Autism Spectrum Disorders in Survivors of Extreme Prematurity

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KEYWORDS

• Prematurity • Autism spectrum disorders • Brain
• MRI • Outcome

The impact of extreme prematurity on the neurodevelopmental outcome in survivors is enormous.[1–6] Advances in perinatal and neonatal care have resulted in dramatic increases in survival of premature infants, most strikingly among the smallest and sickest.[2,3,7,8] Unfortunately, this decrease in mortality has not been accompanied by a similar decrease in long-term neurodevelopmental morbidity among survivors.[3,5,9] Ex-premature infants are at substantial risk for significant and costly lifelong disabilities.[10,11] Of particular concern is the risk for significant higher-order neurodevelopmental impairment in ex-premature children reaching school age. In some studies, up to 50% of ex-preterm infants experience difficulties in executive functioning, learning, and behavior, often requiring special educational support.[12–14] These children are at increased risk for attentional difficulties, hyperactivity,[15] social-behavioral, and communication dysfunction,[16] and for psychiatric disorders in adolescence[16] and adulthood.[14,17–22] Failure to cope with the demands of adulthood is more prevalent among survivors of prematurity, with lower educational and income attainment, and difficulties establishing a family.[11]

Converging lines of evidence point to a significantly increased risk among extremely premature infants for subsequent development of cognitive, learning, behavioral, and

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psychoaffective disturbances. Recent reports also suggest an increase in atypical social-behavioral functioning in this population that is strongly suggestive of autism spectrum disorders (ASD). These recent data have triggered a vigorous and highly charged debate, given the potential implications for this growing population of prematurity survivors, their caretakers, and society at large. This article reviews available evidence for prematurity and ASD, examines the potential role of early life neuroanatomic antecedents for these behavior patterns in survivors of extreme preterm birth, and explores future directions in this emerging area of research.

AUTISM SPECTRUM DISORDERS

ASD are a heterogeneous group of behaviorally defined, neurodevelopmental disorders characterized by impaired development in communication, social interaction, and behavior.[23] There are three broad categories (ie, autism, Asperger syndrome, and pervasive developmental disorder not otherwise specified), each with a wide range of effects but shared core symptoms. At the lower-functioning end of the autism spectrum, individuals have impaired reciprocal social interaction, abnormal development and use of language, and repetitive and ritualized behaviors. Conversely, those with Asperger syndrome are higher-functioning with normal intelligence but abnormalities in social interaction. When a child has autistic symptoms that do not fit another ASD diagnosis, pervasive developmental disorder not otherwise specified may be diagnosed.[23]

The earliest behavioral signs of ASD emerge between 1 and 2 years of age, and include impaired social attention, language development, and emotional reactivity.[23] Given the importance of early detection and intervention for children with ASD, the American Academy of Pediatrics has recently published guidelines endorsing autism-specific screening for all children at age 18 months.[24] Early screening tools for ASD, such as the Modified Checklist for Autism in Toddlers (M-CHAT), incorporate items that capture these early signs of ASD. These screening tests identify children who warrant formal testing for the diagnosis of ASD, which is usually made between 2 and 4 years of age.

ASDs are increasingly recognized as a major public health issue in childhood and beyond.[25,26] Although ASD was once considered a rare disorder, the Centers for Disease Control and Prevention recently estimated its prevalence at around 1 in 150.[25] The personal and familial impact of these conditions is often catastrophic. Likewise, the economic cost of ASD to society is enormous, with an estimated annual cost as high as $35 billion per year and an individual lifetime cost of $3.2 million.[27] The potential contribution from increasing survivors of extreme prematurity to this growing population of children with ASD is explored herein.

