Neurodevelopmental Disorders of the Cerebellum: Autism Spectrum Disorder

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Abstract Autism spectrum disorder (ASD) is a neurodevelopmental disorder with an incidence of 1 in 68 children. Cerebellar abnormalities have been observed in many ASD patients. The cerebellum is an elaborate brain region critically important for motor learning and coordination of movement, and increasing lines of evidence indicate that the cerebellum also contributes to emotion and cognition. In this chapter, we will review the genetic and environmental factors that may cause cerebellar deficits in ASD patients. Structural and functional cerebellar abnormalities based on neuroimaging and histopathological studies and current approaches to management will be discussed.

Keywords Cerebellum • Neurodevelopmental disorders • Motor skills • Language • Cognition • Autism spectrum disorder

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Introduction

Autism is a commonly occurring complex neurodevelopmental disorder. Leo Kanner, a child psychiatrist (1943), first described patients with "a powerful desire for aloneness" and "an obsessive insistence on persistent sameness" as "early infantile autism" [1–4]. A similar behavioral disorder, "Asperger's syndrome," was reported by Hans Asperger [5]. To avoid using different terminologies, these disorders were together named "autism disorders" in 1987. Recently, the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) collectively designated all autism-like disorders as "autism spectrum disorder" (ASD) [3].

ASD is characterized by a triad of symptoms: (1) impairment in social interaction, (2) communication difficulties, and (3) restricted, repetitive, and stereotyped patterns of behavior [3, 6–10]. Current methods can diagnose the ASD in children as young as 2 years old, and males are four times more likely to be diagnosed with ASD than females [11]. The prevalence of ASD is estimated at 1 in 68 children in the United States [12] and 1–2% in Asia, Europe, and North America (see chapter "Epidemiology of Cerebellar Disorders"). The etiology of ASD is complicated: in some patients it is unknown, and in some cases, individuals are affected due to gene mutations and/or environmental factors [7]. However, the interplay of genetic, environmental, and epigenetic factors probably underlies the mechanisms of ASD [8, 13].

A subset of ASD patients, about one in five, display increased head circumference and brain volume in early childhood, typically until 5–6 years of age [14, 15]. In these patients, the cortical white matter, the thickness of the corpus callosum, and the volume of cerebrospinal fluid (CSF) in the subarachnoid space are increased at the age of 6–9 months [16–18]. The frontal cortex has been reported to be larger, probably due to increased neuronal density in the prefrontal cortex [19]. Other brain regions that are prominently implicated in ASD include the cerebellum; brainstem and limbic system, including the hippocampus; and basal ganglia [20]. These areas are most likely responsible for the symptoms of those patients with abnormalities related to social behavior, executive functions, atypical use of language, and difficulties with speech [21]. Additionally, enlargement of the amygdala and caudate nucleus may cause anxiety and repetitive behavior [22].

Recent advances in molecular genetics and imaging technologies have shown that the cerebellum is one of the most consistently affected brain regions in ASD patients [8, 23, 24]. The cerebellar neurodevelopmental deficits in ASD include abnormalities in the cerebellar cortex, neurodegeneration, and impaired cerebellar circuits. Together, these deficits affect motor, sensory, language, and cognitive functions [25–28].

Autism Spectrum Disorder Pathogenesis

Emerging evidence from genetic association studies and postmortem human brain tissue indicates that ASD is either hereditary or caused probably by de novo mutations in a number of genes. Additionally, certain environmental risk factors have

been proposed to be causative in ASD. The set of molecular pathways, neural circuits, and behaviors affected in the different autisms is highly complex, and as a result, it has been difficult to uncover the neurobiological underpinnings of ASD [9, 29]. How the cerebellum contributes to the etiology of ASD has been particularly underappreciated.

The cerebellum develops from early embryogenesis to the first year postnatally in human. This long period of pre- and postnatal cerebellar development makes it susceptible to many risk factors [30–34]. In this section, we briefly review the findings regarding currently identified genetic and environmental risk factors in ASD. Epigenetic susceptibility factors have been discussed in chapter "Epigenetics and Cerebellar Neurodevelopmental Disorders."

