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Review article

Purkinje cell vulnerability and autism: a possible etiological connection

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Abstract

Autism is a neurological disorder of unknown etiology. The onset of the abnormal growth and development within the brain is also not known. Current thought by experts in autism is that the time of onset is prenatal, occurring prior to 30 weeks gestation. However, autism comprises a heterogeneous population in that parents report either that their child was abnormal from birth, or that their child was developmentally normal until sometime after birth, at which time the child began to regress or deteriorate. Anecdotal reports suggest that some children with autism have significant illness or clinical events prior to the development of autistic symptoms. Conceivably, these children may become autistic from neuronal cell death or brain damage sometime after birth as result of insult. To support this theory is that marked Purkinje cell loss, the most consistent finding in the autistic disorder, can result from insult. Evidence suggests that the Purkinje cell is selectively vulnerable. This article discusses a theory that the selective vulnerability of the Purkinje cell may play a role in the etiology of autism, and suggests that a future direction in autism research may be to investigate the possibility of neuronal cell loss from insult as a cause of autism. Results of a small pilot survey are also discussed.

Keywords: Autism; Onset; Purkinje cell; Insult; Etiology; Heterogeneity; Gliosis; Vulnerability

1. Introduction: autism prevalence, symptomatology, and etiology

Autism and pervasive developmental disorder (PDD) are relatively common developmental disorders. Epidemiological studies from the 1980's estimated autism to occur in more than one out of every 1000 children [1,2]. However, a recent study by Baird et al. [3] (1999) reported a prevalence rate in autism of one in 333 children. Recent reports from the California Department of Developmental Services also suggest that the rates in autism are increasing, implicating the importance of external or environmental factors that may be changing [4,5]. The cause of autism is unknown [6].

Persons diagnosed with autism are grouped together under the behaviorally defined diagnosis of autism or autistic spectrum disorder due to similar behavioral symptomatology [7]. The symptomatology of autism/PDD includes: (1) qualitative impairment in the ability to interact socially, characterized by the 'autistic aloneness'; (2) qualitative impairment in communication, that can range from being completely nonverbal to a delay in acquisition of spoken language and abnormal speech patterns; and (3) restricted, repetitive, and stereotyped patterns of behavior and activities, e.g. restricted or narrow interests, obsessive desire for sameness, and abnormal body movements (abnormal posturing, hand flapping, toe walking, and rocking) [6,8,9]. Autism is a poorly understood disorder that results in a significant lifelong disability, and stress on families and caregivers. Parents of children with autism experience more stress than parents of children with other disabilities [10].

Though autism/PDD is a neurological disorder, is not clear whether the neurological problems are primary in nature or if another system is malfunctioning and negatively impacting the neurological system. The possible involvement of another system is evidenced by the biomedical studies in autism/PDD that disclose a variety of abnormalities, not only in the neurological system [11–16], but in the immune system [17–19], and the digestive system as well [20,21]. In addition, abnormal metabolic indicators have been found [22,23]. The diversity of the biomedical findings

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and their variety of selection in different patients suggests that persons with autism/PDD comprise a heterogeneous population in regard to etiology [7,24,25].

Persons with autism also show heterogeneity in that they appear to develop autistic symptoms at various points in development. This paper discusses the neurological mechanisms that may be a part of the etiology in children that are reported to have a developmentally normal period prior to the onset of autistic symptoms. The selective vulnerability of the cerebellar Purkinje cell is described, and how the Purkinje cell vulnerability may play a role in the cause of autism is discussed. Results of a small pilot survey are discussed, as well as the current state of research in this area, and possible future directions.

2. Autism: onset, parental reports, and possible neurological basis

The onset of the abnormal growth and development within the brain in autism is not known. Current thought by experts in autism, such as Bauman et al. [26], is that the time of onset of the neurological problems is prenatal, occurring prior to 30 weeks gestation. Bauman et al. [26] stated that the absence of gliosis (which will be defined and discussed in a later section.) found in their autopsy study suggests that the abnormalities occurred during early development. However, autism comprises a heterogeneous population in that parents report either that their child was abnormal from birth, or that their child was developmentally normal until sometime after birth, typically 15–24 months, at which time the child began to regress or deteriorate [7,27,28]. Typically reported is loss of verbal, nonverbal, and social abilities [25,27]. Information provided by parents of children that were developmentally normal until a later onset does not fit with the current thought of the time of neurological onset of autism as being prenatal in all cases. It is conceivable that some of these children become autistic from neuronal cell death or brain damage sometime after birth as result of insult [29].