Etiology of ASD

Although a broad range of etiologies has been implicated in the development of ASD, prevailing consensus favors a multifactorial pathogenesis. A growing body of evidence supports the presence of abnormal fetal brain development in ASD. Many researchers adhere to a triple-hit hypothesis for the development of ASD.[28] In this paradigm, ASD develops in individuals with (1) an underlying biologic vulnerability who experience (2) varying degrees of exogenous stressors (3) during a critical period of brain development.[28–31] The notion that the underlying predisposition to ASD is caused by a single gene defect has been refuted, and current understanding is that the risk of developing ASD is modified by multiple susceptibility and protective genes.[28] The putative genetic factors implicated in ASD form part of a vast and complex area of research that is

beyond the scope of this article. Rather, this article explores the other two arms of this triple-hit paradigm, namely the potential role of insults to the immature brain during a critical period of brain development in prematurely born infants. Early life insults may play a role in the development of ASD. Clinical data support the notion of a vulnerability period during the second and third trimester of gestation for subsequent development of ASD and are summarized later.[32,33]

WHAT IS THE RELATIONSHIP BETWEEN PREMATURITY AND ASD?

Prematurity-related Risk Factors and ASD

To date, population-based studies have consistently identified prematurity and low birth weight[34–38] as important perinatal risk factors for the development of ASD. A recent large population-based study of adults born at very low gestational age compared with term-born adults described a significant increased risk for ASD, with a relative risk of 7.3 among those born at 28 to 30 weeks gestation, increasing to nearly 10 in those born at 23 to 27 weeks gestational age.[11] These data suggest that the incidence of ASD among survivors of preterm birth is inversely related to gestational age.

Obstetric complications and intrapartum hypoxia (eg, bleeding during pregnancy, maternal hypotension, cesarean delivery, fetal distress, low Apgar score)[29,35,39,40] and a history of neonatal intensive care[33] have also been reported to increase the risk of autism. Parental infertility and advanced maternal and paternal age at birth are additional risk factors that have been associated with ASD.[39,41,42] Interestingly, a higher prevalence of ASD has recently been linked with in vitro fertilization compared with the general population.[43]

Available evidence suggests that pregnancy, delivery, and neonatal complications increase the risk for ASD through independent etiologic pathways that likely interact with a genetic predisposition, thereby interfering with brain maturation at critical points in development.[29,30,44,45] It is important to note that, to date, population-based studies generally reflect a population born preterm over two decades ago, and the prevalence of ASD among ex-premature infants born in the modern era remains unknown. Given that the greatest advances in survival are among the most premature and critically ill infants, the need to better define the risk of ASD in these new survivors of extreme preterm birth is of unquestionable importance. Moreover, given the established risk of preterm birth associated with in vitro fertilization,[46,47] the complex relationship between in vitro fertilization, prematurity, and ASD needs further definition. Taken together, large population-based studies are needed to allow for a more precise and detailed assessment of exposures and potential confounders for a more conclusive investigation of prematurity-related risk factors and ASD.

Prematurity and Evidence for Social-behavioral Dysfunction

Current understanding of the behavioral and psychosocial health of survivors of very preterm birth indicates that these children are at increased risk for social-behavioral dysfunction. Most notably, low birth weight and gestational age have been identified as important perinatal risk factors for disturbances in social interaction, communication, and behavior[48] and later psychoaffective disorders in adulthood.[18,19,49] During childhood and adolescence, very low birth weight children exhibit greater internalizing and externalizing behavior problems than their peers, and attentional difficulties and hyperactivity.[15,16,50,51] A high prevalence of difficulties with social integration, such as excessive shyness, withdrawn behavior, and more difficulties in establishing social contacts, and antisocial behaviors has also been described.[21,52,53] Noteworthy is the fact that preterm adolescents are far more likely to experience psychiatric symptoms

(46%) than controls (13%), particularly attention deficit, anxiety symptoms, and relational problems.[54,55]

More recent literature has underscored significant concerns about the ability of these children to cope with the demands of adulthood, including lower levels of educational attainment and income, and difficulties with establishing a family.[22] From a social-behavioral perspective, extremely low birth weight adults are reported to have an overall lower level of social competence characterized by significantly higher shyness, behavioral inhibition, lower extraversion and higher neuroticism, impaired interpersonal relationships, and overall lower sociability and emotional well-being than their normal birth weight counterparts.[14,20,22] The personality profile of adults born very preterm is increasingly characterized by behavioral inhibition and negative affectivity, and decreased positive affectivity, collectively, placing them at risk for mental health problems, such as anxiety and depression.[16,21,22] Interestingly, despite increased recognition of psychosocial impairments among prematurity survivors, to date these problems remain clinically underdiagnosed.[56]

