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Review Article

Autism spectrum disorders (ASD) diagnosis and management; current trends and future direction: a review article

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Abstract: Autism Spectrum Disorder (ASD) is a commonly seen neurodevelopmental disorder in children. The characterization of ASD by age is inappropriate, with the presence of stereotypic behaviour and impaired social communication. This disorder is hypothesized to result from cerebral dysfunction arising from a complex interaction among environmental, genetic, and epigenetic factors. Worldwide, ASD prevalence has reached more than 1%, leading governments, schools, and health care providers to establish strategies and programmes to resolve this complicated disorder. A high level of concern must be maintained in children with poor school performance, problem behaviours, speech issues, or developmental delay. An evaluation of a suspected ASD child is not difficult if a standardized approach is used. Early intervention leads to marked improvements in social communication skills, imitation, and cognitive and adaptive function. This current review analysed the epidemiology, causes, social-economic impacts and effective tools available in diagnosing and managing ASD. This study also provides the future direction for the diagnosis and management of ASD.

Keywords: Autism Spectrum Disorder (ASD), behaviour, diagnosis, management, speech or developmental delay

Introduction

ASD is a neurodevelopmental disorder characterized by communication impairment and social and repetitive or restricted behaviours [1]. ASD starts from childhood and continues to remain in adolescence and adulthood. The conditions are evident in most situations within the first five years of life. Several comorbidities are often present in ASD individuals, including depression, anxiety, attention deficit hyperactivity disorder (ADHD) and epilepsy. In persons with ASDs, the intellectual level functioning is highly variable, ranging from severe disability to higher stages [2]. ASD affects one in every 700 to 1000 people, and one in every 1000 people has classic autism symptoms. At a global level, 3 to 4 boys per each girl are affected by ASD. It includes five clinical groups under the autism spectrum disorder umbrella, including Asperger syndrome, autistic disorder, pervasive developmental disorder, Rett syndrome, and childhood disintegrative disorder; it affects emotional, cognitive, and social skills. Specific autism etiologies and neural bases remain largely unknown; it has been suggested that modifications in multiple genes combined with environmental factors constitutes the cause for the autism phenotype development [3, 4]. About 5 million Americans are affected by ASD, with an approximate incidence in children, around 1.7% [5]. Its manifestations are primarily behavioural with variable severity and cognitive function, characterized by early disruption in social interaction and communication, restrictive, repeated loss of interest in various activities and stereotyped behaviour patterns. It is most often accompanied by sensory processing disorders, impairment of adaptive function, self-injury or aggression. The central main symptoms are usually diagnosed clinically based on the parameters defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5). Early and accurate diagnosis is important in ensuring children are offered the optimum support and advice, enabling them to

achieve the best quality of life [6]. This current review aims to understand what the current ASD diagnosis and management entails and the future direction of diagnosis and management of ASD.

Epidemiology

It is estimated that worldwide one in 160 children has an ASD [2]. The Centers for Disease Control and Prevention (CDC) estimates about 1.68% of United States (US) children at the age of 8 years are diagnosed with ASD [5, 7]. The worldwide prevalence of ASD is at 0.76 per cent, as estimated by the World Health Organization (WHO), which represents only about 16 per cent of the global child population [8]. The prevalence of ASD in the US more than doubled between 2000-2002 and 2010-2012 according to estimates from the Autism and Developmental Disabilities Monitoring Network (ADDM) [5]. Although reflecting on trends in the US may be too early, the prevalence of ASD appeared to stabilize between 2014 and 2016 without a statistically significant increase [7]. ASD is found in all socioeconomic, racial, and ethnic groups, but its diagnosis is far from universal. Caucasian children with ASD are identified more frequently than Hispanic or black children [5]. Some genetic diagnoses have a higher incidence of comorbidities with ASD relative to the general population, including Rett syndrome, Down syndrome, tuberous sclerosis, fragile X, among others; nevertheless, these identified genetic conditions are reported for a relatively limited number of total cases of ASD [4, 9, 10]. Studies on sex chromosome aneuploidy children have identified a particular profile of male social functioning that indicates a greater susceptibility to autism [11-14]. Several chromosome sites, particularly chromosome X, 2, 3, 7, 15, 16, 17, and 22 are correlated with an elevated risk of ASD due to increased chromosomal microarray use [15]. Prematurity and increased parental age are the other risk factors for ASD [16] because they have a higher likelihood of conveying changes with older gametes, bringing about extra obstetrical complications, including prematurity [17].

Causes

The neurobiological disorder of ASD is affected by both environmental and genetic factors. Research has continued to expand our understanding of possible etiological pathways within ASD, but there is currently no strong trigger. The epidemiological data suggest that there is no evidence of a causal association between ASD, rubella vaccine, mumps, and measles. Previous research indicates that a causal relationship was riddled with methodological flaws [20, 21]. Also, there is no clear evidence found that the childhood vaccine can enhance ASD risk. Evidence reports of the potential association of containing aluminium adjuvants and preservative thiomersal in inactivated vaccines and the ASD risk potentially concluded that vaccines might not raise the ASDs risk [2]. Studies that are related to neuropathological factors are limited but have shown variations in limbic system defects, cerebellar architecture and connectivity, with cortical changes in the frontal and temporal lobe, along with other precise abnormalities [9, 20, 21].

