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Early Screening and Diagnosis of Autism

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Abstract: **Autism Spectrum Disorders have for some time been the focus of intense interest for clinicians and researchers because of the high prevalence of the disorders among children in the community. Particular attention has been paid to the early diagnosis of the disorder and to the intensive therapeutic intervention. Currently the best prognosis for autism lays in the early diagnosis and intervention. But diagnosis of autism at an early age is challenging due to the existing phenotypic and etiological heterogeneity among ASD individuals. There are many screening scales for autism, but their specificity and sensitivity vary to varying degrees. Therefore, an efficient early diagnosis method is needed. This paper presents a review of the early detection of ASD.**

Keywords: Autism spectrum disorder; Early diagnosis; Early screening tool; Imaging diagnosis

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1. Introduction

Autism spectrum disorder (ASD) is a complex neurobiological disorder characterized by neuropsychological and behavioral deficits. Deficits in social communication as well as restricted interests and repetitive behaviors are the major autistic symptoms and visible after a certain age. It results in related functional impairments in social contexts. It is one of the fastest growing disabilities. Its current prevalence rate in the U.S. estimated by the Centers for Disease Control and Prevention is 1 in 68 births.

Previous studies showed that about l/5 of the parents whose children with ASD can find some abnormal behaviors of children when they are 10 months old, about 2/5 of parents with children during 11-17 months could find the abnormal behaviors. About 2/5 of parents with 18 to 24 months old children can find something abnormal as well. In other words, at least 4/5 of the parents could find abnormal behavior before their children are 2 years old. However, as a result of regional economy, culture and parents' lack of understanding of ASD, most of the children at the age of 3, 4 later can be diagnosed [1].

Ismail et al. [2] proposed that critical and sensitive periods of brain development in health and disease can create "windows of opportunity" for neuromodulatory interventions that are not commonly seen in adult brain and probably augment plasticity responses and improve clinical outcomes. The theory of "the first 1000 days of life" suggests that fetus period and two years after birth are window of opportunity for intervention.

Early identification and intervention can significantly improve the prognosis of infants with a strong plasticity of the nervous system and enable them to better integrate into society [3]. As a result, the American academy of pediatrics hopes to bring forward the age of ASD identification to 2 years old (the current average age is 4 years old) [4].

Most institutions in the world currently make the diagnosis of ASD by administering both a play-based assessment (Autism Diagnostic Observation Schedule, ADOS) and a parent interview (Autism Diagnostic Interview- Revised, ADIR). But most clinicians make the diagnosis according to a clinical judgment with international diagnostic criteria without any diagnostic assessment in China [5]. Some clinicians consider the screening results to be the final diagnosis without using any additional diagnostic instruments [6]. Some adopted the Childhood Autism Rating Scale (CARS) as the diagnostic instrument. So there's a certain amount of errors in the diagnosis of autism, several autism screening scales are described below.

2. Early screening tool

Screening can be divided into primary screening and secondary screening. Primary screening is available to all children. It is designed to identify infants and young children at risk for ASD, quickly and effectively. Secondary screening is mainly for infants and children with positive primary screening, which provides a basis for subsequent early diagnosis and intervention.

2.1. Primary screening tool

The checklist for autism in toddlers (CHAT) is the first early screening tool in the world. It focuses on the common attention and hypothetical play ability of 18-month-old children [7]. Baird et al. [8] followed 16,235 children for 6 years and found that CHAT had a high specificity, but its sensitivity was not high (less than 40%), so it is easy to cause missed diagnosis. Swedish researchers found that CHAT screening could do not improve early identification

of ASD children before they were 3 years old [9]. The modified checklist for autism in toddlers (M-CHAT) is an improved version of CHAT. It is one of the most commonly used screening scales in the world for children aged 18-24 months. The sensitivity and specificity of M-CHAT can be as high as 0.85 and 0.93 [10]. It reduces the missed diagnosis due to functional regression in children with ASD and is currently used in the American healthcare system [11].

