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On the origins of autism: The Quantitative Threshold Exposure hypothesis

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ABSTRACT

The Quantitative Threshold Exposure (QTE) hypothesis is a multifactorial threshold model that accounts for the cumulative effects of risk factor exposure in both the causation of autism spectrum disorder (ASD) and its dramatic increase over the past 30 years. The QTE hypothesis proposes that ASD is triggered by the cumulative effects of high-level exposure to endogenous and environmental factors that act as antigens to impair normal immune system (IS) and associated central nervous system (CNS) functions during critical developmental stages. The quantitative threshold parameters that comprise a cumulative risk for the development of ASD are identified by the assessment of documented epidemiological factors that, in sum, determine the likelihood that ASD will occur as a result of their effects on critically integrated IS and CNS pathways active during prenatal, neo-natal and early childhood brain maturation. The model proposes an explanation for the relationship between critical developmental stages of brain/immune system development in conjunction with the quantitative effects of genetic and environmental risk factors that may interface with these critical developmental windows. This model may be useful even when the individual contributions of specific risk factors cannot be quantified, as it proposes that the combined quantitative level of exposure to risk factors for ASD rather than exposure to any one risk factor *per se* defines threshold occurrence rates.

Introduction

Autism represents a broad-spectrum group of neurological disorders associated with language and social impairments that range in severity from the mild dysfunction characterized by Asperger's Syndrome, to classic autism, that, in its extreme form, causes severe cognitive and developmental deficits classified as pervasive developmental disorder-not otherwise specified (PDD-NOS). Up to 50% of autism cases are also associated with some degree of cognitive impairment. Since first described by Kanner in 1943, both the biological and environmental factors with potential links to autism have received close scrutiny, while diagnostic and behavioral criteria have been elaborated in the form of a spectrum of behaviors that critically involve deficits in brain development affecting socialization and verbal communication [1].

The dramatic upswing in the incidence of autism spectrum disorders (ASDs) over the past several decades has unleashed a flurry of hypotheses to account for this disturbing trend. Two decades ago, autism was detected in 1 in 1000 children; as of 2014 an estimated 1 in 88 children has been identified with ASD [2] (see Fig. 1). This increase cannot be fully accounted for by the refinement of detection and diagnostic procedures. Over the past decade, a large body of research has probed the nature of these etiological risk factors [3]. Approximately 10% of children with ASD show genetic, neurologic or metabolic differences that may be etiologically linked to this disorder. As detection and surveillance of autistic disorders in recent years have included neuro-imagery alongside monitoring of age-appropriate behavior, neuro-structural differences in the developing brain in children with ASD have been identified [4]. In this context, inflammation has been identified as a contributing factor responsible for these neuro-structural differences. Additional studies have also identified genetic changes, pre-natal conditions, vaccines and even the environmental milieu as contributory factors in the development of autism [5]. Nevertheless, no specific link has been established between any of these potential risk factors and the development of ASD. Rather, specific genetic profiles and epigenetic factors, such as maternal prenatal immune system dysregulation/activation, have shown a correlated increased risk for the development of autism.

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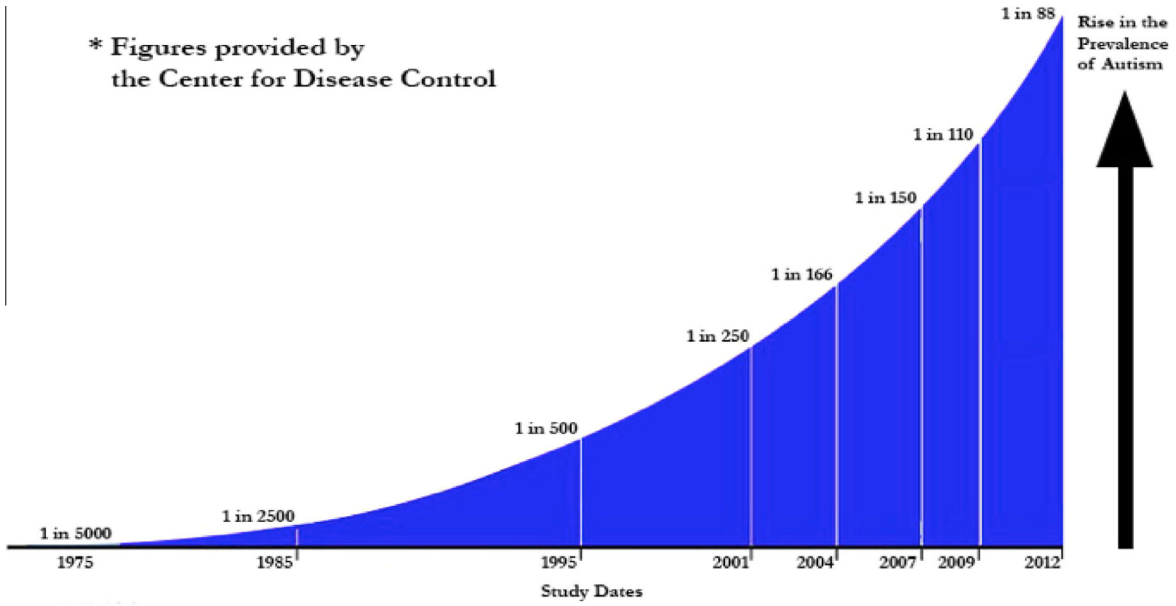