Genetic Factors

Several lines of evidence have revealed that ASD is a neurodevelopmental disorder determined largely by genetic factors [35]. For example, twin studies have higher concordance rates for monozygotic twins than for dizygotic; approximately 80% of monozygotic twins are concordant compared to 10% of dizygotic twins, with a heritability of over 90% [36]. Recently, genome-wide association studies have identified many genes as risk factors for ASD. These genes span several chromosomal loci, and many are highly expressed in, and are involved in, the development of the cerebellum [37, 38]. Sadakata et al. [38] categorized these genes based on their role in development of the nervous system and synapse development and function. Some of these genes, such as CDH9, CDH10, RELN, and PTEN, are involved in developmental process such as neuronal differentiation, migration, and circuit formation. An important category of ASD-associated genes regulates synaptic adhesion and synaptic transmission, including genes encoding for neurexins, neuroligins, leucine-rich repeat transmembrane neuronal proteins (LRRTMs), Shanks, and SynGAP [39–42]. Another category of ASD risk genes encodes for proteins required for transcription and translation such as EN2, TSC1, FMR1, and MECP2 [38, 43].

Chromodomain-helicase-DNA-binding protein 8 (CHD8), previously called Duplin, is one of the genes most strongly associated with ASD [44, 45]. It was the first identified in the screen for novel interactors within the canonical Wnt/β-catenin pathway [46]. CHD8 is an ATP-dependent chromatin-remodeling factor [47] and may serve as a "master regulator" for other ASD risk genes during fetal development [44, 48]. Knockdown of CHD8 in human neural stem cells affects the expression of several ASD risk genes [44], and human patients with mutations in CHD8 display ASD symptoms and have macrocephaly and gastrointestinal difficulties [37]. Taken together, these data suggested that CHD8 targets a set of genes during brain development and regulates other ASD risk genes [44]. Some of the ASD risk genes regulate developmental processes in the cerebellum [13]. These include genes encoding for Reelin, RORα, EN2, BDNF, neuroligins, and neurexins [8, 49].

RELN dysregulation has been observed in a subset of autistic individuals (reviewed by Ishii et al. [36, 49]). Reelin, encoded by the RELN gene (located on chromosome 7 in human and chromosome 5 in mice), is a 388 kDa extracellular matrix glycoprotein which is essential for proper neuronal migration and positioning during embryonic and perinatal development of the brain/cerebellum [8, 36]. Though the precise mechanisms of RELN's role in ASD pathogenesis is uncertain, trinucleotide repeat expansion in the RELN gene has been observed in autistic individuals [8, 49]. Persico et al. (2001) first reported that the polymorphic GGC repeats located in the 50 untranslated region (50 UTR) of the RELN are associated with ASD disorder [50]. The finding was subsequently replicated in three studies [51–53], but there were no confirmed association between the triplet repeats in the 50 UTR of the RELN and autism. The family-based association analyses revealed that many CGG repeats present in RELN alleles may cause ASD particularly in patients with speech difficulties [54].

Reelin mutations in mouse models lead to irregular cortex formation and abnormal layering which may be responsible for behavioral and neurological disorders [55]. Adulthood changes in Reelin protein level caused cognitive impairment and reduced synaptic plasticity [55–58]. Given that the genetic evidence implicates RELN in the etiopathology of ASD, it has been attempted to add biochemical evidence by measuring the Reelin level in brain tissue and blood by using Western blotting. They showed that the levels of Reelin were significantly reduced in patients with ASD [59].

Several lines of evidence indicate that genes encoding retinoic acid receptor-related orphan receptors (RORs) are also associated with ASD. The RORα, RORβ, and RORγ are nuclear receptors that regulate a range of physiological processes during brain development [60–62]. RORα and RORγ are broadly expressed in the body, whereas RORβ expression is more restricted to the central nervous system [62, 63]. RORα protein expression significantly decreases in the brains of ASD patients probably through epigenetic alterations [64]. Devanna and Vernes demonstrated that miR-137, a microRNA implicated in neuropsychiatric disorders, targets a number of genes associated with ASD including RORα [65]. RORα is a transcription factor that is critically important for development of the cerebellum [60, 61, 66]. The role of the RORα in neural development has been demonstrated in mouse strain *staggerer*, which harbors a spontaneous deletion within RORα [67]. These mice have small stature and develop ataxia and hypotonia. The major neural deficit was underdevelopment of the cerebellar cortex with a pronounced deficiency in both granule and Purkinje cells [67]. Furthermore, disruption of RORα in *staggerer* mice shows behavioral phenotypes such as abnormal spatial learning, reduced exploration, limited maze patrolling, and perseverative behavior, which are associated with ASD [61, 62].

