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Review Article

Is it Time to Begin Prenatal/Neonatal Screening for Autism Risk?

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Introduction

Epidemiological data showing an alarming increase in the incidence of autism in North America, Europe and many other parts of the world are no longer news. Fortunately, these distressing statistics have prompted new research on the causes of autism and the implementation of community programs that offer early diagnosis and intervention tools. Yet another critical approach, that may not get the attention it deserves, is autism prevention. The ability to mitigate autism risk factors based on an understanding of the cause and effect basis of this disorder would have the potential to dramatically impact its incidence. Ultimately, this is the only way in which the rising statistical tide of autism incidence can be thwarted.

The prevention of autism requires an understanding of at least some of its physiological causes and the identification of biomarkers suitable for screening so that autism risk can be assessed on an individual basis. From a scientific perspective, this approach requires reproducible data on the etiology of this disorder, the genetic and environmental risk factors primarily responsible for its occurrence. While we are a long way from achieving a complete understanding of the causes of autism and the disrupted brain functions that characterize this developmental disorder, a review of the rapidly accumulating clinical data suggests that sufficient understanding of the contributory factors exists at present to initiate risk assessment protocols and preventive approaches for individuals identified as "at risk". What follows is a comprehensive overview of the identified risk factors of autism that could be incorporated into a predictive biomarker assessment protocol with prenatal and neonatal applications.

Identified Prenatal/Neonatal Risk Factors for Autism

Genetic biomarkers for autism spectrum disorder (ASD)

Although inherited genes may influence autism risk, autism is NOT a single gene disorder and, to date, no single gene has been identified whose involvement in the disorder would qualify for a population based genetic screen. Several hundred genes have been implicated variably in autistic individuals; however, no group of genetic differences has been reproducibly linked to this disorder. The extraordinary recent increase in ASD incidence rules out certain etiological risk factors as the primary cause of ASD. For example, the physiological role of genetic mutations as a cause of ASD, based on known mutational frequency rates, is far too low to account for the observed increase in ASD incidence. This observation essentially rules out genetic mutations as the sole cause of ASD. Therefore, we are left to conclude that epigenetic factors linked to the environment are the root cause of the increased incidence of autism spectrum disorder (ASD). Based on these considerations, an effective, comprehensive autism screening tools should include both genetic data and epigenetic environmentally identified risk factors.

Examples of candidate genetic biomarkers for ASD risk factor assessment screens

Genome-wide association studies have identified gene variations statistically associated with ASD. Among the most common are deletions and duplications at the Neurexin 1 (NRXN1) locus [1]. Whole exome sequencing has identified genetic mutations associated with autism including SNC2A, CHD8, DYRKIA, POG2, GRIN2B, and KATNAL2, cadherin (CDH9), cadherin 10 (CDH10), semaphorin 5A (SEMA5A), and taste receptor, type 2, member 1 (TAS2R1) [2-8].

Gene polymorphisms linked to ASD risk include methylenetetrahydrofolate reductase (MTHFR) [9]. The MTHFR 677T-variant allele is associated with a 2.79-fold increased risk. Other allelic variants of this gene may, alternatively, confer a protective function against autism [10]. Interestingly, mothers testing positive for this MTHFR 677 TT allele who took prenatal vitamins showed a lower risk for having a child diagnosed with ASD than women who did not take vitamin supplements [11]. A small

study by Iossifov et al. [12] identified gene-disrupting mutations including nonsense, frameshift and splice mutations [12], that were twice as common in children with ASD than controls; the majority of these were paternal in origin and linked to parental age [13].

Environmental Biomarkers for ASD

The landmark Hall Mayer population twin study estimated that environmental factors account for approximately 50% of autism risk [14]. Environmental autism risk factors have been identified in extensive epidemiological studies to include maternal fetal exposure to infectious disease, inflammatory and autoimmune phenomena, as well as exposure to antigenic and pro-inflammatory environmental factors. The incidence rates of several potential risk factors for ASD correlates with observed increases in ASD incidence over the past several decades, including increased incidence of pediatric infectious disease, and increased obesity/ diabetes type-2 in parents of child-bearing age. Epidemiological data on pediatric illnesses show an elevated incidence of childhood infections, asthma and other autoimmune disorders, whose rate of increase has occurred in parallel to that of ASD. These environmental risk factors linked to ASD may induce physiological changes involving testable biomarkers for ASD risk [15].

Examples of candidate metabolic biomarkers for risk factor assessment Screens

Meta-analyses of more than two dozen research studies examining blood samples from individuals with ASD reported decreased levels of antioxidants glutathione, glutathione peroxidase, and increased levels of oxidized glutathione [16]. In addition, urinary antioxidant levels were also decreased in individuals with ASD; the reduction correlated with ASD severity. In contrast, the levels of lipid peroxidation products in the urine of individuals with ASD were elevated [17]. Additional measures of oxidative status that are elevated in the urine of individuals with ASD include plasma F2t-isoprostanes (F2-IsoPs); highest levels were observed in individuals with gastrointestinal disturbances linked to ASD [18]. Neopterin excretion is associated with increased levels of reactive oxygen systems linked to immune system activation. Neopterin levels are significantly higher in children with autism than controls, making its presence in urine a potential biomarker for ASD [19].