A small exploratory analysis of young children's neocortical architecture showed a cortical laminar architecture with focal disruption in most subjects, indicating problems with the neuronal differentiation and formation of cortical layers [22]. In children with ASD, brain overgrowth has been identified both in terms of increased extra-axial fluid and cortical size. These are ongoing research areas both in terms of possible biomarkers and their etiology [23, 24]. Genetic factors play a role in ASD susceptibility, with siblings of patients with ASD carrying an increased risk of diagnosis compared to the general population [25-27]. Whole-exome sequencing methods and studies related to genome-wide associations have expanded our ASD susceptibility gene understanding, and learning about the related to the genome-wide association has expanded our ASD susceptibility gene understanding, and learning more about these genes functions will shed light on possible biological mechanisms [28]. For instance, ASD candidate genes include those who play a significant role in neuronal excitability, brain development or neurotransmitter function [29, 30]. Most ASD-related genetic defects encode proteins involved in activity-dependent neuronal changes or those specific to the neuronal synapse, including regulatory proteins such as transcription factors [25, 31].

It has been shown that those with advanced paternal and maternal age are at enhanced risk of having an ASD child [32]. Maternal history of

autoimmune disorders has been postulated, such as psoriasis, thyroid disease or diabetes but the study findings remain mixed [33, 34]. According to recent research, another field of concern is immune activation during pregnancy or maternal infection and could be a possible risk factor [35-37]. There were also records of both longer and shorter inter-pregnancy periods raising the risk of ASD [38]. Children born prematurely were found to have an elevated ASD risk in addition to other disorders related to neurodevelopment [38]. In an earlier epidemiological study, low birth weight, preterm delivery, low Apgar scores, caesarian delivery and uterine bleeding were identified as a few factors more consistently correlated with autism [39]. A recent meta-analysis identified the association of several risk factors including pre-, peri- and postnatal periods with ASD and the results showed that during the prenatal period, the factors including maternal and paternal age ≥35 years, mother's and father's race, antepartum hemorrhage, threatened abortion, gestational diabetes and gestational hypertension were significantly associated with the risk of autism. During the perinatal period, the factors associated with autism risk were fetal distress, preeclampsia, breech presentation, no labor, induced labor, spontaneous labor, parity ≥4, gestational age ≤36 weeks and caesarian delivery. During the postnatal period, the factors associated with autism risk were brain anomaly, male gender, postpartum hemorrhage and low birth weight [40]. However, to identify the factors that are associated with ASD risk, the research is continuously going, but no solid determinations have been made [41].

Social and economic impacts

ASDs can substantially restrict an individual's capacity to participate in society and carry out routine activities. ASDs also have negative social consequences and educational challenges for the person, as well as employment issues. ASDs threaten people with these conditions and their families with substantial economic and emotional pressure. Caring for children with severe ASD conditions can be demanding, particularly regarding parental support and where access to services is inadequate. Consequently, the participation of caretakers is widely recognized as a vital component of caring for ASD children. Although some people with ASD can live independently, some have serious disabilities and need support and lifelong treatment [2].

Diagnosis

ASD can be diagnosed accurately in children from two years of age with early intervention helping these patients. The average diagnostic age, however, is between 3 and 6 years. It was thought that one of the reasons for this delay is the immense difficulty in diagnosing these disorders at an early age. A variety of factors contribute to this: a) language delays and social deficits that cannot be detected until the child starts to relate to pre-school peers, and b) the appearance of symptoms is very complex and varies in age [42, 43]. The detection and diagnosis of ASD, by the American Academy of Neurology (AAN) emphasize the need for a double approach (**Figure 1**). To discover any changes in the children's neurodevelopment for strict monitoring or deviations from typical, it is significant that specialists stay alert from the child's birth, which is the first stage. To identify the child's clinical characteristics is the second level diagnosis of ASD and then perform three assessment phases [44].

First phase, possible cases identification: The goal is "to check the parents observations" or "to identify the manifestations regarding the social interaction and the child's communication and behaviour" [44].

Second phase, global evaluation: Attempts to observe the significance and the consistency of the child's behavioural and neurological manifestations to validate the findings from the physicians who referred the child to the specialist or parents' concerns [44].

Third phase, specific diagnosis: sets out the definitive ASD diagnosis and describes its type. To this end, the knowledge provided by the specialists and the parents who have seen the patient are contrasted and the required tests are applied to correlate the evidence with the DSM-5 diagnostic manual criteria [44].

In the diagnosis of ASD, the DSM-5 is regarded as the gold standard and is closely mirrored by the implantable cardioverter-defibrillator (ICD). Similar to the Kanner children first identified, the DSM-5 classifies ASD based on repetitive