Converging evidence points to an increased risk among extremely premature infants for significant future psychiatric and emotional problems. Despite increasing reports of atypical social-behavioral functioning among survivors of extreme preterm birth, little is currently known about the true prevalence of ASD in this vulnerable population.

Prematurity and ASD: What is the Evidence?

The potential role of ASD in the spectrum of social-behavioral dysfunction described in this population has been underexplored. Anecdotal experience in the clinical follow-up of ex-preterm infants in recent years has suggested that a subgroup of infants born very preterm exhibit noticeably atypical social behavioral characteristics, many of which are similar to those typically documented in young children with ASD. Until recently, however, studies linking very low birth weight and ASD have been few and limited largely to small subgroups of higher functioning adolescents and young adults with Asperger disorder,[55,57] or those with severe retinopathy of prematurity.[58] Studies that have reported an association between ASD and prematurity are summarized in **Table 1**. Msall[58] using a parental questionnaire reported a higher prevalence of autism in a cohort of extremely preterm infants (<1251 g) with unfavorable vision status (ie, severe retinopathy of prematurity) (8.5%) versus those with favorable vision status (0.8%) at 8 years of age. Indredavik and colleagues[16,55] have reported increased scores on the Autism Spectrum Screening Questionnaire and an increased prevalence of Asperger syndrome–like symptoms (assessed by interview) in very low birth weight adolescents. The authors speculated that very low birth weight adolescents exhibit a milder form of ASD, and experience particular deficits with encoding and interpreting subtle cues of social relations,[59] which likely implicates cognitive and emotional mechanisms and impaired brain connectivity (described later).

The recent availability of validated screening instruments for detection of early signs of ASD[60] has facilitated the early screening of infants to prompt appropriate referrals for specialized autism diagnostic testing.[61] Stimulated by observations of autism-like behavioral profiles in clinical follow-up of very premature infants, together with the greater availability of ASD screening tools for toddlers, the author and others have recently begun to explore the potential relationship of ADS and survivors of extreme preterm birth. The author's group published the first study that examined the relationship between early signs of autism in young toddlers with a history of extreme prematurity.[62] They performed initial screening for early autistic features using the M-CHAT in a consecutive series of 91 ex-preterm infants born less than

Table 1
Rates of ASD in follow-up studies of infants born preterm

Author	Year	Sample Size	Birth Weight GA	Sample Characteristics	ASD Measure	Age at Follow-up	Rates of ASD
Msall et al[58]	2004	24	<1250 g	Preterm and severe ROP	Parental questionnaire	14–15 y	7 (8.5%) severe ROP 1 (0.8%) favorable vision status
Indredavic et al[55]	2005	104	<1500 g	Preterm and SGA	ASSQ	14–15 y	4 symptoms of Asperger's 1 ASD (2%)
Limperopoulos et al[64]	2007	86	<32 wk GA	Preterm with CBH Preterm with SPI Preterm controls	M-CHAT SCQ (subset)	1–5 years	13 (37%) M-CHAT 5 (33%) SCQ
Limperopoulos et al[62]	2008	91	<1500 g <31 wk GA	Preterm	M-CHAT	18–24 mo	23 (25%)
Kuban et al[63]	2009	988	<28 wk GA	Preterm	M-CHAT	24 mo	212 (22%)
Limperopoulos et al (Limperopoulos, 2009)		42	<32 wk GA	Preterm with CBH	ADOS DSM-IV	6–9 y	12 (28%)