The most consistent neurological abnormalities found in persons with autism is marked Purkinje cell loss in the cerebellum (as determined by histopathological examination); and atrophy of the cerebellar folia (as determined by in vivo neuroimaging) [11–16,30–33]. Of particular clinical interest, research suggests Purkinje cells die relatively easily compared to other types of neurons [34]. Several studies have shown that Purkinje cell loss can result from insult, and in some cases be selectively vulnerable. For example, Purkinje cells are selectively vulnerable to ischemia (inadequate blood supply) [34,35]; hypoxia (inadequate oxygen supply) [34,36]; excitotoxicity (e.g. seizures, metabolic insufficiencies) [35,37–41]; G protein dysfunction [42–44]; viral infections [45]; vitamin deficiencies (e.g. thiamine) [37]; heavy metals (e.g. mercury, lead, bismuth) [46–49]; toxins (e.g. bilirubin, phenytoin, ethanol, alkaloids, toluene) [35,38,50,51]; as well as from chronic malabsorption syndrome (e.g. celiac disease, inflammatory bowel disease) [52–54].

The basic nature of neurons in regard to location, function, and chemical makeup allows for a hierarchy of neuronal vulnerability of selective neuronal populations. Why the Purkinje cell may be susceptible to insult is discussed in the next section.

3. Why is the Purkinje cell vulnerable?

The Purkinje cell is an exceptionally large (50–80 μm) inhibitory neuron in the cerebellum that receives extensive excitatory input from both parallel fibers (from granule cells) and climbing fibers (from the inferior olivary nucleus) [55]. Parallel fibers make about 200,000 connections on each Purkinje cell and input from these neurons trigger calcium influx [56]. Climbing fibers release glutamate or aspartate at all levels of the soma and dendrites of the Purkinje cell firing synchronously, forming one of the most powerful connections in the nervous system [34,55–57]. The response of the Purkinje cell is a large action potential followed by a high frequency of smaller action potentials (complex spikes) that is associated with a calcium influx that is unparalleled in the nervous system [55,56]. As a result of the high level of excitatory amino acid synaptic connections and the response of the Purkinje cell that is mediated by voltage-gated and receptor-gated calcium channels, the Purkinje cell has an exceptionally high metabolic demand [34]. A high metabolic demand combined with constant input from the inferior olive and large amounts of calcium stores and influx, makes the cell vulnerable [58,59]. Excessive rises in intracellular calcium is associated with excitotoxicity, and can cause cell death [60].

The current thought in autism is that Purkinje cell loss is not due to cell death, but abnormal development during gestation. The main reason for this assumption is, as mentioned earlier, the absence of gliosis. Gliosis is proliferation of neuroglial tissue that can follow neural damage [61]. Nervous system damage as a result of insult (e.g. metabolic insufficiencies, epilepsy, brain injury, toxins, infarction, viral infection, ischemia, excitotoxicity, etc.) can lead to neuronal death, neuronal degeneration, apoptotic cell death, injury, cell loss, and gliosis [61]. However, there is recent evidence of gliosis associated with Purkinje cell loss in the cerebellum of some children with autism. This evidence will be discussed in the next section.

4. Evidence of gliosis in some children with autism

The absence of gliosis reported in the autopsy study by Bauman et al. [26], mentioned earlier, does not support the theory that some of the abnormalities in autism are a result

of insult after birth. However, some research studies in autism support the theory of neural damage as a result of insult in some children with autism. For example, absence of gliosis is not a consistent finding on autopsy. A recent autopsy report by Bailey et al. [15] found that the Purkinje cell loss was sometimes accompanied by gliosis and an increase in glial fibrillary acidic protein (GFAP). GFAP is elevated in acute and chronic situations of nerve cell damage [62]. The authors stated that the patchy glial cell hyperplasia found in their study suggests the possibility of postnatal loss of Purkinje cells. In addition, a study by Ahlsen et al. [62] that examined the levels of GFAP in the cerebrospinal fluid of children with autism, found GFAP to be at three times the level of the control group. The authors state that the results could implicate gliosis and unspecified brain damage in children with autism [62].

