

Autism and Cerebellar Mutism: A Review of the Neuroanatomical Findings

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Abstract

Autistic Spectrum Disorder (ASD) is behaviorally defined syndrome characterized by atypical social interaction, disordered verbal and non-verbal communication, restricted areas of interest and limited imaginative play. The prevalence of ASD is considered to be approximately 4 to 5 per 1000, but numbers differ according to criteria used for diagnosis [1].

Individuals with ASD have three core features; 1. Impairments of reciprocal social interactions, 2. Abnormal development and use of language and 3. Repetitive and ritualized behaviors and a narrow range of interests. In addition to the core features of autism, there are common co-morbid neurological disorders. The prevalence of mental retardation in the autism spectrum is approximately 30%. Epilepsy prevalence associated with autism varies from 5% to 44%. Anxiety and mood disorders are also very common in autism.

There is heterogeneity in the onset of autism. Although some children have signs of development delays between 0-18 months of life, up to 40% of children with ASD initially demonstrate the near-normal development until 18-24 months.

As Brunelle et al. says: All the results are converging toward the description of anatomical and functional anomalies in the regions of the so-called "social brain" [2]. Several brain regions such as frontal lobe, the superior temporal cortex, the parietal cortex, and amygdala have been implicated in social behavior. But the recent developments make us think more about the role of cerebellum in ASD. This review presents an overview of the neuroanatomical abnormalities that occur within ASD. We discuss the findings that have advanced our understanding of cerebellar organization in ASD.

Keywords: Autistic spectrum disorder; Cerebellum; Cerebellar mutism

Introduction

Since the view of ASD has changed greatly, the hypothesis of an organic etiology has gradually become more important. Besides the well-known morphological and functional abnormalities, there are also many paths which have begun to be explored by current imaging techniques. When we consider cerebellum as the common source of the pathology in ASD and Cerebellar Mutism (CM), it could be said that three major neuropathologic findings have been described: (1) curtailed development of neurons in the forebrain limbic system (anterior cingulate gyrus, hippocampus, subiculum, etorhinal cortex, and mamillary body (2) decreased number of Purkinje cells in the cerebellum (3) age-related differences in cell size and neuronal number in the cerebellar and the inferior olivary nuclei, suggesting an evolving process and disturbance in the synaptic relationships of these structures.

Typically brain development is comprised of several stages, including proliferation and migration of neurons, creation of dendritic arbors and synaptic connections, and eventually dendritic pruning and programmed cell death. Any deviation at one or more of these stages could produce catastrophic downstream effects.

There is consensus that differences in neuroanatomy play critical role in ASD. Related to many functions of the brain, cerebellum has to be investigated much more.

Neuroanatomical Findings in Autism

Brain overgrowth

Currently, one of the most prominent theories of the neuropathology of ASD is that the brain undergoes an abnormal development time course that appears to include a period of early overgrowth followed by deceleration in age-related growth in some individuals with ASD

which is particularly noted in the frontal and temporal cortices and amygdala [3,4]. The leading cause of this developmental trajectory could be either excessive prenatal neurogenesis due to genetic or environmental alterations, or aberrant connectivity of neurons due to excessively developed dendrites and synapses with dysregulated manner or, an inflammatory response leading to excessive microglial activation. Existing MRI studies suggest that children with ASD and ages between 18 months to 4 years have 5%-10% abnormal enlargement in total brain volume. The abnormal brain enlargement observed in children with ASD is mainly in white matter, not gray matter [4]. Although enlargements in gray and white matter have been reported in frontal, temporal and parietal lobes, the largest and most consistent increases have been reported in the frontal lobes.

There could be three cellular factors to explain the overgrowth of brain in autism.

1. The number of neurons: An increase in the number of neurons is unlikely to be the sole factor in accelerated cortical growth in autism. Head circumference and MRI studies suggest that brain enlargement becomes evident between 6 and 12 months of age. However neurogenesis is a prenatal event.