Engrailed 2 (EN2), a homeobox transcription factor, has been associated with normal cerebellar development, and mutations or deletions of EN2 result in reduced cerebellum volume and structural abnormalities [68, 69], which are both associated with susceptibility to ASD [70]. Brain-derived neurotrophic factor (BDNF) plays a key role in the development of the nervous system and modulation of neuronal activity, both of which impact complex human behaviors. Several studies have been performed to measure peripheral blood levels of BDNF in an attempt to

find a biomarker for children with ASD. Peripheral blood levels of BDNF are known to be highly correlated with brain BDNF levels [71]. Although there is no consistency in the association between BDNF levels in blood and ASD, a recent review by Xiao-Yan et al. (2016) using meta-analysis indicated that there are increased peripheral blood levels of BDNF in ASD patients [72]. Furthermore, $Ca2^{+}$-dependent activator protein for secretion 2 (CADPS2) contributes to normal cerebellar development by enhancing release of BDNF and neurotrophin-3 (NT-3) [73, 74]. The CADPS family is a secretory-related protein family that regulates secretory granule exocytosis, which in vertebrates consists of two genes, CAPS1/CADPS1 and CAPS2/CADPS2. The expression level of the CAPS2 has been observed to be unusually high in some patients with ASD [38, 75].

Mutations in the methyl CpG-binding protein 2 (MECP2) gene are known to cause Rett syndrome, a disorder characterized by language impairments, motor deficiencies, and stereotypical behavior [76], which is under the umbrella of ASD. Patients with Rett syndrome frequently have cerebellar atrophy that increases with age [13] (see chapter "Epigenetics and Cerebellar Neurodevelopmental Disorders").

Tuberous sclerosis complex (TSC) is a genetic disease that causes benign tumors in the body, including the brain [77]. Mutation in the TSC1 and TSC2 genes causes TSC with a neurodevelopmental disorder that involves higher rates of ASD [77, 78]. TSC produces a protein that negatively regulates the target of the rapamycin (mTOR) signaling pathway to control molecular and cellular process. Tsai et al. (2012) designed a mutant mouse model in which the gene for Tsc1 is not expressed in Purkinje cells [78]. These mutant mice displayed ASD-like behaviors, such as abnormal social interaction and ultrasonic vocalization, and inflexibility. In addition, recent discovery has shown that the granule cells/Purkinje cells are important for cognitive processing in the cerebellum [79]. These studies are significant because they demonstrated a clear involvement of the cerebellum in non-motor functions as well [78].

Environmental Factors

It has been suggested that the risk of developing ASD increases with exposure to environmental factors such as teratogenic substances (e.g., thalidomide, valproate, and misoprostol), infection with viruses (e.g., influenza, rubella, and cytomegalovirus) during pregnancy, and advanced age of parents (for reviews, see references [38, 80, 81]).

Some environmental risk factors such as exposure to valproic acid during prenatal development may cause abnormalities in cerebellar development and ASD [82]. In rat, valproic acid exposure reduces the number of Purkinje cells in the cerebellum accompanied by increases in the number of apoptotic cells [83]. Cole et al. (2011) have shown changes in cerebellar gene expression in mice treated with chlorpyrifos [84]. Dermal exposure of young adult mice to chlorpyrifos causes increased glial fibrillary acidic protein expression of the cerebellum [85]. Furthermore, Purkinje cell numbers are reduced in rats prenatally exposed to chlorpyrifos [86]. Other factors

such as organophosphate pesticides and antiepileptic drugs have been shown to affect cerebellar development and potentially cause ASD [87].

Maternal fever is another environmental risk factor that affects the cerebellum and leads to apoptosis. It also interferes with neuronal maturation and may cause heat shock protein activation during cerebellum development in ASD [88–90].