Interestingly, Bauman et al. [63] reported that the Purkinje cells were enlarged in the children, whereas the cells were small and pale in the adults. The authors theorized that the cellular enlargement was a result of a compensatory mechanism. However, neuronal damage can result in cell swelling, inflammatory reactive edema [61].

The selective vulnerability of the Purkinje cell and the evidence that Purkinje cells are depleted in persons with autism may suggest that the susceptibility of this neuron to injury and death plays a role in the cause of autism. To support this theory is anecdotal reports of some children with autism that are developmentally normal until sometime after birth, when they begin to regress or deteriorate. Results of a small pilot survey on this matter are discussed in the next section.

5. Parental survey results and the possibility of insult

In autism, anecdotal reports and some studies suggest that often the period of deterioration and/or regression observed in children with autism is marked by an illness or significant physiologic event. Surveys completed during a treatment study by Kern et al. [25] revealed that of the 20 children with autism or PDD in the study, only three children (15%) were reported by their parents to be abnormal from birth, while 17 (85%) were reported to have deteriorated and/or regressed sometime after birth. Of the 17 (85%) that were reported to have an onset after birth, only two (12%) were reported to have no significant events prior to the appearance of autistic features. In contrast, the other 88% were reported to have significant events prior to the appearance of autistic features. Two were reported to have problems start at 2 months of age following meningitis. Two were reported to have problems in the 8th and 9th month following onset of seizures (one after becoming ill subsequent to immunizations). Eleven (85%) were reported to have developed problems between 15 and 24 months; of these children, nine followed a significant event (five after becoming ill subsequent to immunizations, three after severe and prolonged fever and infection, and one after febrile seizures with roseola). Two children (18%) were reported to have an onset between 2 and 4 years (both after becoming ill subsequent to immunizations). In addition, four of the later onset children (15 months–4 years) also had marked changes in bowel function at the same time as the significant event with the development of chronic and severe diarrhea.

Though the data is from a small population, some of these findings can be shown in other research. For example, other studies have shown that approximately one-third of children that enter the autistic state by deterioration and/or regression from a prior normal state of development are reported to have developed seizures at the time of onset [64]. Also, in a study by Wakefield et al. [65], children were reported to have regressed following immunizations and extreme changes in gastrointestinal function manifested by chronic and severe diarrhea.

In addition, some studies suggest that these children have been exposed to environmental or neurotoxins. For example, blood lead levels in children with autism have been found to be elevated [7]. Blood levels of aromatic hydrocarbons, such as benzene, trimethylbenzene; triethylbenzene, ethylbenzene, trichloroethylene, styrene, toluene, and xylene have been found to be elevated above toxic levels [66]. Sources of aromatic hydrocarbons compounds, commonly occurring in industrialized nations [67], could be water, dry cleaning chemicals, indoor sources (e.g. new home materials), kerosene stove, smoking, car engines, etc. [68–70].

6. Current state of research in this area of autism

There has been to date, no comprehensive reports on the incidence or of the types of events that precede this period of deterioration/regression reported often by parents. Nor has there been any investigation into the possible underlying relationships or possible common denominators to these precursors. The research on this issue of onset is very limited. One reason for the lack of investigation into these reports is that the information from parents is considered to be unreliable [71]. Though many parents report a developmentally normal period prior to deterioration and/or regression, it is assumed that the information is incorrect [71]. Interestingly, though parental reports on the issue of incidence prior to the development of autistic symptoms is assumed to be unreliable, several studies have shown that parental concerns about speech and language development, behavioral and developmental issues are highly sensitive [72–74] and reliable for early developmental screening [75].

Reports of incidence prior to the onset of autism have not been investigated, and the cause of autism remains elusive. Considering that parental reports of incidence prior to the onset of autism have not been investigated, and the cause of

autism remains elusive, assuming that the information from parents of children with autism is unreliable and not worth investigating may not be good science. Better science may be to not assume, but to investigate all reasonable leads.