Abbreviations: ADOS, autism diagnostic observation schedule; ASSQ, autism spectrum screening questionnaire; CBH, cerebellar hemorrhagic injury; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition; GA, gestational age; M-CHAT, Modified Checklist for Autism in Toddlers; ROP, retinopathy of prematurity; SCQ, Social Communication Questionnaire; SGA, small for gestational age; SPI, supratentorial parenchymal injury.

or equal to 1500 g prospectively recruited at birth. They reported that an alarming 25% of ex-preterm infants (mean of 21 months corrected age) tested positive on these autism screening instruments. Abnormal M-CHAT scores correlated highly with internalizing behavioral problems on the Child Behavior Checklist and socialization and communication deficits on the Vineland Adaptive Behavior Scale. Importantly, with the exception of three children, the cohort was otherwise not affected by significant visual, auditory, and motor (eg, cerebral palsy) impairments. Perinatal risk factors associated with a positive autism screening included lower birth weight, chorioamnionitis, acute intrapartum hemorrhage, male gender, and illness severity on admission.

Kuban and colleagues[63] in a subsequent study also examined the prevalence of a positive screen for ASD using the M-CHAT in a large multicenter study of preterm infants born less than 28 weeks of gestation, and reported more than 21% screened positive for ASD. The authors also examined the impact of sensorimotor and cognitive impairments on a false-positive screening. Major motor (eg, cerebral palsy), cognitive (eg, mental retardation), and significant visual and hearing impairments accounted for more than 50% of the positive M-CHAT screens in their cohort. For example, children with major visual or hearing impairments were eight times more likely to screen positive. Among the subgroup of children who were free of motor, cognitive, visual, and hearing impairments, 10% screened positive, nearly double the expected rate. Noteworthy is the fact that cognitive impairment is frequently present in children with ASD; adjusting for this variable likely underestimates the true prevalence.

A third study to report an association between prematurity and ASD by the author's group examined the developmental consequences in a subgroup of ex-preterm infants with cerebellar hemorrhagic injury,[64] a form of brain injury increasingly recognized among survivors of extreme preterm birth.[65–69] Children underwent formal neurologic examinations and a battery of standardized developmental, functional, and behavioral evaluations, and autism screening questionnaires at a mean age 32 months. Results indicated that children with isolated cerebellar injury versus preterm age-matched controls demonstrated significantly greater motor disabilities, language delays, and cognitive deficits. Notably, 37% of infants with cerebellar injury tested positive for early signs of autism using the M-CHAT. The author speculates that cerebellar hemorrhagic injury in preterm infants was associated with a high prevalence of pervasive neurodevelopmental disabilities and may play a critical and underrecognized role in social, affective, and behavioral dysfunction (discussed later).

Collectively, these initial data strongly suggested that early autistic behaviors seem to be an underappreciated feature in survivors of extreme prematurity, and that these behaviors might be increased by injury and growth failure (see later) to the premature cerebellum. These provocative preliminary findings clearly require confirmation using definitive autism diagnostic tests. One important limitation of the studies summarized previously is that the cut-off scores of screening measures are typically designed to maximize the identification of children at greatest risk, and consequently may compromise both false-positive and false-negative results. Furthermore, the extent to which these initial positive screen rates are transient or indicative of a milder form of ASD that is specific to extreme preterm survivors or merely reflective of future social-emotional impairments is unclear. Long-term studies are urgently needed to examine the sensitivity and specificity of the M-CHAT, and determine the true prevalence of ADS in infants born preterm.

To date, formal follow-up evaluations using the Autism Diagnostic Observation Schedule and *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* criteria in the author's cohort of ex-preterm children with isolated cerebellar hemorrhagic injury who tested positive on initial screening using the M-CHAT (described

previously) are revealing that approximately 30% of children meet diagnostic criteria for ASD (Limperopoulos, 2009). The relationship between perinatal risk factors and topography of cerebellar injury is currently under investigation. Ongoing research is needed to better elucidate the prevalence, mechanisms, and neural basis of autism spectrum features in ex-preterm children.