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2. The extent of neuronal dendritic growth and number of synapses: For early brain overgrowth in autism, the neuronal dendritic growth and increased number of synapses is the most likely candidate. In a newborn brain dendritic sprouts and synaptic connections between neurons are sparse. Over the next few years there is dramatic increase in dendritic volume and synaptic connections. If dendrites grow excessively or do not undergo the same degree of efficient synaptic pruning, the result may be aberrant connectivity between neurons alongside overall brain enlargement. Although this is the most likely candidate few postmortem studies have looked at neuronal dendritic arborization or synapses in autism [5].
3. The number and size of glial cells: Intermediate increase of the number of glia could account for increase in brain size. Gliogenesis occurs prenatally and varies between the oligodendrocytes, astrocytes and microglia. Main functions of oligodendrocytes is to insulate in a myelin sheath and comprise approximately 75% of glial cells in gray matter. Although the number of oligodendrocytes (25 billions in the gray matter) does not increase dramatically after birth, the process that form the myelin sheath around neurons extend out and wrap axons. Astrocytes comprise 17% of glia in the brain. Their main function is to regulate the external chemical environment of neurons. There are 6 billion astrocytes in cerebral gray matter. Astrocytes are generated almost entirely prenatally from the same progenitor cell population as neurons; however, their volume may increase significantly in response to inflammatory signaling with swelling of both the soma and the inflammation-sensing processes. If glia account for some of the cerebral volume increase in children with autism, a neuroinflammatory response involving microglia may be a likely culprit. Microglia are resident phagocytes, constantly eliminating damaged neurons, accumulated debris and infectious agents. Although microglia only comprise 6% of the glia in the brain (approximately 2 billion), unlike neurons and other glial populations, microglia readily increase in number in response to immune challenges. In addition, although they are normally small relative to other glia, they are capable of dramatic morphological changes, if strongly stimulated with pro-inflammatory factors. Under these completely normal conditions, microglia became activated and the cell body may swell as much as 4 times its normal volume. All these factors related to glial cells result in an increase overall brain size in autism.

The scenario described is just one of several possible combinations of the above mentioned cellular factors that might occur in the autistic brain during this early critical period of development.

Minicolumns

For over a century, neuroanatomists have remarked on the columnar structure of the neocortex. The smallest column has come to be called the minicolumn or microcolumn. The minicolumn can be identified by the stacking of neuronal cell bodies, particularly in layers III and V of the neocortex. It has been proposed that minicolumns are the basic functional unit of the brain, although the significance of the vertical organization of neurons has been a topic of much debate.

The mature brain is comprised of approximately 100 billion neurons and perhaps three times as many glial cells [6]. The cerebral cortex is a laminated sheet of gray matter that is 2-4 mm thick, and in most regions, neurons are organized six horizontally arranged cellular

layers. In general, the input layer is layer IV, projections to other parts of the cortex arise primarily from layers II and III, and projections to subcortical regions arise from layers V and VI.

Neurons are extremely diverse in both size and function. Approximately 80% of neurons are excitatory. Many of these are projection neurons, such as pyramidal neurons, which are primarily located in layers III, V, and VI and send long distance connections to other parts of the brain. Smaller interneurons, located in all layers, are primarily inhibitory and project only locally. The remaining cells are predominantly glia, which is generally thought of as support cells involved in immunity and synaptic maintenance, but have also been found to play a wide array of other roles as well. The cortex demonstrates vertical functional units that are arranged as radial columns, or cortical columns, that span across the six cortical layers. Each cortical column comprises multiple narrower panlaminal "minicolumns", each of which in turn contains 80-100 radially arranged neurons. Minicolumn formation has been associated with early stages of cortical development when postmitotic neurons ascend in linear arrays along radial glial scaffolding. Neurons in each cortical column are believed to respond to similar stimuli and perform similar functions.

Minicolumnar irregularities have been observed in frontal and temporal lobes of the brain with the cell columns that were more numerous, smaller, and less compact in their configuration [7]. Although the number of cells per minicolumns were normal, abnormally narrow minicolumns resulted with short connecting fibers, that were thought to be the reason for the deficiency in inter-areal and callosal connectivity [8].

White matter

White matter is more homogenous than gray matter and is comprised primarily of myelinated axons. Within the cerebrum there are both short distance (10-30 mm) and long distance fibers (30-170 mm). At that point, white matter plays a unique role in communication and synchronization.

Several studies have revealed significant differences in white matter volume [9-11]. Abnormalities of white matter pathways that carry the information between the key regions should be considered profoundly since the functional Magnetic Resonance Imaging (fMRI) and Diffusion Tensor Imaging (DTI) studies increased the importance of the phenomenon of "atypical connectivity". A recent multicenter magnetic resonance imaging study has shown spatially distributed reductions in white matter volume allocated to the (1) corticospinal and cerebellar tracts (2) frontal connections, including the uncinate fasciculus and the fronto-occipital fasciculus (3) internal capsule comprising descending frontostriatal and thalamocortical ascending projections and (4) arcuate fasciculus connecting the Broca and Wernicke areas [12].