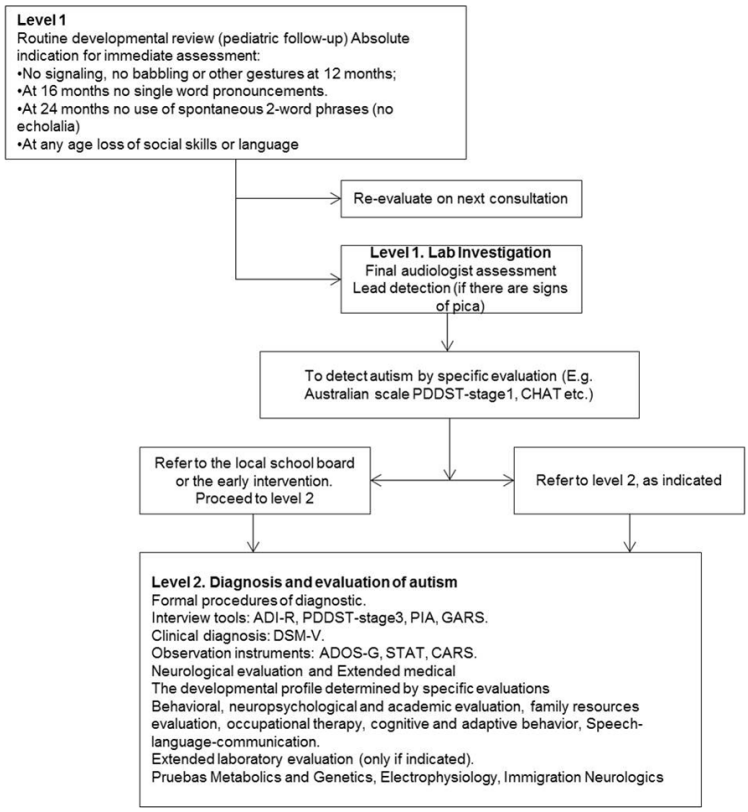

Figure 1. Levels of diagnosis for autism.

behaviours, the prevalence of limited social communication with deficits, providing a grade between 1 and 3 for each of these two categories based on severity. A child with milder symptoms and 'requires support' comes under category 1. A child with severe symptoms and 'requires very substantial support' comes under category 3. Often included with a diagnosis are clinical records with any associated language impairments, intellectual impairments, environmental factors, genetic conditions or medical conditions. In subsequent revisions, the ICD and the DSM have extended diagnostic criteria; specifically, the reclassification of pervasive developmental disorders not otherwise specified (PDD-NOS) and Asperger's by the DSM-5 now falls under a single ASD diagnosis [45].

Since autism has no biological diagnostic markers, the judgement is strictly clinical, based on the behavioural manifestations given by the DSM-5 criteria. The manual of DSM-5 states that the important characteristics of ASD disorders are persistent social deterioration and social interaction, reciprocal communication (criteria A), repetitive activities, interests, or restrictive and behavioural patterns (criteria B). Since early childhood, these symptoms limit or impede daily function (criteria C and D). Also, the disorder's manifestations vary greatly depending on the chronological age, autistic condition severity and development level. Based on the characteristics of the individual and his/her environment, the stage of obvious functional deterioration will vary [46, 47].

Differential diagnosis

Unidentified hearing impairment: "Other domains will be normal despite speech delay that is compensated for by gestures".

Intellectual Disability/Global developmental delay (GDD): In all fields, the impairment level will be appropriate and equal for the developmental age.

Social communication disorder: Difficulties in social communication result in functional limitations, but there are no repeated behaviours or deviant sensory responses.

ADHD: That is the most frequent misdiagnosis. Hyperactivity is only a symptom that is not pathognomic of ADHD. Impulsivity, hyperactivity and inattention are found in ADHD, but it is normal to have social skills, play, communication and intellect [48].

Diagnosis role in research

Heterogeneity of research participants

The broad criteria for diagnosis of ASD lead to a heterogeneous pool of participants in the research. In her book, Rethinking Autism [49], Lynn Waterhouse proposes abandoning ASD diagnosis DSM-5 for study. Other researchers suggest that the DSM-5 be amended to include more ASD subtypes [50]. Also, without a

reclassification, SPARK by the Simons Foundation [51], one of the largest ASD research projects to date, narrows participants' pools via a questionnaires series, excluding those who have identified epilepsy, or genetic disorders.

Future of diagnostics

The practice standard for ASD diagnosis is first by submicroscopic copy number variants (CNV) detection and microarray for large, followed by whole-genome sequencing (WGS) or whole-exome sequencing (WES). Several genomic techniques were used to understand the molecular mechanism of ASD, including epigenomics and transcriptomics, and finally inform clinical treatment. Testing of cell-free DNA (cf-DNA) is becoming an important diagnostic method. This form of test or screening is also referred to as the Non-Invasive Prenatal Test (NIPT). Fetal cf DNA in maternal plasma may be tested for potential genetic disorders or associated conditions with single nucleotide polymorphism-based approaches or next-generation sequencing techniques. As previously mentioned, using clinical genomics or genetic testing as an *in vitro* screen method can be a possible way to classify people at risk of autism.

Advances in ASD clinical care continue to rely on collaborative, multidisciplinary research efforts. Current efforts are underway to classify functional subtypes of genetic-ontological methods that may gain clinical intervention in addition. This includes investigating broader gene disruption-associated phenotypes that share molecular properties, such as CHD8 protein-regulated genes [52, 53]. Identifying gene disruptions measurable neurological effects, such as an electrophysiological (EEG) signature, may convert into functional biomarkers of ASD, which are important for clinical trials [60]. In the meantime, the genetic subtype's pharmacotherapies development, including SCN2A, would need further information about the neurodevelopmental disability reversibility and timing of genetic expression. Therefore, continued systematic phenotyping will be important for the success of the clinical trial on genetic ASD subtypes [52].

Management of ASD

The main goals of the management of ASD are to treat co-morbid conditions, reduce maladaptive behavior, promote learning and problem solving, consider educational placement, communication and social skills, build cognitive skills, provide coping assistance to families, and families for youth with ASD who are in adulthood and adolescence (**Figure 2**). A multidisciplinary team consisting of individualized management should be prepared.

1) Clinician (psychiatrist, general practitioner or experienced pediatrician) - if indicated, for holistic assessment and pharmacotherapy.