Examples of candidate neurologic biomarkers for ASD risk factor assessment screens

Additional biomarkers with risk factor involvement include neuropeptides serotonin, glutamate, GABA, BDNF, and dopamine and noradrenaline [20,21]. A positive correlation between severity of clinical symptoms and plasma GABA levels has been observed in ASD. Some of these biomarkers can be assayed by urinalysis [22].

Examples of candidate immune system biomarkers for ASD risk factor assessment screens

Immune dysfunction is linked to autism risk; there are numerous biomarkers in this category that could be targeted for autism risk assessment [23]. Cytokines that can cross permeable blood brain barrier may serve as biomarkers of the immune system dysregulation, an important risk factor for ASD [24]. TGF-beta, CCL2, and CCL5, IgM and IgG classes of immunoglobulin in the blood represent testable biomarkers that correlate with ASD severity [25]. Alterations of Th1/Th2 ratio is another testable biomarker for ASD [26]. Autoantibodies produced in autoimmune phenomena have been identified in individuals with ASD; cerebrospinal fluid (CSF) testing for these biomarkers could be included in an ASD risk factor screen.

Anti-ganglioside M1 antibodies [27], antineuronal antibodies [28], and serum anti-nuclear antibodies [29] comprise potentially testable biomarkers whose levels have been shown to correlate with the severity of autism. Anti-neuron-axon filament protein (anti-NAFP) and glial fibrillary acidic protein (anti-GFAP) [30], antibodies to brain endothelial cells [31], myelin basic protein [32], and anti-myelin associated glycoprotein, might be included in CSF biomarker testing protocols [33].

Examples of candidate infectious disease biomarkers for ASD risk factor assessment screens

Serious maternal infections during pregnancy increase the risk of ASD since maternal antibodies may cross the placenta to affect brain development in the fetus [34]. Cytokines that cross the placenta may affect aspects of fetal neurogenesis [35]. Research has shown that increased levels of IFN-γ, IL-4, and IL-5 during pregnancy were a risk factor for autism [36,37]. Braunschweig et al. identified a group of clinically significant maternal autoantibody biomarkers linked to autism risk [37,38]. The study authors suggested that these biomarkers could be used to identify autism risk in infants whose mothers displayed abnormal autoantibody parameters [38].

A Model Autism Risk Assessment Protocol

Consistent with the Quantitative Threshold Exposure (QTE) Model for Autism risk, that suggests that, since autism is a multifactorial disorder, multiple genetic and environmental risk factors taken together may determine the cumulative risk for ASD, this risk assessment protocol involves a broad spectrum, multi-layered screening protocol to assess autism risk. The QTE model is a multifactorial hypothesis that predicts that the quantitative assessment of combined risk factors linked to autism may facilitate the construction of an autism "at risk" profile which could be used as a basis for recommending preventive approaches in individuals designated at risk based on these assessment criteria. Moreover, data obtained from these testing protocols could be used to refine and quantitate the assessment of the predictive value of individual and combined autism biomarkers [39].

Phase 1: Prenatal assessment

Recent discoveries of the connections between the maternal immune system [IS] and prenatal brain development suggest that routine prenatal screening for chronic disorders associated with immune system dysfunction may be useful in identifying women at heightened risk for giving birth to a child with autism. Epidemiological studies have shown that the incidence of IS

disorders, including systemic lupus erythematosus [SLE], rheumatoid arthritis [RA] and chronic obesity in combination with insulin-resistant diabetes, has increased significantly over the past several decades and that pregnant women with these conditions are at increased risk for having a child with autism. For this reason, physiological parameters associated with these prenatal conditions that can be detected before onset or at early stages of disease may serve as biomarkers for increased autism risk. This critical cause/effect relationship provides the rationale for prenatal autism risk factor assessment using biomarkers associated with chronic immune conditions that may impair the neurodevelopmental functions of microglia because of their inappropriate immunological activation. In addition, a family history of the incidence of ASD among genetically related individuals is an important screening parameter as ASD recurrence risk is an important genetic component of ASD.

Phase 2: Ongoing prenatal assessment

In pregnant women who are designated at risk based on phase 1 assessment, ongoing monitoring of infectious disease occurrences, monitoring of autoimmune parameters and relevant biomarker screening would be initiated and continued throughout the course of the pregnancy. In addition, genetic screening to assess mutations potentially linked to autism risk may be indicated, particularly in families who have positive history for ASD.

Phase 3: Neonatal assessment

Abnormal screening data obtained in prenatal assessment would necessitate neonatal ASD biomarker screening using methods with limited invasiveness, including blood test and urinalysis to assess the levels of designated biomarkers in the major categories linked to ASD. For neonates testing positive in risk factor assessment, follow-up screening through age 3 would be indicated, since this is the temporal span for ASD occurrence.

Phase 4: Early intervention protocols for neonates identified "At-Risk"

The connection between abnormal IS function and impaired neural development suggests preventive approaches that can be used to decrease the overall risk for ASD in infants and children aged 0-3 years designated at risk for ASD. Infants whose biomarker levels suggest at-risk designation due to their correlation with biomarkers profiles in children previously diagnosed with ASD would be recommended for early intervention, ideally before the presentation of overt symptoms of ASD. These preventive approaches would include an early life environment between 0-3 years in which exposure to environmental factors that may hyper stimulate the immune system to potentially induce neurodevelopmental injury is minimized.

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Conflict of Interest

No conflict of interest.

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