When we mention the white matter abnormalities in ASD, also smaller corpus callosum size must be noted [13,14]. For, it is the most prominent white matter tract in the cortex.

It has been suggested that in ASD, anatomic underconnectivity between frontal and parietal areas affects executive functioning and is accompanied by abnormalities in connecting fibers [15]. Differences in the neurodevelopmental trajectory of white matter has been reported in ASD [16]. However, the results of a recent study on white matter has reported that clear maturational differences exist in social cognition and limbic processing regions only in children/adolescents and not in adults with ASD. This could be an anatomical evidence for improvement with age [17].

With a DTI study, Shukla et al. has shown that autistic subjects has several abnormal foci of fractional anisotropy as corpus callosum, anterior and posterior limbs of the internal capsule, cingulum, anterior thalamic radiation, and corticospinal tract. These findings revealed that white matter abnormalities show tract-specific patterns in ASD [18].

Amygdala

Amygdala plays an important role in predicting reward values and motivation, processing of faces, recognition of emotions, emotional memory [19], detecting threat, [20] fear and anxiety [21]. Deeley et al. has shown that the amygdala modulates “social brain” regions such as fusiform/extra-striate cortices [22]. In this context, it has been proposed that ASD’s biological basis includes abnormalities of limbic structures, including the amygdala. Thereby, amygdala has been studied in autism.

The sizes of the amygdala have been variously reported to be normal, smaller, and larger [23]. However, current results also suggest that amygdala enlargement is associated with more severe anxiety [24] and worse social and communication skills [25].

Many neuropathological studies and MRI studies have revealed contradicting results. In 2004, Schumann’s study has shown that the differences of the amygdala volumes between ASD and control groups vary by age, diagnostic subtype, and anatomical location. In this study, enlargement of amygdala present in young autistic patients was not found in older subjects [26].

Finally, by a recent in vivo magnetic resonance imaging study, it was shown that the individuals with ASD have complex differences from controls in the structure, function, and metabolism of the amygdala and hippocampus [27].

Superior temporal sulcus

Superior Temporal Sulcus (STS) is one of the critical structures for ASD, which is vital to the processing of speech. With Brodman area 21(BA 21) on the inferior edge, and BA 22 which is called also the auditory association area on the superior edge and BA 42, known as the primary auditory cortex [28], STS has many functions depending on which other areas in the cortex are activated as well.

It was reported that individuals with autism failed to activate STS voice-selective regions, although they presented a normal cortical response for non-vocal sounds [29]. Reduction in concentration of the grey matter of the STS has been shown by several MRI morphometric studies using voxel-based morphometry (VBM) [30,31].

Redcay et al. identified reduced left lateralization of language functions in the same study that they have shown an increase in right sided activation when compared with chronological age controls [32]. After replication by several other studies, these findings raised hope for defining ASD earlier.

Fusiform area

The fusiform gyrus is part of the temporal lobe that responds selectively to images of faces as opposed to other kinds of objects. Face Fusiform Area (FFA) of the fusiform gyrus is suggested to be specifically activated by control subjects during facial recognition. It has been investigated particularly by using Positron Emission Tomography (PET) and fMRI studies and its abnormality is related to one of the diagnostic criteria for autism; lack interest in faces.

Activations in the fusiform face area are reported as reduced in individuals with ASD [33]. Also, abnormally concentrated gray matter

in the right fusiform gyrus of autistic patients is revealed in a VBM study [34].

Previously, it was suggested that the individuals with ASD don’t use FFA in visualizing faces [35]. But now, it has been understood that they are quite capable of activating their FFA with additional stimuli. This finding is known as “the threshold theory” [36].

Anterior cingulate cortex

Anterior cingulate cortex (ACC) is active in a wide variety of cognitive and emotional tasks. It is known as a part of the limbic system for its role in response inhibition task.

In a structural MRI and PET study, Haznedar et al. found that the right anterior cingulate area was significantly smaller in relative volume and also metabolically less active in the individuals with ASD [37]. ACC dysfunction was also reported by another study which has shown the greater activation in the ACC during a continuous performance task with associated reward [38]. Gray and white matter abnormalities were shown by recent studies [39,40]. Ohnishi et al. has reported perfusion abnormalities of ACC in a SPECT study [41].

Cerebellum

Several volumetric studies in individuals with ASD have found increase in cerebellar volume [42,43]. The size of the vermis was reported to be either larger or smaller due to the heterogeneity of the disease [44]. Carper et al. suggested that frontal overgrowth may be a result of excessive excitatory output from the cerebellum. It was thought to be a consequence of reduced inhibitory Purkinje cell input to deep cerebellar nuclei [45].