2) Clinical psychologist or developmental pediatrician-for assessment of: i) Core symptoms: These are the Indian Scale for Assessment of Autism and the INCLEN: ASD Consensus Clinical Criteria [54, 55]. Both of these rating scales have yet to be well known in children [56]. Internationally recommended tools are Autism Diagnosis Observation Schedule General (ADOS-G) and Autism Diagnosis Interview-Revised (ADI-R). Due to the lack of specialized training providers and expenses, both are not widely used in India. For the severity assessment, the Childhood Autism Rating Scale (CARS) is widely used. Recently, for diagnostic purposes, two Indian tools have been established, which require further assessment. ii) Cognitive function: Tools that evaluate nonverbal and verbal competencies separately should be used to accurately evaluate cognitive capacity (i.e., Leiter's scale and Mullen's scale). iii) Adaptive function: The Vineland Adaptive Behavior Scale (second edition) rates the quality and frequency of different skills that are actually seen during activities of daily living (ADL). Irrespective of quality, it's better than measures of growth that only calculate whether or not there is ability.

3) Speech-language pathologist-language assessment assists with eating difficulties and offers alternative forms of communication or speech therapy.

4) Pediatric neurologist/geneticist - if warranted.

5) Occupational therapist - Develops ADL-based skills training and offers Sensory Integration (SI) therapy, if necessary (predominant sensory issues). During play activities, SI offers controlled sensory stimuli meant to improve the

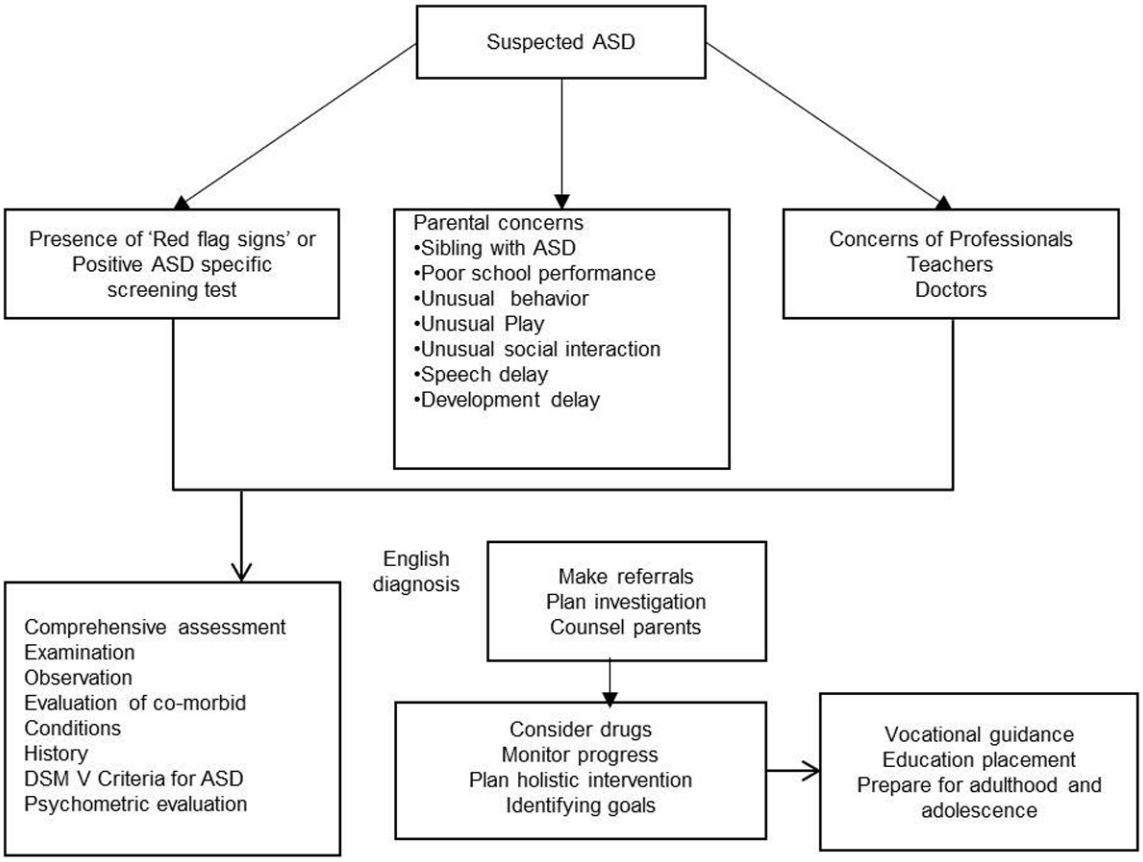

Figure 2. Algorithmic approach to management of a child with suspected ASD.

way the child responds to movement, sight, sound and touch.

6) Behavior analyst - for behavior change treatment.

7) Special educator - to devise an Individualized Education Strategy and to decide on placement in education (integrated/inclusive, normal school, or, special).

8) Adolescent and child psychiatrist.

9) Psychiatric social worker - for providing family support.

Unfortunately, there are limited numbers of multidisciplinary centres which offer all these services. For providing high-quality intervention, there is a paucity of experienced and trained personnel. Professionals with experience and qualifications working with ASD children are important. Experts sometimes have to multitask [48].

Psychological and behavioural management

Once an ASD diagnosis is established, deficits are dealt with using a multi-faceted team approach [4]. Play therapies, speech, behavioural and occupational training are regular treatments. For ASD, there are no therapies available in the pharmacological field; however, peoples receive some medication to overcome comorbidities, including ADHD and seizures. In some areas, children can obtain support services in schools, including intellectual disabilities, learning disorders, etc. [57]. Because of gaps in contact with people living with ASD, family and caregivers often struggle to relate. They are frequently encouraged to seek mutual pleasure with behaviours encouraging teamwork as part of the care. Alongside traditional therapies, families and individuals with ASD may also seek community support. This can include websites or online support groups. One such popular website is Autism Speaks [58], which allows people to connect, as well as re-

ceive moral support and access the latest research.