Viral infections can affect cerebellar and neocortical development during pre- and neonatal and cause neuropathy in ASD [91, 92]. Influenza virus also has the same impact on cerebellum development such as reduced the number of Purkinje cells and interruption in migration of Purkinje and granule cells during perinatal development, which may cause deficits in working memory and behavioral impairments [93–96] (see chapter "Infections of the Cerebellum").

Functional gastrointestinal disorders (FGIDs) are disorders independent of organic or physiological conditions that are the most common causes of GI disorders in children with ASD. FGID symptoms include abdominal pain, constipation, irritable bowel syndrome, and functional dyspepsia [97]. The FGIDs are associated with impaired behaviors and sensory responses, as well as changes in sleep patterns [98]. It is suggested that inadequate brain-gut interactions may be responsible for these symptoms in ASD patients [97]. Changing the gut microbiome to treat the ASD behaviors such as anxiety and depression is a new line of study that hopes to find alternate treatments for ASD patients [99, 100].

The exposure to air pollution, which may cause immune responses, is another likely environmental risk factor for ASD [101]. The immune response results in activation of immune cells and antibody production and increases the leukocyte migration to the brain tissue by increasing diffusion through the blood-brain barrier. It is suggested that maternal immune activation at a critical time points impair cerebellar morphology and a variety of motor and non-motor behaviors [102]. The abnormal level of blood immunological markers in ASD patients is evidence of interactions between genetic/environmental factors with their immune system in these patients is shown [103, 104] (see chapter "Neuroimmune Mechanisms of Cerebellar Development and Its Developmental Disorders: Bidirectional Link Between the Immune System and Nervous System").

Diagnosis of ASD

Studies on patients with ASD using advance brain imaging, genetic, and behavioral observations improved our knowledge of ASD symptoms. As of yet there are no biomarkers for the diagnosis of ASD, and currently clinical diagnosis of these patients is based on behavioral observations combined with patient history [22, 105]. Three ASD diagnosis criteria – social reciprocity, communication, and restricted/repetitive behavior – have been published by *DSM*-IV. However, it recently has been revised by *DSM*-V and International Classification of Diseases, Tenth Edition (ICD-10), into two domains of diagnosis criteria, (1) deficits in social communication/interaction and (2) restricted and repetitive behaviors, with

evidence of persistent symptoms that cause functional impairment [105]. Murphy et al. (2016) highlighted three key issues, sleep, GI problems, and epilepsy, regarding physical health that may be important in the diagnosis of ASD patient [105]. The mental health issues are present both in adults and children with ASD, which include mood and anxiety disorders, obsessive-compulsive disorder (OCD), attention-deficit hyperactivity disorder (ADHD), and psychotic disorders. These persist from childhood to adulthood in both sexes. Additionally, ASD patients have specific cognitive anomalies, including poor planning, decision-making, timing, and motor skills, which impact their daily activities [105–107].

The Cerebellum and ASD

Cerebellar malformations have been associated with a range of developmental impairments and behavior disorders including ASD (see review by Bolduc and Limperopoulos [31]). Motor impairment and clumsiness has been noted as an important feature in ASD [108]. It is shown that about 80% of children with ASD have motor coordination deficits, which have a positive correlation with the severity of the ASD and intellectual disabilities [109, 110]. Cerebellar motor dysfunction in ASD includes eye movement abnormalities, fine and gross motor deficits, gait, balance and coordination impairment, postural instability, and motor learning deficits [109, 111]. Motor impairments are among the earliest signs of an autistic phenotype [112]. It has been shown that motor impairments are predictive of the ASD outcome. During early movement activities, individuals, who are later diagnosed with ASD, have poor fine and gross motor skills that are accompanied by delays of language development [109, 113]. Similarly, difficulties in oral and manual motor skills in infancy can label individuals as an ASD patient, and late speech fluency is predictable [114]. In addition, early motor delays are more common in infants at risk for ASD and are related to later communication delays [115]. Therefore, the timing of language acquisition may serve as an indicator for neurodevelopmental and behavior disorders and may be a marker to diagnose people with ASD.

Emotional/behavioral disturbance and communication disorders may be associated with the motor task performance in ASD patients [116]. It has been suggested that the lack of gesture and imitation in ASD patients might be related to motor dysfunction, providing a mechanism by which cerebellar dysfunction could impact the core social communication symptoms of patient with ASD [109, 117].