When studied during motor task, cerebellar function has shown differences from control groups. Studies of fMRI revealed activation pattern of different areas: an increase in motor activation in the anterior cerebellar hemisphere and the contralateral vermal lobule VI [46,47].

Abnormal neural activity in the cerebello-thalamo-cortical projections were accused of causing maldevelopment of the frontal lobe and other brain regions that receive this input. It was proposed that cognitive functions can be affected in ASD in this way [48]. In autopsic studies, decreased number of Purkinje cells in the cerebellar hemisphere and vermis has been reported in autistic cases [49]. Neuropathologic studies revealed smaller cell size and decreased cell-packing density of Purkinje cells [4,43].

Cerebellar Mutism

Acquired neurological childhood mutism may be caused by damage to different regions in the context of various etiologies. Core features of mutism and subsequent dysarthria are 1) mutism after resection of a cerebellar mass lesion; 2) delayed onset of mutism after a brief interval of 1-2 days of relatively normal speech postsurgery; 3) transient mutism that lasts from 1 day to 6 months followed by a severe dysarthria, which recovers completely in 1-3 months; 4) frequent association with other neurological manifestations such as long tract signs and neurobehavioral abnormalities [50]. A vast majority of these children display evident dysarthric features after the period of mutism, such as slow speech rate, monotonous, and ataxic speech. In the phase of speech recovery, language disturbances, such as word finding difficulties, a grammatism, a dynamic language, characterized by a lack of verbal initiative, comprehension deficits and reading or writing problems also have been found. Extension of the spectrum of Mutism subsequent dysarthria syndrome with symptoms such as emotional lability, poor

oral intake, decreased spontaneous initiation of movements, impaired eye opening, urinary retention, depressed affect, agitation, apathy and transient cortical blindness lead to the introduction of the broader term Posterior Fossa Syndrome (PFS) [50].

The posterior fossa syndrome (PFS) consists of transient cerebellar mutism, cognitive symptoms, and neurobehavioral abnormalities that typically develop in children following posterior fossa tumor resection. The incidence of acute presentation of mutism, dysarthria and dysphagia post-surgery as relatively high, affecting around one in three cases [51,52]. Brain stem invasion, midline tumor location, younger age, absence of radiographic residual tumor [53], histopathologic diagnosis and socioeconomic level of the patient's family [52] are all important risk factors for the development of PFS. The most common feature is mutism, but oropharyngeal dyspraxia, emotional lability and neuropsychiatric symptoms occur. Usually a significant correlation is found between duration of mutism and severity of neurological symptoms [50]. Significant correlations are also found between duration of mutism and abnormalities on SPECT scans of the left temporal lobe, the left and right basal nuclei, and the right frontal lobe [50]. Although the mutism is transient, speech rarely normalizes and the syndrome is associated with long-term adverse neurological, cognitive, and psychological sequelae [54]. Palmer et al. showed that patients treated for medulloblastoma and suffered with cerebellar mutism, had an increased risk for neurocognitive impairment for over 12 months postoperatively [55]. In PFS, non-motor language symptoms consisted of a rhammatism, anomia, impaired verbal fluency, comprehension deficits, and spontaneous research. According to Morgan et al. speech deficits may persist even up to 10 years post-surgery of the children with posterior fossa tumors [56]. They also stated that patients with unilateral lesions, poorer outcomes were associated with right cerebellar tumors compared to left, consistent with the notion based on adult data that speech is controlled by reciprocal right cerebellar/left frontal interactions. These results also confirm the important role of the cerebellum in the control of fine speech movements in children. The role of the cerebellum in higher cognitive functions beyond coordination and motor control has recently attracted significant interest in the scientific community, and might change the neurosurgical approach to these lesions. Neurocognitive deficits included executive dysfunctions, concentration deficits and visuo-spatial disorders. Following Functional neuroimaging studies during the phase of mutism by means of SPECT showed perfusion deficits in the anatomic-clinically suspected supratentorial areas subserving language dynamics, syntax, naming, executive functioning, affective regulation, and behavior [57]. According to Di rocco et al. pre-existing language impairment can be considered a subclinical state of Cerebellar Mutism Syndrome (CMS) in some children with posterior fossa tumor [58]. However in some children with pre-existing language impairment, the tumor resection may improve the linguistic abilities, as well as the other neurocognitive performances. They also stated that children with normal preoperative language function did not develop post-operative mutism [58]. A significant improvement of frontal perfusional deficits paralleled the clinical remission of mutism. These results add the view that PFS might represent a cerebello-cerebral diaschisis phenomenon, reflecting the metabolic impact of the cerebellar lesion on supratentorial cognitive and affective functions [57]. These SPECT scan findings suggest that these impairments are secondary to supratentorial metabolic hypofunction following cerebellar surgery.