Prognosis

The prognosis for an individual with ASD is as heterogeneous as the diagnosis. Those on the mild end of the spectrum, known as Aspergers, with an average to high intelligence quotient (IQ), will also enter mainstream schooling, advance into the workplace, and develop social communication skills with therapeutic support. It is not uncommon for individuals at the highest end, many of whom would have previously received a diagnosis of Asperger's, to embrace and capitalize on their atypical neurodevelopment [59, 60]. While an interest in objects, a rigid need for sameness, routine, and detail can stifle social interaction, imagination, and versatility. The same qualities can be extremely useful in a field that needs a limited focus on objects, precision, and strict adherence to routine. The prognosis for those with a serious diagnosis is much less positive. Severe cases may never learn to communicate, and they remain in a world that is withdrawn from peers and family. ASD treatment aims to improve the patient's and others' quality of life. Due to communication difficulties for those with ASD, family and caregivers often fail to connect and are encouraged as part of therapy to find mutual enjoyment in activities that foster bonding [61, 62]. Several factors relate to improved prognoses: psychotherapeutic intervention as early as possible, and for those who score well on intensive, nonverbal intelligence tests, with slight or no mental retardation they will have some communicative language development before the age of six. Cooperation between specialists such as educators, occupational therapists, speech therapists, psychologists, neuroscientists, psychiatrists and neurologists is crucial for continuing to foster understanding and allowing patients to be approached more appropriately [63-65].

Future direction

Gene therapy, as an efficient treatment for ASD, seems to hold promise. The first preclinical studies in monogenic ASD have recently been published, involving both gene silencing and replacement. This study can be applied to polygenic ASD with a better understanding of ASD etiology [66]. Interestingly, converging lines of evidence from genetically modified mice, especially models of monogenic disorders and disease-causing copy number variants, such as Rett syndrome (RTT) [67], Tuberous Sclerosis Complex (TSC) [68], Phelan-McDermid syndrome (PMDS) [69], support the hypothesis that ASD has common underlying pathophysiology involving changes in cellular properties that lead to abnormal neural network activity and behavioural deficits [31]. The use of genome editing is another potential revolutionary therapy. We hope that the strategies of Clustered Regularly Interspaced Short Palindromic Repeats-gene (CRISPR-gene) editing will soon be used more and more in ASD models to alleviate neurodevelopment issues and recapitulate normal physiology conditions. Recent research, for example, used CRISPR-Gold, a novel method for delivery of nanoparticles, to target striatal mGluR5 levels in Fragile X syndrome (FXS) mice. Besides effective mGluR5 levels reduction, the study found that repetitive behaviours in FXS mice were rescued subsequently [70].

Conclusion

In conclusion, ASD is common among children. Therefore, screening for ASD in all young children should be practised universally. The current article analyzed the significant tools available in the diagnosis and management of ASD. The study also provides the future direction for ASD diagnosis and management, which will help clinicians decide the best teraputic practices.

Disclosure of conflict of interest

None.

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References

[1] Hyman SL, Levy SE and Myers SM. Identification, evaluation and management of children with autism spectrum disorder. Pediatrics 2020; 145: e20193447.
[2] World Health Organization. Autism spectrum disorders. World Heal Organ 2019.
[3] Oviedo N, Manuel-Apolinar L, de la Chesnaye E and Guerra-Araiza C. Aspectos geneticos y