2.2. Secondary screening tool

Infant-toddler checklist (ITC) is mainly suitable for infants aged from 12 to 24 months. The American academy of pediatrics guidelines recommend it as a secondary screening tool for infants under 18 months of age. It is used to assess communication and social skills in children. The researchers find that it has high sensitivity, specificity and effectiveness [12]. Screening tool for autism in two year olds (STAT) is suitable for kids aged from 24 months to 36 months. However, Stone et al. [13] found that when the dividing line was 2.75, it was also applicable to high-risk children aged 12-23 months, and its sensitivity and specificity could be as high as 0.95 and 0.7.

2.3. Other screening tools

The Social Communication Questionnaire (SCQ) was originally designed as a screening tool for children 4 years of age or older enrolled in epidemiological research or for studies comparing individuals with ASD and other clinical groups [14], and it is now used clinically. It was derived from the Autism Diagnostic Interview Revised (ADIR), a parent interview used to diagnose ASD in combination with other measures. The SCQ is strongly correlated with the ADI-R ($r = 0.71$, $p < 0.001$) [15].

The SCQ has high internal consistency (Cronbach's alpha = 0.87). It also has good discriminative validity when distinguishing between children with ASD and non-ASD diagnoses at all intelligence quotient levels, but particularly when used with children 4 years of age or older and children from clinical populations. The sensitivity of the SCQ, or ability to correctly classify children with ASD, is about 96% in samples of children without intellectual disability. The specificity of the SCQ, or ability to correctly classify children without ASD, is about 80% in samples of children without intellectual disability [16]. Specificity of the SCQ drops considerably when used with children who have intellectual impairments.

Social Responsiveness Scale (SRS) has high internal consistency (Cronbach's alpha = 0.76), and has good discriminant validity. Sensitivity and specificity are 0.85 and 0.75, respectively, when the SRS total score of 75 is used as the cutoff [16]. Previous research also suggests that the SRS could be a cost-effective assessment for measuring ASD symptoms in school and clinical settings. Specifically, the SRS has been found to be useful at differentiating between children with ASD and those without ASD. The SRS has also been used to track the severity of ASD symptoms over time, and it has been found to be useful for assessing response to interventions [17]. However, SRS scores are known to increase in the presence of some child behavior challenges, such as Attention Deficit / Hyperactivity Disorder [18], and mood disorders [19]. Further, child behavior problems as measured by the Child Behavior Checklist (CBCL) account for a large proportion of the variance in SRS scores [20] suggesting that behavior problems may impact screening performance.

SRS and SCQ effectively detect developmental and behavioral challenges, but may not reliably differentiate them from ASD. Screening individuals from minority and lower socioeconomic backgrounds is also problematic. If these screens are routinely used with large populations of minority and low-income families, the likely high false positive rate could tax limited resources. It doesn't mean that the SRS and SCQ are ineffective screens when used in the general population. Indeed, both the SCQ and SRS performed adequately for the combined sample and equally well for both boys and girls overall [21]. However, refining these screens to be more effective, regardless of the child's behavioral presentation and across cultures, could help reduce the impact of false positives.

3. Early diagnosis

3.1. Respond to facial expressions

Toddlers with autism focused more on the mouth area of the face and were less able to judge than the eye area [22].Therefore, detection of gaze and position can help in the diagnosis of autism [23]. Bekele et al. [24] used a virtual-reality-based facial expression intervention system that monitors eye gaze and physiological signals for ten ASD adolescents and ten normal adolescents in emotion recognition tasks. The differences between the ASD and normal groups were determined by using eye tracking indices and performance data. Weigelt et al. [25] found quantitative difference in facial discrimination between autistic and normal subjects as autistic subjects possess impaired facial identity recognition and eye discrimination. Studies show that the increased response to direct gaze triggering unprompted mental state attributions is reduced in autistic subjects, and they show increased response to averted gaze than the direct gaze [26].

