few drugs have proven to be useful. Other drugs are still in clinical trials.

In several controlled studies, risperidone proved to be efficacious in treating irritability and aggression in ASD patients of all ages. Risperidone is FDA approved for the treatment of irritability in ASD children and adolescents [34]. One multicenter double-blind placebo controlled trial conducted by McCracken *et al*. assessing risperidone use for irritability in ASD showed a 69% response rate, with more efficient reduction of irritability, stereotypic behaviors, hyperactivity and noncompliance, particularly when combined with training of the parents [35].

Aripiprazole (known as Abilify), a third generation antipsychotic drug used for the treatment of schizophrenia, major depression and psychosis, has also been FDA approved for use in treatment of irritability in autistic individuals. Randomized controlled trials using aripiprazole in autistic patients resulted in less irritability, hyperactivity and stereotypies compared to placebo. Side effects included weight gain, tremor and sedation [36].

Fluoxetine is more effective in treatment of repetitive behaviors in adults and adolescents with ASD compared to children with ASD [34]. The SOFIA study (Study of Fluoxetine In children with Autism), the largest double-blind placebo controlled trial of fluoxetine in autistic

children, concluded that the drug is not effective for repetitive behaviors in this population [34].

Another study on liquid fluoxetine in 45 children and adolescents with autism concluded that fluoxetine was superior to placebo in treatment of repetitive behaviors [37]. Fluoxetine may reduce anxiety in autistic individuals as noted in a small open-labeled study [38].

Buspirone, a serotonergic agent with anxiolytic and antidepressant effects, reduced anxiety and irritability in an open label clinical trial in 22 autistic children. The side effects were minimal with only one patient experiencing abnormal involuntary movements [39].

Methylphenidate was moderately efficacious for reducing hyperactivity in ASD and may result in adverse effects. Clonidine is reported to reduce sleep initiation latency and night awakening in ASD [34].

CONCLUSION

Autism spectrum disorders are defined by deficits in social and verbal communication and repetitive and stereotyped behaviors not explained by global neurodevelopmental delay. Variable severity levels exist. The disorder impacts daily life. Genetic studies have linked these disorders to known syndromes as well as to recently discovered autism susceptibility genes. Novel neuroimaging studies, specifically diffusion tensor imaging, have identified involvement of white matter tract regions responsible for socio-emotional processing. Risperidone and aripiprazole are FDA approved for irritability in ASD children and adolescents. Use of fluoxetine alleviates anxiety in selected patients. Early identification and intervention with ABA, speech, psychomotor and occupational therapies are crucial as is social integration into regular nurseries and schools. Early diagnosis and intervention with therapies remains the mainstay of insuring an improved outcomes and a better chance at full integration into society.

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