neuroendocrinos en el trastorno del espectro autista. Boleten Med Hosp Infant Mex 2015; 72: 5-14.
[4] Yoo H. Genetics of autism spectrum disorder: current status and possible clinical applications. Exp Neurobiol 2015; 24: 257-72.
[5] Baio J, Wiggins L, Christensen DL, Maenner MJ, Daniels J, Warren Z, Kurzius-Spencer M, Zahorodny W, Robinson Rosenberg C, White T, Durkin MS, Imm P, Nikolaou L, Yeargin-Allsopp M, Lee LC, Harrington R, Lopez M, Fitzgerald RT, Hewitt A, Pettygrove S, Constantino JN, Vehorn A, Shenouda J, Hall-Lande J, Van Naarden Braun K and Dowling NF. Prevalence of autism spectrum disorder among children aged 8 years - autism and developmental disabilities monitoring network, 11 sites, United States, 2014. MMWR Surveill Summ 2018; 67: 1-23.
[6] Ellison-Wright Z and Boardman C. Diagnosis and management of ASD in children and adolescents. Prog Neurol Psychiatry 2015; 19: 28-32.
[7] Xu G, Strathearn L, Liu B and Bao W. Prevalence of autism spectrum disorder among us children and adolescents, 2014-2016. JAMA 2018; 319: 81.
[8] Baxter AJ, Brugha TS, Erskine HE, Scheurer RW, Vos T and Scott JG. The epidemiology and global burden of autism spectrum disorders. Psychol Med 2015; 45: 601-13.
[9] Sztainberg Y and Zoghbi HY. Lessons learned from studying syndromic autism spectrum disorders. Nat Neurosci 2016; 19: 1408-17.
[10] Reddy KS. Cytogenetic abnormalities and fragile-x syndrome in autism spectrum disorder. BMC Med Genet 2005; 6: 3.
[11] Demily C, Poisson A, Peyroux E, Gatellier V, Nicolas A, Rigard C, Schluth-Bolard C, Sanlaville D and Rossi M. Autism spectrum disorder associated with 49, XYYYY: case report and review of the literature. BMC Med Genet 2017; 18: 9.
[12] Tartaglia NR, Wilson R, Miller JS, Rafalko J, Cordeiro L, Davis S, Hessl D and Ross J. Autism spectrum disorder in males with sex chromosome aneuploidy. J Dev Behav Pediatr 2017; 38: 197-207.
[13] Ross JL, Roeltgen DP, Kushner H, Zinn AR, Reiss A, Bardsley MZ, McCauley E and Tartaglia N. Behavioral and social phenotypes in boys with 47,XYY syndrome or 47,XXY klinefelter syndrome. Pediatrics 2012; 129: 769-78.
[14] Bardsley MZ, Kowal K, Levy C, Gosek A, Ayari N, Tartaglia N, Lahlou N, Winder B, Grimes S and Ross JL. 47,XYY syndrome: clinical phenotype and timing of ascertainment. J Pediatr 2013; 163: 1085-94.
[15] Johnson CP and Myers SM. Identification and evaluation of children with autism spectrum disorders. Pediatrics 2007; 120: 1183-215.
[16] Agrawal S, Rao SC, Bulsara MK and Patole SK. Prevalence of autism spectrum disorder in preterm infants: a meta-analysis. Pediatrics 2018; 142: e20180134.
[17] Parner ET, Baron-Cohen S, Lauritsen MB, Jørgensen M, Schieve LA, Yeargin-Allsopp M and Obel C. Parental age and autism spectrum disorders. Ann Epidemiol 2012; 22: 143-50.
[18] Maisonneuve H and Floret D. Affaire Wakefield: 12ans d'errance car aucun lien entre autisme et vaccination ROR n'a été montré. Presse Med 2012; 41: 827-34.
[19] Dyer C. Lancet retracts Wakefield's MMR paper. BMJ 2010; 340: c696.
[20] Skefos J, Cummings C, Enzer K, Holiday J, Weed K, Levy E, Yuce T, Kemper T and Bauman M. Regional alterations in purkinje cell density in patients with autism. PLoS One 2014; 9: e81255.
[21] Stoodley CJ, D'Mello AM, Ellegood J, Jakkamsetti V, Liu P, Nebel MB, Gibson JM, Kelly E, Meng F, Cano CA, Pascual JM, Mostofsky SH, Lerch JP and Tsai PT. Altered cerebellar connectivity in autism and cerebellar-mediated rescue of autism-related behaviors in mice. Nat Neurosci 2017; 20: 1744-51.
[22] De Rubeis S, He X, Goldberg AP, Poultney CS, Samocha K, Cicek AE, Kou Y, Liu L, Fromer M, Walker S, Singh T, Klei L, Kosmicki J, Shih-Chen F, Aleksic B, Biscaldi M, Bolton PF, Brownfeld JM, Cai J, Campbell NG, Carracedo A, Chahrour MH, Chiocchetti AG, Coon H, Crawford EL, Curran SR, Dawson G, Duketis E, Fernandez BA, Gallagher L, Geller E, Guter SJ, Hill RS, Ionita-Laza J, Jimenz Gonzalez P, Kilpinen H, Klauck SM, Kolevzon A, Lee I, Lei I, Lei J, Lehtimäki T, Lin CF, Ma'ayan A, Marshall CR, McInnes AL, Neale B, Owen MJ, Ozaki N, Parellada M, Parr JR, Purcell S, Puura K, Rajagopalan D, Rehnström K, Reichenberg A, Sabo A, Sachse M, Sanders SJ, Schafer C, Schulte-Rüther M, Skuse D, Stevens C, Szatmari P, Tammimies K, Valladares O, Voran A, Li-San W, Weiss LA, Willsey AJ, Yu TW, Yuen RK; DDD Study; Homozygosity Mapping Collaborative for Autism; UK10K Consortium, Cook EH, Freitag CM, Gill M, Hultman CM, Lehner T, Palotie A, Schellenberg GD, Sklar P, State MW, Sutcliffe JS, Walsh CA, Scherer SW, Zwick ME, Barett JC, Cutler DJ, Roeder K, Devlin B, Daly MJ and Buxbaum JD. Synaptic, transcriptional and chromatin genes disrupted in autism. Nature 2014; 515: 209-15.
[23] Shen MD, Kim SH, McKinstry RC, Gu H, Hazlett HC, Nordahl CW, Emerson RW, Shaw D, Elison JT, Swanson MR, Fonov VS, Gerig G, Dager SR, Botteron KN, Paterson S, Schultz RT, Evans AC, Estes AM, Zwaigenbaum L, Styner MA, Amaral DG, Piven J, Hazlett HC, Chappell C, Dager S,

Estes A, Shaw D, Botteron K, McKinstry R, Constantino J, Pruett J, Schultz R, Zwaigenbaum L, Elison J, Evans AC, Collins DL, Pike GB, Fonov V, Kostopoulos P, Das S, Gerig G, Styner M, Gu H and Piven J; Infant Brain Imaging Study Network. Increased extra-axial cerebrospinal fluid in high-risk infants who later develop autism. Biol Psychiatry 2017; 82: 186-93.

[24] Hazlett HC, Gu H, Munsell BC, Kim SH, Styner M, Wolff JJ, Elison JT, Swanson MR, Zhu H, Botteron KN, Collins DL, Constantino JN, Dager SR, Estes AM, Evans AC, Fonov VS, Gerig G, Kostopoulos P, McKinstry RC, Pandey J, Paterson S, Pruett JR, Schultz RT, Shaw DW, Zwaigenbaum L and Piven J; IBIS Network; Clinical Sites; Data Coordinating Center; Image Processing Core; Statistical Analysis. Early brain development in infants at high risk for autism spectrum disorder. Nature 2017; 542: 348-51.