7. Cerebellar impairment and autism

An argument against this theory is that some persons with cerebellar damage do not develop autism. A reason for this may be that multiple parameters play a role in the development of autism, such as onset of pathology in relation to age and stage in development, as well as the function of the areas of neuropathology in the cerebellum, and their relationship with the rest of the brain. Autism comprises a combination of social, language, and cognitive deficits [6]; thus, a combination of areas of pathology may be important. The cerebellum has vast interconnections with the cerebral cortex and other parts of the brain, and evidence suggests that the cerebellum modulates and coordinates different functions throughout the brain [76]. Certain areas of the cerebellum are involved in functions that are found to be abnormal in autism [11,77]. For example, the cerebellum, particularly the vermis, has been shown to modulate (inhibit/disinhibit) sensory input at the level of the brain stem, thalamus, and cerebral cortex [78]. Stimulation of the vermis can cause hypersensitivity to touch and sound [79]. Persons with autism sometimes over- or under-respond to sensory stimuli, and can be hypersensitive to stimuli [6,80]. Multimodal sensory neurons (auditory, visual, somatosensory) from the superior colliculus (SP) project to the vermis, and the vermis has projections back to the SP, indicating a multisensory feedback loop [77]. Persons with autism sometimes have issues of multimodel sensory integration, and show evidence of a lack of central coherence of sensory information [8]. A feedback loop has also been found between the cerebellum and the septal-hippocampus, an area thought to be important in emotional behavior, suggesting a role of the cerebellum in affectual components in autism [81]. The right cerebellum has been shown to work with the left frontal and anterior cingulated areas in word generation tasks [82]. Lesions of the right cerebellum result in problems in word selection and production [83]. Lesions of the vermis can result in dysarthria and abnormal speech rhythm [84]. A main feature in autism is impairment in communication, which can range from being nonverbal to a delay in the acquisition of the spoken language and abnormal speech (abnormal pitch, intonation, rhythm, and rate) [6]. The cerebellum has been shown to have interconnectivity with areas involved with attention, gaze control, and control of head and eye movement (reticular formation, SC, dorsolateral prefrontal cortex, posterior parietal cortex, pulvinar) [85,86]. Persons with autism can have difficulty with gaze; they may stare into space, avoid eye contact, or look at objects from unusual angles [87]. Those same areas are involved in the shifting of attention. Persons with autism can have difficulty with shifting of attention, and can become fixated with certain stimuli, while ignoring more important (even dangerous) ones [8].

Current evidence suggests that the cerebellum is used to integrate and modulate information (sensory and motor) to help us interpret and respond to our world [76], and that once a process is familiar, the less the cerebellum is involved [88]. Activation of the cerebellum peaks when performance is naïve; once a process is automatic, the cerebellum is not involved [83]. Recent evidence suggests that the cerebellum is involved in the memory storage process in associative learning (of discrete behavioral responses) [89]. It may be that the role of the cerebellum in associative learning is pivotal. Once learning has occurred and the connections formed in other parts of the brain, the effect of cerebellar function may diminish, making normal function of the cerebellum critical during the early stages of development and less so as a person ages. Thus, the point of pathological dysfunction of the cerebellum during development may be a key factor in the development of autism.

8. Conclusion

Neurons come in a variety of shapes and sizes, but more importantly with different biochemical compositions and requirements. The variety in the basic nature of neurons in regard to location, function, and chemical makeup allows for a hierarchy of neuronal vulnerability of selective neuronal populations to a variety of insults [36]. It has been shown that Purkinje cells can be selectively vulnerable to certain types of insult [34,36]. It has also been shown that Purkinje cell loss is a consistent finding in the autistic disorder [15]. In the recent autopsy report of six people with autism by Bailey et al. [15], the authors stated that in regard to timing of onset it would be premature to conclude that any single developmental event led to these findings, that some signs were suggestive of a developmental basis and yet other factors influencing neuronal cell survival also seem to be important. Anecdotal reports suggest that some children with autism have significant physiological events that could result in neuronal insult prior to the development of autistic symptoms, yet these reports have not been investigated.

Due to the dramatic rise in the incidence of autism in the last 10 years, a meaningful effort needs to be made in the understanding of the cause of autism and the factors that influence its occurrence. A future direction in autism research may need to include a novel tact, and investigate the possibility of neuronal cell loss from insult as a cause of autism. One approach is through clinical studies that investigate parental reports and the clinical aspects associated with autism. In addition, basic research can examine this issue further through histological examination, and through models.

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