NEUORANATOMIC SUBSTRATES FOR ASD AND PREMATURITY

Neuroimaging and neuropathologic studies in ASD have shown a heterogeneous array of anatomic findings in the cerebrum and cerebellum.[70,71] Although a comprehensive review of this literature is beyond the scope of this article, the potential relationship between altered brain development in ASD and the role of prematurity itself and prematurity-related brain injury is explored.

One of the most striking observations in autism research to date is the lack of neuroimaging studies that have focused on early neuroanatomic development at the age of clinical onset of autism.[71] Conversely, studies have focused largely on subjects a decade or more after the onset of the disorder, and primarily on higher-functioning autistic individuals. Consequently, there is a glaring lack of early neuroimaging data from around the time of autism diagnosis (ie, between 2 and 4 years of age).[71] Moreover, because ASDs are typically diagnosed around age 2 or later, no studies have reported the pre-existing neuroimaging findings in children subsequently diagnosed with ASD. Existing data largely reflect neuroanatomic changes years after the onset of autism, delineating the end result of the pathology of autism rather than the structural changes taking place before or during the emergence of ASD symptoms.[71,72] The neuroanatomic antecedents of ASD remain essentially unknown at the present time. Longitudinal neural anatomic studies before the emergence of ASD features are urgently needed.

Neuroimaging, Prematurity, and ASD

Evidence for neuroimaging abnormalities and ASD in survivors of preterm birth is currently limited to a handful of reports, which are summarized next.

Impaired connectivity

Skranes and colleagues[73] demonstrated that very low birth weight adolescents with symptoms of Asperger disorder all had white matter reduction and ventricular enlargement on MRI. Moreover, higher scores on the Autism Spectrum Screening Questionnaire were significantly correlated with impaired connectivity characterized by reduced fractional anisotropy values on diffusion tensor imaging in the external capsule and superior fascicle on the left side. The authors speculate that the low fractional anisotropy values may be associated with damage to the immature developing white matter that has long-term consequences on microstructure and connectivity. This damage in turn leads to poor connectivity in commissural and association tracts and impairs the abilities that demand cooperation between different brain regions. Specifically, the external capsule contains fibers that connect the temporal and fontal lobes.[74] These findings corroborate neuroimaging studies reporting white matter abnormalities in the frontal, superior temporal cortex, and temporoparietal junction,[75] and neuropathology reports of smaller frontal and temporal cortical minicolumns in individuals with autism.[76,77]

Impaired cerebellar growth and development

Using advanced three-dimensional volumetric MRI studies in premature infants, the author's group has demonstrated a particularly rapid growth period for the immature

cerebellum during the third trimester of gestation, a growth rate that far exceeds that of the cerebral hemispheres.[78] In late gestation, proliferation and migration of the cerebellar granule cells are particularly prominent events,[79] and such insults as hemorrhage and hypoxia-ischemia may injure these immature granule cells, with secondary effects on other cell populations[80] ultimately impairing cerebellar growth and development.[81]

Impaired growth and development of the cerebellum in premature infants may be grouped into two broad categories, based on early neonatal MRI studies.

The first category of cerebellar growth impairment observed in preterm infants is evidence of direct cerebellar injury during the neonatal period. Cerebrovascular (often hemorrhagic) injury is an important and previously underrecognized form of injury to the immature cerebellum, particularly in the extremely low gestational age infant. Although the pathogenesis for this type of injury remains unknown, it is likely related to impaired cerebral autoregulation and vascular fragility of the cerebellar germinal matrices.[82] The author's group has shown that ex-preterm infants with isolated cerebellar hemorrhagic injury were significantly more likely to score positive on initial autism screening compared with those infants without cerebellar injury.[64] Moreover, the presence of associated supratentorial injury (eg, periventricular leukomalacia, periventricular hemorrhagic infarction) did not further increase the risk for testing positive on early autism screening in these infants. It is noteworthy that socialization difficulties and a positive autism screening were almost exclusively associated with injury to the vermis (**Fig. 1**). Recent findings also suggest that unilateral cerebellar hemorrhagic injury is associated with region-specific contralateral cerebral gray and white matter volume reductions in the sensorimotor, premotor, dorsolateral prefrontal, and mid-temporal cortices, suggesting trophic withdrawal (ie, cerebellocerebral crossed diaschisis [Limperopoulos, 2009]). The potential role of such remote contralateral cerebellocerebral growth failure in the subsequent development of cognitive, affective, and behavioral impairment, including ASD, remains unknown.