[25] Kim H, Keifer C, Rodriguez-Seijas C, Eaton N, Lerner M and Gadow K. Quantifying the optimal structure of the autism phenotype: a comprehensive comparison of dimensional, categorical and hybrid models. J Am Acad Child Adolesc Psychiatry 2019; 58: 876-886, e2.

[26] Sandin S, Lichtenstein P, Kuja-Halkola R, Larsson H, Hultman CM and Reichenberg A. The familial risk of autism. JAMA 2014; 311: 1770.

[27] Risch N, Hoffmann TJ, Anderson M, Croen LA, Grether JK and Windham GC. Familial recurrence of autism spectrum disorder: evaluating genetic and environmental contributions. Am J Psychiatry 2014; 171: 1206-13.

[28] Walsh CA, Morrow EM and Rubenstein JL. Autism and brain development. Cell 2008; 135: 396-400.

[29] McDougle CJ, Erickson CA, Stigler KA and Posey DJ. Neurochemistry in the pathophysiology of autism. J Clin Psychiatry 2005; 66: 9-18.

[30] Rubenstein JL and Merzenich MM. Model of autism: increased ratio of excitation/inhibition in key neural systems. Genes Brain Behav 2003; 2: 255-67.

[31] Zoghbi HY. Postnatal neurodevelopmental disorders: meeting at the synapse? Science 2003; 302: 826-30.

[32] Croen LA, Najjar DV, Fireman B and Grether JK. Maternal and paternal age and risk of autism spectrum disorders. Arch Pediatr Adolesc Med 2007; 161: 334.

[33] Xiang AH, Wang X, Martinez MP, Page K, Buchanan TA and Feldman RK. Maternal type 1 diabetes and risk of autism in offspring. JAMA 2018; 320: 89.

[34] Croen LA, Grether JK, Yoshida CK, Odouli R and Van de Water J. Maternal autoimmune diseases, asthma and allergies and childhood autism spectrum disorders. Arch Pediatr Adolesc Med 2005; 159: 151-7.

[35] Croen LA, Qian Y, Ashwood P, Zerbo O, Schendel D, Pinto-Martin J, Daniele Fallin M, Levy S, Schieve LA, Yeargin-Allsopp M, Sabourin KR and Ames JL. Infection and fever in pregnancy and autism spectrum disorders: findings from the study to explore early development. Autism Res 2019; 12: 1551-1561.

[36] Choi GB, Yim YS, Wong H, Kim S, Kim H, Kim SV, Hoeffer CA, Littman DR and Huh JR. The maternal interleukin-17a pathway in mice promotes autism-like phenotypes in offspring. Science 2016; 351: 933-9.

[37] Estes ML and McAllister AK. Immune mediators in the brain and peripheral tissues in autism spectrum disorder. Nat Rev Neurosci 2015; 16: 469-86.

[38] Schieve LA, Tian LH, Drews-Botsch C, Windham GC, Newschaffer C, Daniels JL, Lee LC, Croen LA and Danielle Fallin M. Autism spectrum disorder and birth spacing: findings from the study to explore early development (SEED). Autism Res 2018; 11: 81-94.

[39] Newschaffer CJ, Croen LA, Daniels J, Giarelli E, Grether JK, Levy SE, Mandell DS, Miller LA, Pinto-Martin J, Reaven J, Reynolds AM, Rice CE, Schendel D and Windham GC. The epidemiology of autism spectrum disorders. Annu Rev Public Health 2007; 28: 235-58.

[40] Wang C, Geng H, Liu W and Zhang G. Prenatal, perinatal and postnatal factors associated with autism. Medicine (Baltimore) 2017; 96: e6696.

[41] Ruzzo EK, Pérez-Cano L, Jung JY, Wang LK, Kashef-Haghighi D, Hartl C, Singh C, Xu J, Hoekstra JN, Leventhal O, Leppä VM, Gandal MJ, Paskov K, Stockham N, Polioudakis D, Lowe JK, Prober DA, Geschwind DH and Wall DP. Inherited and de novo genetic risk for autism impacts shared networks. Cell 2019; 178: 850-866, e26.

[42] Giangaspro EC and Pertejo MA. Instrumentos para la deteccion precoz de los trastornos del espectro autista. Pediatr Aten Primaria: Asociacion Espaola de Pediatria de Atencion Primaria 2007; 9: 301-15.

[43] Kim SK. Recent update of autism spectrum disorders. Korean J Pediatr 2015; 58: 8-14.

[44] Alvarez-Alcantara E. Trastornos del espectro autista. Rev Mex Pediatr 2007; 74: 269-76.

[45] Association AP. Diagnostic and statistical manual of mental disorders (DSM-5®). American Psychiatric Publishing 2013.

[46] Blazer-Dan, Burke-Jack, William C, Castellanos X and Joel D. Trastorno del espectro autista. Manual diagnóstico y estadístico de los trastornos mentales. España 2014; 50-9.

[47] Cabrera. Generalidades sobre el autismo. Rev Colomb Psiquiat 2007; 36: 208-20.