3.2. The link between multisensory temporal function and speech processing

Stevenson et al. [27] revealed the relation between multisensory temporal function and speech processing in ASD individuals. The ASD and typically developing participants underwent three tasks: (a) an audiovisual simultaneity judgment task that includes single stimulus per run, audio, and visual-leading stimuli, (b) a McGurk task including audio only, visual only, and audiovisual presentations, and (c) auditory and visual temporal-order judgment tasks including run with auditory and visual stimuli. The sensory representations are the building blocks of higher order domain of speech perception. They observed weak binding between the multisensory temporal function and audiovisual speech processing using the McBurk effect that in turn causes communication barriers in ASD individuals.

3.3. Response to name

The decline in the rate of response to name is thought to be an early warning sign of ASD and a characteristic of infancy with broader autism phenotypes. Miller et al. [28] had a related study design. A response to name task was tested at 6, 9, 12, 15, 18, and 24 months of age in 156 infant siblings of children with ASD (high-risk) or typical development (low-risk). At 36 months of age, participants were classified into 1 of 3 outcome groups: group with ASD (n = 20), high-risk group without ASD (n = 76), or low-risk group without ASD (n = 60). Differences in longitudinal performance were assessed using generalized estimating equations, and sensitivity and specificity for identifying ASD were calculated. Differences in age 36-month functioning were examined between infants who developed ASD and repeatedly vs infrequently failed to respond to name.

They found that the infants who developed ASD were more likely to fail to orient to their names than infants who did not develop ASD. At 9 months of age, infants developing ASD were more likely to fail to orient to their names, persisting through 24 months. Sensitivity/specificity for identifying ASD based on at least 1 failure between 12 and 24 months were estimated at 0.70 in this sample. One-half of the infants who developed ASD had repeated failures in this timeframe, and demonstrated lower age 36-month receptive language, and earlier diagnosis of ASD than infants with ASD who had infrequent failures. In addition to recommended routine broad-based and ASD-specific screening, response to name should be regularly monitored in infants at risk for ASD. Infants who consistently fail to respond to their names in the second year of life may be at risk not only for ASD but also for greater impairment by age 3 years.

3.4. Atypical social attention

Atypical social attention is one of the earliest behavioral markers of ASD and often apparent by 12 months of age [29]. An eye-tracking study by Chawarska et al. [30] reports reduced social attention in 6-month-old infants later diagnosed with ASD. At 6 months, infants' oculomotor activity was evaluated during a dynamic audiovisual presentation on a video monitor. The stimuli were designed to capture, in a task-relevant fashion, the spontaneous regulation of visual attention in response to the ebbs and flows of social events. The stimulus consisted of a 3-minute video of an actress filmed in a setting containing four toys positioned at each corner of the screen and a table with ingredients for making sandwiches. The model made a sandwich: looking at the camera and attempting to engage the participant use eye contaction and infant-directed speech; and looking at the toys in the corners of the screen. Sometimes the referenced toy is stationary, sometimes it is moving.

Compared to the control groups, 6-month-old infants later were diagnosed with ASD attended less to the social scene when they did look at the scene, they spent less time monitoring the actress in general and her face in particular. Limited attention to the actress and her activities was not accompanied by enhanced attention to objects.

3.5. Imaging diagnosis

Functional brain imaging techniques used in autism include fMRI [31], MEG [32], EEG [33], SPECT [34], and PET [35]. The biggest feature of fMRI is that it can provide both structural imaging and functional imaging with high spatial resolution. In fact, fMRI has become the most commonly used important tool in the study of brain function.

Neuroanatomical and imaging studies have found cerebellar abnormalities in ASD children, such as decreased cerebellar volume, decreased number of purkinje cells, and abnormalities in hippocampal gyrus, basal ganglia, temporal lobe and cerebral cortex. In recent years, fMRI researches show that brain function in children with ASD is different from that in normal children, including the amygdala, the limbic system in the hippocampus, the frontal lobe, and the temporal lobe. However, there is currently no neurobiological basis for ASD etiology.

Levman et al. [36] found that corpus callosum volumetric abnormalities among autistic patients were associated with brain overgrowth in early childhood (0-5 years old), followed by a shift towards known decreased volumes in later ages. The substantive differences were also observed in the ventricles and regionally distributed volumetric measurements.

