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Optic Nerve Hypoplasia and Autism: Common Features of Spectrum Diseases

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Autism is a developmental disorder characterized by impaired social interaction, problems in verbal and nonverbal communication, and stereotyped or repetitive activities and interests. Rather than a single condition, autism is today generally regarded as consisting of a spectrum of pervasive developmental disorders that together are known as autism spectrum disorders (ASDs).

Optic nerve hypoplasia (ONH) is a congenital condition characterized by underdeveloped optic nerves and neurological impairment involving endocrine dysfunction and developmental delay, with or without brain malformations that are visible by way of neuroimaging tools. Increasing in prevalence, ONH is now the leading single ocular cause of blindness in children in the developed world, affecting 10.9 per 100,000 births (Patel, McNally, Harrison, Lloyd, & Clayton, 2006; Hatton, Schwietz, Boyer, & Rychwalski, 2007).

Clinical observations and recent reports indicate a high frequency of ASDs in children with ONH (Ek, Fernell, & Jacobson, 2005; Parr, Dale, Shaffer, & Salt, 2010). In children with ONH, there are additional characteristics of ASD beyond those attributable to visual impairment alone, such as echolalia and stereotypic motor movements. We argue that ONH, like ASDs, should be considered a spectrum disorder to account for the range of severity in outcomes and symptoms associated with this condition. In addition, we believe the similarities in the two conditions illustrate the possibility of a shared neurodevelopmental origin. Comparing the similarities in these conditions may lead to a greater understanding of the risk factors contributing to either condition, as well as potential clinical outcomes, as the relationship is further explored.

ASD and blindness

It is not surprising that ASDs are prevalent in children with ONH when one considers that published data indicate ASDs are overrepresented in the visually impaired population, with prevalence estimates as high as 1 case of autism in every 4 visually impaired persons (Brown, Hobson, Lee, & Stevenson, 1997), compared to 1 out of 110 in the general population (Rice, 2009). The behaviors and characteristics of children with vision impairment that resemble those of children with ASDs, including echolalia, pronoun reversal, stereotypic motor movements, and delays in developing pretend play, are often attributed to the vision impairment itself (Andrews & Wyver, 2005). These behaviors may be termed "blindisms," since they are explainable in the context of vision impairment. (For example, rocking or spinning may provide needed vestibular stimulation in a child with limited mobility due to lack of vision; language development and social interactions may be impaired in congenitally blind children due to their lack of concrete experiences and visual models.) The similarity of these "blindisms" to "autistic-like" behaviors, coupled with the absence of autism diagnostic measures designed for use with people who are blind or visually impaired, complicates the diagnosis of ASDs in children who are visually impaired." Thus, the debate concerning whether "true" autism is prevalent in children who are visually impaired remains unresolved.

ASDs and ONH

Most reports of ASDs in children with vision impairment (ASDVI) are limited to children

who have severe congenital blindness regardless of any cause (Brown, Hobson, Lee, & Stevenson 1977; Ek, Fernell, Jacobson, & Gillberg, 1998). There are a few reports focused specifically on children with ONH. In a group of 13 Swedish children with ONH and blindness, 6 had ASDs and 3 had "autistic-like" conditions. The remaining 4 children did not fall on the autism spectrum (Ek, Fernell, & Jacobson, 2005). Parr and colleagues reported in a sample of 83 children with ONH and severe vision impairment (with acuities of worse than 6/30), 31 (37%) had social, communicative, and repetitive or restricted behavioral difficulties. The majority of those (26 out of 31) were clinically diagnosed with autism (Parr, Dale, Shaffer, & Salt, 2010).

Unlike the previous studies of ASDs and ONH that focused only on children with severe visual impairment, a prospective study of children with ONH (Garcia-Filion, Epport, Nelson, Azen, Geffner, Fink et al., 2008) studied children with a range of visual impairment from mild to severe. A modified version of the Social Responsiveness Scale was implemented at age 5 years with a subset of 46 children from the original cohort to screen for ASDs. In this pilot study, based on parent reports, 21 (46%) of the participants demonstrated deficiencies in reciprocal social behavior (social awareness and the ability to participate in give and take communication), and more than half of that group (12) scored in the severe range on the scale. In a typical population, the severe range of reciprocal social behavior is associated with a clinical diagnosis of autism. This screening measure, however, has not been validated for children with visual impairment; therefore, the association of the scores on the Social Responsiveness Scale with a diagnosis of autism cannot be confirmed. Despite including children with a range of visual acuities, including those with unilateral ONH, among the sample, the findings from this prospective study of children with ONH are consistent with the rates of ASDs reported by Parr and colleagues (2010), all of which have demonstrated high levels of autism characteristics in children with ONH. This finding lends support to the concept of there being a neurological basis, rather than a visual reason, for these behaviors and impaired social interaction and communication since the study on ONH included children of varying levels of vision, including those with unilateral ONH. Therefore, the ASD behaviors cannot be attributed solely to the vision impairment. Both autism and ONH are neurological conditions, thus the ASD behaviors are likely neurological in origin.