The second category of cerebellar growth impairment is present in the absence of direct injury to the cerebellum detected by MRI. Using quantitative MRI studies, the author and others[78,83,84] have also shown an increased risk for impaired cerebellar growth in ex-premature infants. Such cerebellar growth impairment is already detectable by quantitative MRI as early as term gestational age equivalent.[78] Whether this growth impairment is caused by cellular injury below the current resolution of MRI, loss of maternal-placental growth factors, or environmental factors injurious to the immature cerebellum remains unknown.[82] Importantly, decreased total cerebellar volume at term equivalent in the absence of direct cerebellar injury is associated with higher M-CHAT scores in toddlers born preterm, controlling for total brain volume and gestational age (Limperopoulos, 2009) (**Fig. 2**). These data support the notion that impaired development of the cerebellum (in the absence of direct cerebellar injury) in the preterm infant may be associated with long-term atypical socioaffective development in this vulnerable population. Taken together, these data suggest that both direct and indirect mechanisms of cerebellar injury seem to stunt cerebellar growth and development in the preterm infant. Likewise, these findings provide important insights into the highly integrated anatomic and functional interactions between the immature cerebrum and cerebellum, and suggest significant remote trophic effects between these structures during development. It is also reasonable to suggest that early life impairment of cerebellar growth plays a central but previously underrecognized role in the long-term cognitive, behavioral, and social deficits associated with brain injury among premature infants.[64] The full extent of the role of cerebellar injury, however, in

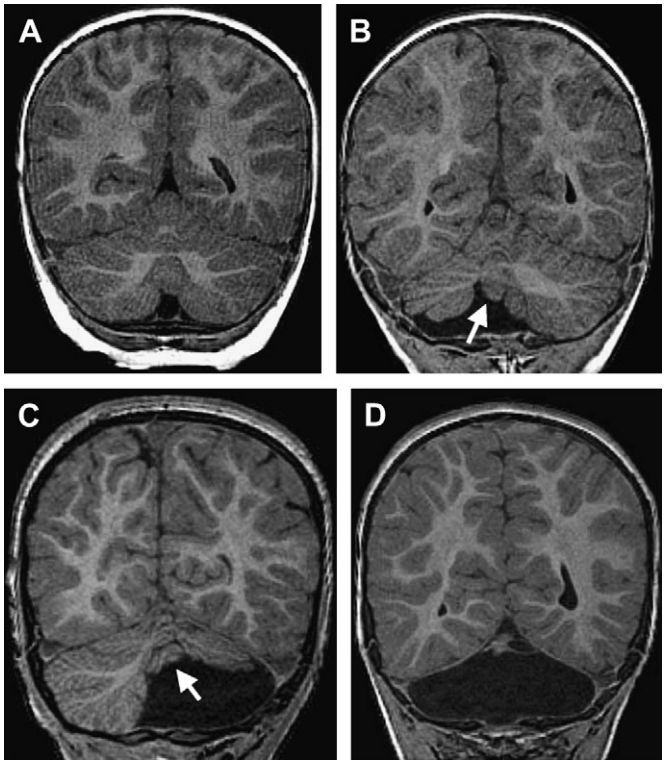

Fig. 1. Relationship between cerebellar injury topography and early signs of ASD. (*A*) Example of a normal cerebellum. (*B*) Unilateral right cerebellar injury without injury to the vermis. (*C*) Unilateral cerebellar and vermis hemorrhagic injury. (*D*) Extensive (near complete) bilateral cerebellar-vermis injury.

the genesis of social behavioral deficits among premature infants remains to be determined.