ASD and Cerebellar Structure Abnormalities

Cerebellar abnormalities are the most consistently reported brain structural changes in ASD, such as decreased cerebellar cortex, which is a key landmark for diagnosis in ASD brains [109, 118]. Cerebellar enlargement has been reported in ASD young

children in comparison with the total brain volume and may be associated with the cerebellar white matter [26, 119, 120]. However, the growth rate declines later during development and eventually results in a smaller cerebellar volume by adulthood in ASD patients [120, 121].

By MRI, cerebellar lobules VI and VII are hyperplastic in patients with ASD, and it is suggested that these alterations may be responsible for increased stereotype and repetitive movements [122]. The language impairment in ASD may be associated with a decreased volume of the vermis and anterior lobe and abnormal left lateralization in lobule VIIIA [123, 124]. A study conducted using voxel-based morphometry suggested that structural differences such as increase and decrease in cerebellar gray and white matters are related to specific abnormalities at the different stages of cerebellar development in ASD patients [109, 125].

Neurohistological studies show changes in the anatomy of the cerebellum in patients with ASD, including a decrease in the number of Purkinje cells [126, 127], immature cerebellar development [128–130], morphological changes in the size of the cerebellar nuclei which are small and abnormal, and an increase in the number of Bergmann glia cells [131, 132]. The low density of the Purkinje cells in the cerebellum of ASD patients was observed in the vermis, Crus I–II, lobules IV–VI, and lobule X [133]. The smaller size of Purkinje cells may indicate the occurrence of an atrophic process [134]. Because of the large size, and due to numerous synapses with the parallel and climbing fibers, Purkinje cells have a high metabolic demand. Therefore they have extensive amounts of calcium storage that may cause increases in intracellular calcium, which elevates the risk of excitotoxicity and cell death [135].

It has been reported that the cortical-pontine-cerebellar-thalamic circuit is immature and abnormal both functionally and anatomically in patients with ASD [9]. It is also shown that the cerebellar input and output pathways in relation to neocortical areas are unusual in ASD patients [136, 137]. The corticopontocerebellar pathway carries inputs that originate from the primary sensory and motor cortex, posterior parietal, prefrontal, orbitofrontal, cingulate, temporal, and basal nuclei and projects to the cerebellum [138, 139]. Outputs originate from the cerebellar nuclei and through the thalamus project to the neocortex [140–142]. These circuits are specialized for cognitive and behavioral activities such as executive functions, language, and emotions. Thus, the cerebellum may be responsible for cognitive impairment, sensorimotor behavior, and social disconnection in ASD [13].

Eye gaze abnormalities during social interaction are an early diagnostic indicator in ASD patients. Gaze fixation is naturally used to fix the fovea on an image or object. The oculomotor system maintains fixation, which is supported by the nuclei of the brainstem. Therefore, inputs from the frontal eye fields and superior colliculus actively block the saccades away from the object of interest [143]. The pontine nuclei stimulate Purkinje cells in lobules VI–VII vermis cerebellum, and inhibitory outputs from the oculomotor vermis help to stop undesired eye movements and keep an image on the fovea [144] which could potentially be used as an early marker of ASD patients.

Control of upper limb movement is related to the frontoparietal cortex as well as the cerebellar cortex and its output nuclei [145]. Upper limb and manual motor deficits that are associated with atrophy of the intermediate and lateral cerebellum

involve lobules I–V as well as more lateral areas of lobules V–VI extending into Crus I–II in patients with upper limb ataxia. [146]. These loops are responsible for regulating the amplitude, duration, and timing of movements [147, 148]. Patients with ASD have difficulties coordinating grasping and reaching activities [149]. These difficulties may be caused by central defects in integrating sensory feedback information and motor output as well as deficits in neocortical-posterior cerebellar circuitry. The compromised motor learning in individuals with ASD could be related to disturbances in the anterior cerebellar lobules IV–VI and their connectivity to frontal as well as parietal regions of the cortex. These effects may damage upper limb and manual motor actions that ultimately impact the patient's ability to control motor behavior and learn new skills. Therefore, the development of more complex social motor skills in these patients is disabled. Medial and intermediate cerebellar circuits affected by insufficiency in both sensory feedback and forward control appear to cause motor impairments and difficulties in posture, gait, and walking in ASD patients [150]. The motor deficits start from infancy and extend to adolescence and adulthood [108, 151–153].