Although making an accurate diagnosis of autism is a problem in evaluating children with ONH, the similarities between ASDs and ONH extend beyond the characteristics and behaviors assessed with measures for ASDs, and the overlap is striking. Characteristics of autism that have been observed clinically in children with ONH include: repetitive behavior; echolalia; "sing-song" language tone; difficulty engaging in the give and take of interactions; obsessions; nonocular self-stimulatory behaviors; hypersensitivity to certain sounds, textures, tastes, and smells; and other behaviors that are qualitatively different and result in more functional impairment than the behaviors seen in children with other types of visual impairments. Other characteristics shared by children with ONH and those with ASDs that are not diagnostic features of ASDs, include neuro-radiographic findings, seizures, gastrointestinal (GI) disturbances, and sleep dysfunctions.

An example of comparable impairment in central nervous system connectivity is the reduction in the size of the corpus callosum as illustrated on magnetic resonance imaging (MRI) for children with both conditions. *Corpus callosum* is the structure in the brain that connects the two hemispheres, accounting for much of the inter-hemispheric communication in the brain. In a sample of children with ASDs, Vidal and colleagues detected signifi-

cant reductions in the genu and splenium region of the corpus, where fibers from the orbitofrontal cortex, the parahippocampal gyrus, and the visual association cortex, respectively, cross the midline (Vidal, Nicolson, DeVito, Hayashi, Geaga, Drost et al., 2006). This finding is important, because the orbitofrontal cortex may play a role in the interpretation of social and emotional cues, a skill many children with ASD lack. Likewise, in the prospective study of children with ONH, 39% had corpus callosum hypoplasia, and this was significantly associated with increased risk for impaired personal-social and adaptive skills (Garcia-Filion et al., 2007). In children with ONH, the rates of corpus callosum hypoplasia between those with and without autism have not yet been examined.

Another example of impairment in the central nervous system in children with ONH or autism is the high prevalence of epilepsy among this population. In the general pediatric population, the prevalence of epilepsy is 2- to 3%. This proportion increases to 12% in children with ONH (McCulloch, Chaplin, & Brochert, 2010) and up to 21% in those with ASDs (Tuchman & Cuccaro, in press), and epilepsy becomes more common when there is a co-morbidity of mental retardation.

Children with ONH and those with ASDs also experience increased GI dysfunction. In a prospective study of ONH, 20 (31%) of 61 subjects met criteria for functional constipation, cyclic vomiting, or adolescent rumination syndrome, or were treated with GI medication according to the survey results from the constipation and reflux sections of the Rome III Diagnostic Questionnaire for the Pediatric Functional GI Disorders (Borchert, Geffner, Garcia-Filion, Fink, & Sutedja, 2011). The rate of GI dysfunction grew even higher when those with previous GI dysfunction (44%) were included in the measure. In a genetic study examining GI conditions in children with ASDs, the incidence of GI dysfunctions was higher in children with ASDs (41%) than in their siblings without autism (9%) or their parents (24%) (Campbell, Buie, Winter, Bauman, Sutcliffe, Perrin et al., 2009). Constipation was the most commonly reported GI problem (Valicenti-McDermott, McVicar, Rapin, Wershil, Cohen, & Shinnar, 2006).

Rates of reported sleep disturbances in individuals with ASDs are variable, but are often more than 50%. For example, in a study of 59 children with an ASD and 40 typically developing control subjects, parent-reported sleep disturbances using the Children's Sleep Habits Questionnaire, as well as actigraphic data, demonstrated that 66% of subjects with ASDs and 45% of control subjects had sleep disturbances (Souders, Mason, Valladares, Bucan, Levy, Mandell et al., 2009). Rivkees and colleagues also used actigraphic data to monitor rest and activity in children with ONH and found abnormal rest-activity patterns in 32% of participants (Rivkees, Fink, Nelson, & Borchert, 2010). As with many of the symptoms common in autism and ONH, subjects with abnormal rest-activity patterns were more likely to have developmental delays.

In addition, although all other congenital ophthalmic conditions are decreasing in the developed world, the prevalence of ONH is increasing, although to a lesser extent than ASDs (a four-fold increase and a more than 10-fold increase in the last 20 years, respectively) (Blohme, Bengtsson-Stigmar, & Tornqvist, 2000; Rice, 2009). The increases in the prevalance of these conditions leads to suspicion that prenatal environmental factors may contribute to their development. And, a common consequence of adverse environmental exposure during fetal development is disrupted axonal wiring in the central nervous system leading to excessive neuronal apoptosis.

Conclusion

As mentioned in the introduction, autism is described as a spectrum disorder to account

for the wide range of severity in outcomes and associated symptoms. ONH, which also has a range in severity and symptoms, should also be described as a spectrum disorder. The similarities between the two suggest a potentially common underlying mechanism.

It is unclear whether the shared symptoms are more common in children with ONH and ASDs than in children with ONH alone. It is also unclear if these symptoms are related to the severity of visual impairment. Addressing these questions is complicated by an inability to accurately and systematically diagnose autism in children with visual impairment, the instruments for diagnosing ASDs need to be modified and validated for this purpose. Nonetheless, the prevalence of autistic-like behaviors and the prevalence of symptoms and signs associated with autism in children with ONH is striking. Further studies of children with ONH and ASDs may lead to identification of common pathogenetic mechanisms.

Research is currently underway to investigate the prenatal environmental risk factors of ONH. The ONH disease distribution survey is designed to identify geographic and temporal clusters of ONH, which may lead to information on risk factors causing ONH, and perhaps contributing to the increase in autism as well. This brief survey can be completed by any parent with a child with ONH at <www.onhsurvey.org>.

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