Neuropathology and Autism

Neuropathologic studies have highlighted evidence of cellular abnormalities and processes that may underlie the neuropathologic substrates of autism. Although

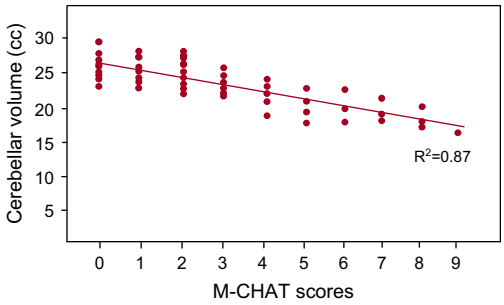

Fig. 2. Relationship between cerebellar volume at term equivalent and M-CHAT scores at follow-up testing between 18 and 24 months corrected age. Higher M-CHAT scores were associated with lower total cerebellar volume at term.

neuroanatomic descriptions from cases of autism are limited, a variety of findings has been described in autopsy studies[28,71,72,85] supporting these cellular and growth abnormalities in the cerebellar, frontal, and temporal cortices. Noteworthy is the fact that 80% of these have demonstrated well-defined cerebellar anatomic abnormalities.[85–89] Importantly, there are no autopsy reports from autistic children around the typical age at diagnosis (ie, 2–4 years). The most commonly described neuropathologic findings in the cerebellum of autistic individuals include glial activation with gliosis, and neuronal degeneration most prominently among the Purkinje neurons.[87]

THE CEREBELLUM: CHANGING CONCEPTS OF ITS FUNCTIONAL ROLES

Available data on the role of the cerebellum and ASD in preterm infants are in harmony with an accumulating experience in older subjects reflecting the relationship between the cerebellum and socioaffective development. Although traditional understanding of the cerebellum's role has been that of a center for motor control,[90] in recent years this traditional view has been challenged by increasing recognition that the cerebellum has an important role in ''higher functions,'' such as cognition, learning, affect, and behavior. Central to this development has been the description of a distinct ''cerebellar cognitive affective disorder''[91] in older children[92–94] and adults[91] following cerebellar injury, particularly to the posterior lobe. The cerebellar cognitive affective syndrome is characterized by a constellation of impairments in executive, visual spatial, linguistic, and affective function. Relevant to survivors of extreme preterm birth is an earlier description of an apparent ''developmental'' form of cerebellar cognitive affective syndrome.[64] Central to the cerebellar cognitive affective disorder is emotional dysregulation, which is usually evident with impaired behavioral modulation and flattening or disinhibition of affect.[95] In addition, obsessive-compulsive traits may be prominent, and behavioral stereotypies and disturbed interpersonal relations that meet criteria for autism.[90] In studies, the features of this developmental cerebellar cognitive affective syndrome show clear overlap with the features of early autism. Of particular note is the fact that these behavioral changes in the cerebellar cognitive affective syndrome are most prominent when the vermis and paravermian regions of the cerebellum are injured, as is the case in a cohort of ex-premature children in which injury to the vermis is strongly associated with early signs of ASD.[64] The relationship between regional cerebellar volumes and ADS in ex-preterm children with cerebellar injury diagnosed with ASD at school age is currently underway.

SUMMARY AND FUTURE DIRECTIONS

Clearly, the most pervasive long-term neurodevelopmental sequelae among survivors of extreme prematurity are those in the areas of cognitive, behavioral, and affective function. Although clinical experience and initial screening tests point to a significant prevalence of autistic-like behaviors in these children, the true nature and severity of these behaviors need further definition. Likewise, the precise mechanisms underlying the development of these autism-like behaviors among ex-premature children are unclear. The precise structure-function relationships between these observations are not yet known. Ongoing research is needed to provide new insight into the true prevalence of diagnosed ASD, and the association between prematurity itself, and the effects of prematurity-related brain injury, and the development of ASD among survivors of extreme prematurity. Importantly, delineation of these relationships provides clinicians with the understanding needed for informed prognostic counseling of future parents of premature infants and for anticipatory guidance, and for the

development of more timely and cost-effective models for early intervention and better allocation of resources.

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