[48] Mukherjee SB. Autism spectrum disorders - diagnosis and management. Indian J Pediatr 2017; 84: 307-14.
[49] Waterhouse L. Rethinking autism: variation and complexity: Academic Press 2013.
[50] Posar A, Resca F and Visconti P. Autism according to diagnostic and statistical manual of mental disorders 5th edition: the need for further improvements. J Pediatr Neurosci 2015; 10: 146-8.
[51] Sparks A. Examining the consequential validity of using an English language proficiency assessment for reclassification decisions; 2019.
[52] Cotney J, Muhle RA, Sanders SJ, Liu L, Willsey AJ, Niu W, Liu W, Klei L, Lei J, Yin J, Reilly SK, Tebbenkamp AT, Bichsel C, Pletikos M, Sestan N, Roeder K, State MW, Devlin B and Noonan JP. The autism-associated chromatin modifier CHD8 regulates other autism risk genes during human neurodevelopment. Nat Commun 2015; 6: 6404.
[53] Sugathan A, Biagioli M, Golzio C, Erdin S, Blumenthal I, Manavalan P, Ragavendran A, Brand H, Lucente D, Miles J, Sheridan SD, Stortchevoi A, Kellis M, Haggarty SJ, Katsanis N, Gusella JF and Talkowski ME. CHD8 regulates neurodevelopmental pathways associated with autism spectrum disorder in neural progenitors. Proc Natl Acad Sci U S A 2014; 111: E4468-77.
[54] Juneja M, Mishra D, Russell PS, Gulati S, Deshmukh V, Tudu P, Sagar R, Silberberg D, Bhutani VK, Pinto JM, Durkin M, Pandey RM, Nair MK and Arora NK; INCLEN Study Group. INCLEN diagnostic tool for autism spectrum disorder (INDT-ASD): development and validation. Indian Pediatr 2014; 51: 359-65.
[55] Ministry of Social Justice and Empowerment. Scientific report on research project for development of Indian scale for assessment of autism. 2009.
[56] Mukherjee SB, Malhotra MK, Aneja S, Chakraborty S and Deshpande S. Diagnostic accuracy of Indian Scale for Assessment of Autism (ISAA) in chidren aged 2-9 years. Indian Pediatr 2015; 52: 212-6.
[57] Guldberg K, Ashbee E, Kossyvaki L, Bradley R and Basulayyim A. Meeting the needs of pupils with autism in qatar: moving forward. Doha: Qatar WISE; 2017.
[58] Autism Speaks. Enhancing lives today and accelerating a spectrum of solutions for tomorrow; 2021.
[59] Cederlund M, Hagberg B, Billstedt E, Gillberg IC and Gillberg C. Asperger syndrome and autism: a comparative longitudinal follow-up study more than 5 years after original diagnosis. J Autism Dev Disord 2008; 38: 72-85.
[60] Howlin P, Goode S, Hutton J and Rutter M. Adult outcome for children with autism. J Child Psychol Psychiatry 2004; 45: 212-29.
[61] Fernell E, Eriksson and Gillberg C. Early diagnosis of autism and impact on prognosis: a narrative review. Clin Epidemiol 2013; 33: 33-43.
[62] Styles M, Alsharshani D, Samara M, Alsharshani M, Khattab A, Qoronfleh MW and Al-Dewik NI. Risk factors, diagnosis, prognosis and treatment of autism. Front Biosci 2020; 25: 1682-717.
[63] Rogel-Ortiz. Autismo. Gac Méd Méx 2005; 141: 143-7.
[64] Calderon RS. El sindrome autista: un acercamiento a sus caracteristicas y generalidades. Rev Educ 2002; 26: 47-61.
[65] Gadia CA and Tuchman RF. Manejo de los ninos con trastornos del espectro autista. Rev Neurol 2003; 36: 166-73.
[66] Benger M, Kinali M and Mazarakis ND. Autism spectrum disorder: prospects for treatment using gene therapy. Mol Autism 2018; 9: 1-10.
[67] Chahrour M and Zoghbi HY. The story of Rett syndrome: from clinic to neurobiology. Neuron: Elsevier 2007; 56: 422-37.
[68] Sundberg M and Sahin M. Cerebellar development and autism spectrum disorder in tuberous sclerosis complex. J Child Neurol 2015; 30: 1954-62.
[69] Jiang Y and Ehlers MD. Modeling autism by SHANK gene mutations in mice. Neuron: Elsevier 2013; 78: 8-27.
[70] Lee JJ, Wedow R, Okbay A, Kong E, Maghzian O, Zacher M, Nguyen-Viet TA, Bowers P, Sidorenko J, Karlsson Linnér R, Fontana MA, Kundu T, Lee C, Li H, Li R, Royer R, Timshel PN, Walters RK, Willoughby EA, Yengo L; 23andMe Research Team; COGENT (Cognitive Genomics Consortium); Social Science Genetic Association Consortium, Alver M, Bao Y, Clark DW, Day FR, Furlotte NA, Joshi PK, Kemper KE, Kleinman A, Langenberg C, Mägi R, Trampush JW, Verma SS, Wu Y, Lam M, Zhao JH, Zheng Z, Boardman JD, Campbell H, Freese J, Harris KM, Hayward C, Herd P, Kumari M, Lencz T, Luan J, Malhotra AK, Metspalu A, Milani L, Ong KK, Perry JRB, Porteous DJ, Ritchie MD, Smart MC, Smith BH, Tung JY, Wareham NJ, Wilson JF, Beauchamp JP, Conley DC, Esko T, Lehrer SF, Magnusson PKE, Oskarsson S, Pers TH, Robinson MR, Thom K, Watson C, Chabris CF, Meyer MN, Laibson DI, Yang J, Johannesson M, Koellinger PD, Turley P, Visscher PM, Benjamin DJ and Cesarini D. Gene discovery and polygenic prediction from a genome-wide association study of educational attainment in 1.1 million individuals. Nat Genet 2018; 50: 1112-1121.