For differential diagnosis posterior reversible encephalopathy syndrome (PRES) should always be considered. The PRES has been described in the setting of malignant hypertension, renal disease,

eclampsia, immunosuppression and following posterior fossa tumor surgery if the patient encountered with severe hypertension during surgery [59]. Aggressive antihypertensive and antiepileptic treatment should be considered for immediate recovery and remission.

Cerebellar Mutism and ASD

Autistic Spectrum Disorder and Cerebellar Mutism are similar diseases in many ways because of the shared cerebellar abnormalities. Disturbances of smooth ocular pursuit that result from cerebellar damage are seen in both ASD and CM. Cerebellar lesions can also produce mutism and dysarthria which are common symptoms in both ASD and CM. Abnormal function of motor initiation occurs is proposed to be occurred in both disease. Because the cerebellum projects to systems involved in motor initiation. The cerebellum also projects to all levels of the reticular activating system, a system that has been suggested to be dysfunctional in both autistic spectrum disorder and CM. Levels of neurotransmitters like serotonin, dopamine and noradrenaline which are modulated by cerebellum, have been suggested to be abnormal in ASD and CM. The cerebellum modulates hippocampal activity and projects via the hypothalamus to the amygdale. Both of these limbic regions have been hypothesized to be dysfunctional in autistic spectrum disorder and CM. Hypothalamic dysfunction is proposed to be the reason for neuroendocrine data and measures of physical growth in ASD and CM. Cerebellum can be responsible for this with monosynaptic connections to hypothalamic nuclei. The cerebellum and two regions within the frontal lobes are active in certain language tasks. Language is abnormal in autistic spectrum disorder and CM. This has been shown in SPECT studies to be cerebellar diaschisis. Therefore, cerebellar lesions in mammals disturb motivated behavior and reduce social interactions, functions that are disturbed in autistic spectrum disorder and CM. Pressure therapy has a calming effect for autistic individuals. A squeezing machine invented by an autistic is completely lined with foam rubber, and the user has complete control over the duration and amount of pressure applied. Squeezing is an effective treatment modality for autistic spectrum disorder. In CM, speech recovery starts from a couple of days to several months postoperatively. Close contact with and/or gently squeezing of patients by hugging with their parents during the postoperative period may act as a squeezing machine and accelerate the recovery. Ozgur et al. reported an autistic patient stated that throughout elementary school her speech was still abnormal. Often, it took her longer than other children to start getting her words out. However, she found it easy to sing. Moreover, in a unique case study of CM, described a 5-year-old boy with medulloblastoma and associated hydrocephalus [60]. On his first day postoperatively, he exhibited cerebellar dysmetria, dysdiadochinesia, and CM. Although motor symptoms continued to improve over the next few weeks, the CM remained. Serendipitously, the patient was exposed to music that they were familiar with or which was their favorite, and they began singing without prompts, but remained mute without the music.

There are studies of series of children treated for posterior fossa tumors that reveal behavioral disorders close to those observed in autism [61].

Conclusions

Anatomic differences of specific brain regions have been reported by several studies and they have been associated with a variety of clinical symptoms. Redcay et al. have reported that impaired social communication and language result from the abnormalities in the Broca and Wernicke areas [62]. There is also evidences that frontotemporal regions and amygdala have been associated with abnormalities

in socioemotional processing [30,34]. It has been suggested that orbitofrontal cortex and caudate nucleus may be linked to repetitive and stereotyped behaviours [63].

For quite some time, we know that cerebellum is involved in a wide range of tasks, including non-motor functions, such as language, thought modulation, emotions, and the ability to organize symbolic activities in a sequential manner. So we propose that cerebellum is related to much more dysfunctions in ASD.

In this article, we didn't mention the neurochemical findings. We didn't even have opportunity to write more about the recent important factors as mitochondrial dysfunction, synaptopathy and genetic variations. For a complete understanding of ASD, all the features of disease and the anatomical structures should be considered. Future research is required to continue to uncover the neuropsychological and neuropsychiatric processes that the cerebellum appears to mediate.

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