In view of the disorder of neural synchronization in autism, the fMRI study on the spontaneous activity of cortex in the sleeping state of autistic children shows that compared with normal children, the synchronous activity of left and right cerebral cortex is weaker, that is, the functional connection is weakened, especially in the functional area related to language. Using this feature to identify autistic children, the accuracy rate reaches 84% [37].

Face recognition and processing is a simple perceptual task for normal people, but it is more difficult for autistic people, who lack eye contact with people. In this task, Karen P [38] found that compared with normal people, people with autism were in the lower level of the activation of multiple cortical areas, such as the fusiform gyrus, the inferior occipital gyrus, the superior temporal sulcus and amygdala and so on.

Sasaki et al. [39] performed brain perfusion single-photon emission computed tomography (SPECT) to detect the abnormal brain region in children with ASD. In all children, SPECT revealed a mixed hypoperfusion pattern, especially in the prefrontal cortex, medial frontal cortex, anterior cingulate cortex, medial parietal cortex, and/or anterior temporal cortex. The results suggest that the frontal lobe and temporal lobe of children with ASD have decreased blood perfusion, and the above areas are related to children's emotions and behaviors, so it can explain some abnormal behaviors of children with ASD.

Aqhdam et al. [40] reported the use of the intelligent model to diagnose ASD in young children based on resting-state functional magnetic resonance imaging (rs-fMRI) data. Convolutional neural networks (CNNs) are by far one of the most powerful deep learning algorithms, are mainly trained using datasets with large numbers of samples. This system is based on CNNs using “combining classifiers,” both dynamic (mixture of experts) and static (simple Bayes) approaches, and “transfer learning” strategy. In addition, since diagnosis of ASD will be much more effective at an early age, samples ranging in age from 5 to 10 years from global Autism Brain Imaging Data Exchange I and II (ABIDE I and ABIDE II) datasets are used.

The accuracy, sensitivity, and specificity of presented model outperform the results of previous studies conducted on ABIDE I dataset. Furthermore, acceptable classification results are obtained from ABIDE II dataset and the combination of ABIDE I and ABIDE II datasets.

They concluded that the proposed architecture can be considered as an efficient tool for diagnosis of ASD in young children. From another perspective, this proposed method can be applied to analyzing rs-fMRI data related to brain dysfunctions.

Imaging examination plays a certain role in the diagnosis of autism, and more importantly, it is used to check whether the brain has organic lesions and clinically identify other diseases with similar symptoms.

4. Conclusion

ASD is a developmental disorder of the nervous system that occurs before the age of 3. In recent years, the prevalence of ASD has increased significantly. The prevalence of ASD among 8-year-olds in the United States has reached 1/68 (1 in 42 Males; 1 in 189 Females). Children with ASD not only bring great psychological and economic burden to the family, but also bring serious economic burden to the society. The adverse psychological factors of parents reduce the effect of children's intervention and even offset the effect of children's intervention, eventually forming a vicious circle. Therefore, early detection and early diagnosis are of great significance for children with autism.

Early diagnosis and early intervention should be realized as far as possible, and timely educational intervention should also be carried out for suspicious children. After 6 months of intervention by Dawson et al. [41], children with ASD of different age groups showed significant improvement in <30 months and 30-36 months. More than 1/3 children with mild ASD have a good prognosis, and some are able to attend regular schools and earn their own living when they grow up.

All kinds of screening tools have certain defects, which can be combined with other screening scales to promote advantages and avoid disadvantages. The correct use of the screening scale is conducive to the early diagnosis of autism. In addition to recommended routine broad-based and ASD-specific screening, other responses of autism should be regularly monitored in infants at risk for ASD. For children with positive screening results, the diagnosis can be confirmed with child behavioral response and imaging diagnosis.

Future clinical research, which should be informed by quality standards, might develop and evaluate standards of assessment and diagnosis, including post-diagnostic support.

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