Cognitive function deficits such as attention and memory impairment, executive function, and cognitive flexibility deficits are common features in ASD [154]. The cerebellum communicates with Brodmann areas 46 and 9 of the prefrontal cortex, which are involved in cognitive functions, memory, planning, decision-making, and cognitive flexibility [155–157]. The cerebellum to prefrontal cortex pathway could affect cognitive functions directly or perhaps indirectly through the ventral tegmental area, which contains dopaminergic neurons that project and terminate in the prefrontal cortex [158]. Notably, the function of the prefrontal cortex dopaminergic pathway is associated with attention selection, cognitive flexibility, and memory [157]. A maldevelopment of connectivity in connection of the cerebellum to this higher-order circuit may explain the cognitive involvement of the cerebellum in patients with ASD.

Assessment and Treatment

There is very limited accurate and practical information to assess, diagnose, and manage ASD conditions. Therefore, because the number of ASD patients has rapidly increased during past decade, there is an urgent need to improve knowledge and develop assessment tools and treatment of ASD patients [105].

ASD diagnosis can be difficult because of a large amount of heterogeneity, varying presentation, and variability in symptoms [159]. There are no biomarkers to diagnose ASD; therefore behavioral presentation of the patients is used for diagnosis [160]. The gold standard for clinical diagnosis in these patients is based on current diagnostic classification systems and proceeding very careful assessment practices. These assessments include physical examination, hearing test, observation of children's behavior, and a structured parent interview that covers the patient's full developmental history [160]. Currently, the best practice to diagnose ASD patients is a step-by-step strategy that is recommended by the American

Psychological Association [161]. This diagnostic strategy starts with child's parent/caregiver concern and followed by a formal diagnostic assessment conducted by a pediatrician or/and appropriate referrals. The formal diagnostic assessment includes medical and functional evaluation such as everyday verbal and nonverbal skills and level of ability as well as analyze/assess of behaviors based on developmental aspect [162]. However, because of differences in cognitive function, age, language level, and the source of information, diagnosis of ASD is very difficult [159].

Children who are diagnosed with ASD need to be reevaluated continuously during preschool years to identify their weakness, inabilities, and difficulties [159]. There are also some diagnostic instruments for ASD such as the Autism Diagnostic Observational Schedule – Generic (ADOS-G) [163], which assesses communication, play, and creative use of materials and possibilities for children who may have ASD. The best Screening Tool for ASD in Toddlers and Young Children (STAT) [164] is structured to identify children between 24 and 36 months of age with ASD. One of the measures of early communication in children 8–24 months is the Communication and Symbolic Behavior Scales (CSBS) [165]. Additionally for the parent interview, there is a clinical diagnostic instrument named the Autism Diagnostic Interview-Revised (ADI-R) that is addressing early development, communication/language, social interactions/interests, and restricted and repetitive behaviors [166]. The Social Communication Questionnaire (SCQ) is an appropriate method to get information from parents [167].

Usually an assessment starts with medical evaluation which will be conducted by physicians and, if the ASD suspected, referring the patient for diagnostic assessment as well as considering the pediatrician as an alternative referral. When diagnosis is confirmed, treatment planning should involve the professional health team [159].

Summary

Many genetic and environmental factors may cause ASD. The mechanisms are unknown, but presumably genetic and environmental factors affect normal brain development and, consequently, lead to functional disorders in patients with ASD.

There is mounting evidence that developmental abnormalities in the cerebellum may underlie the pathogenetic mechanisms that are associated with the ASD phenotype. Cerebellar developmental disorders that are associated with ASD pathogenesis show deficits in motor coordination, balance, motor memory, and higher-order dysfunctions including speech and attention regulation.

The major goal of management in ASD patients is early diagnosis for behavioral and medical interventions to enhance the functional ability of these children. The new approach involving brain-gut-microbiome interactions may provide a biomarker associated with GI disorders that could be helpful in the early diagnosis of these patients. Because the number of ASD patients is increasing, studies are needed to develop assessment tools and treatment, increase public awareness, and develop strategy for health care of patients with ASD.

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