Fig. 1. Rise in autism prevalence 1975–2012.

The Quantitative Threshold Exposure hypothesis

The Quantitative Threshold Exposure (QTE) hypothesis is a multifactorial threshold model that accounts for the cumulative effects of risk factor exposure in both the causation of ASD and its dramatic increase over the past 30 years. The QTE hypothesis proposes that ASD is triggered by the cumulative effects of exposure to endogenous and environmental factors that act as antigens that impair normal immune system (IS) and associated central nervous system (CNS) functions during critical developmental phases.

The QTE hypothesis for ASD is an elaboration of the classical threshold model of disease involving multifactorial risk factors (see Fig. 2). The threshold model presents a normal distribution of risk factors implicated in disease liability with an associated threshold level of quantitative risk factor exposure that precipitates the onset of a multifactorial disorder. An individual will not express a multifactorial disease trait unless the quantitative effects of risk factors, of genetic and/or environmental composition, reach a critical threshold. The threshold model of disease is of particular utility in assessing multifactorial disorders involving critical developmental/exposure windows such as cleft palate and spinal bifida.

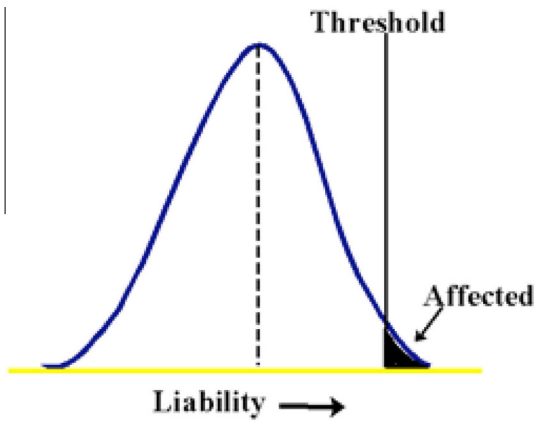

Fig. 2. The threshold model for multifactorial disease.

The quantitative threshold parameters that comprise a cumulative risk for the development of ASD are identified by the assessment of documented epidemiological factors that, in sum, determine the likelihood that ASD will occur as a result of their effects on critically integrated IS and CNS pathways active during prenatal, neo-natal and early childhood brain maturation.

The model rejects the concept that a single genetic or environmental agent is the cause of most cases of ASD. Rather, the QTE hypothesis proposes that it is the quantitative exposure level to any number or combination of genetic and environmental risk factors at critical developmental stages that determines whether the threshold exposure level is sufficient to cause ASD (see Fig. 3).

The QTE hypothesis suggests that the threshold model of multifactorial disease can also explain the developmental dys-regulation responsible for ASD. The model proposes an explanation for the relationship between critical developmental stages of brain/immune system development in conjunction with the quantitative effects of genetic and environmental risk factors that may interface with these critical developmental windows. This model may be useful even when the individual contributions of specific risk factors cannot be quantified, as it proposes that the combined quantitative level of exposure to risk factors for ASD rather than exposure to any one risk factor *per se* defines threshold occurrence rates.

The hypothesis predicts that the greater the number of risk factors and the quantitative amounts of each to which a child is exposed prenatally and in early postnatal life, the greater the likelihood of developing ASD. These risk factors are multifaceted in origin, and have been identified in extensive epidemiological studies to include genetic predisposition, maternal fetal exposure to infectious disease, inflammatory and autoimmune phenomena, as well as exposure to antigenic and pro-inflammatory environmental factors. Taken together, this cumulative exposure may cause an individual to cross the threshold boundary to develop ASD. The model further predicts that, once the threshold exposure level sufficient to impair CNS development to cause ASD is attained, additional increases in quantitative risk factor exposure may determine the severity of ASD, thereby accounting for the spectrum or range of neurological impairments identified in children with ASD.