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Are caesarean sections, induced labor and oxytocin regulation linked to Autism Spectrum Disorders?

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ABSTRACT

The etiology of Autism Spectrum Disorders (ASDs) continues to be elusive. While ASDs have been shown to be heritable, several environmental co-factors, such as, e.g. pre- or perinatal adverse events, could play a role in the pathogenesis of the disorder as well.

Prevalence of ASDs appears to have increased in the last three decades, but the causes of this surge are not fully understood. As perinatal adverse events have increased as well, they have been regarded as logical contributors to the risen prevalence of ASDs. Over the last three decades there has been also a considerable increase in the rates of induced labor and caesarean sections (CS). However, even if a causal association between CS and ASDs increase has been suggested, it has not yet been proven.

Nevertheless, we hypothesize here that such an association is actual and that it might help to explain a part of the increase in ASD diagnoses. Our assumption is based on the wider epidemiological picture of ASDs and CS, as well as on the possible biological plausibility of this correlation, by postulating potential epigenetic and neurobiological mechanisms underpinning this relationship.

Today, several observations point toward the existence of epigenetic dysregulation in ASDs and this raises the issue of the role of environmental factors in bringing about epigenetic modifications. Epigenetic dysregulations in some brain neuropeptide systems could play a role in the behavioral dysfunctions of ASDs. Particularly, some evidence suggests a dysregulation of the oxytocinergic system in autistic brains. Perinatal alterations of oxytocin (OT) can also have life-long lasting effects on the development of social behaviors. Within the perinatal period, various processes, like pitocin infusion or CS, can alter the OT balance in the newborn; OT dysregulation could then interact with genetic factors, leading ultimately to the development of ASDs.

Large long-term prospective studies are needed to identify causal pathways for ASDs and examine whether and how (epi-)genetic susceptibility interacts with obstetric risk factors in the development of ASDs. A better understanding of such a potential interplay could become paradigmatic for a wide range of genetic-environmental interactions in ASDs.

Introduction

Even if in the last years some progress has been made in understanding the causes of Autism Spectrum Disorders (ASDs), its etiology continues to remain elusive in more than 80% of cases [1]. In fact, albeit converging links of evidence point towards altered developmentally regulated brain connectivity and studies of genetic and environmentally modulated epigenetic factors have highlighted the polygenic nature of these conditions, only in 10–20% of the patients, neuro-imaging and neurogenetic techniques have allowed to identify a specific medical and genetic syndrome as a cause of ASD [2,3]. Therefore, while ASDs have been shown to be heritable, a presence of environmental co-factors cannot be excluded [4]. Among these environmental factors, some adverse events during pre- or perinatal periods have been associated with increased risk of ASDs [5]. However, such evidence is not conclusive [6]. Thus, not only the etiology, but also the pathogenesis of the disorder is still a matter of much speculation.

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Background

Increase in ASD prevalence rates

ASDs constitute a class of severe neurodevelopmental conditions caused by atypical brain development beginning during prenatal or early postnatal life and are considered to be life-long conditions, with core symptoms typically emerging in the first few years of life and being permanent across the lifespan [7]. Prevalence of ASDs appears to have increased in the last three decades in all industrialized countries. During the 1960s to 1980s, overall prevalence rates for childhood autism ranged from 2 to 5 cases/10,000 children [8,9]; however, studies performed in the late 1990s to early 2000s reported up to 10-fold higher prevalence rates (30–60 cases/10,000) for autism and/or ASDs [10]. In more recent times, prevalence rates have reached 1% [11]. The causes of this prevalence increase are not fully understood. The broadening of diagnostic criteria and the development of new standardized autism-specific diagnostic tools, with a consequent increased awareness of the condition among parents and medical and education professionals, might in some measure explain the changed prevalence rates [7,12]. Nonetheless, recent US data from the Autism and Developmental Disabilities Monitoring (ADDM) Network seem to indicate that the increasing trend in ASD prevalence is not fading away, even if the expansion of diagnostic criteria has stabilized; collected data for the 2002 and 2006 surveillance years reported an average ASD increase of 57% (from 6.0 to 9.4 ASD cases/1000) [13]. This is a large increase given the short period and the fact that we are now several years beyond the widespread policy changes that directly impacted ASD diagnostic and education classifications. Such data renew the question about the reasons of this trend, which, probably, cannot be explained only by a shift in diagnostic criteria. On the other hand, significant genetic changes should probably not be considered a main cause of this increasing trend, as there is no evidence of a considerable increase of syndromic forms of ASDs, whose prevalence has been reported stable at 10% by researches studies in the last years [2,14,15]. Therefore, considering the possibility of modifications in environmental and/or epigenetic factors, the enduring rise in ASD prevalence points to the possibility that some risk factors have increased, contributing to the rising trend of ASDs [16]. Many researchers trying to understand these risk factors for ASDs today tend to point to the pre- and perinatal period as a key time-frame for the development of ASD pathogenetic pathways [7,17]. Because nearly all of these perinatal factors have been reported to have increased throughout the past two decades, they are logical candidates to be considered as potential contributors to the increased prevalence of ASDs [18].

Increase in cesarean section and induced labor rates

Over the past three decades there has been considerable increase in the rates of caesarean sections (CS), both in industrialized countries and in urban and rural areas of the developing world [19–21]. Present evidence shows that, worldwide, the global rate of CS is estimated to be 15–16%, with even higher rates in middle-income countries [22,23]. The average rate of CS deliveries seems to be 3.5% in Africa, where the reliability of reported rates is however still limited, 15.9% in Asia, and 19% in Europe, with highest rates (36%) in Italy [22,24]. In addition to that, there is strong evidence that CS rates have been progressively increasing over the last three decades [25]. For example, the total US caesarean delivery rate reached 32.9% of all births in 2009, rising 60% from 20.7% in 1996 [26]. In Italy, official data suggest that the CS rate has risen for about thirty straight years from 11.2% in 1980 to 38.4% in 2009 [27]. Also countries like China have experienced unprecedented rise: between 1990 and 2002 the CS rate in Chinese cities rose from 18% to 39% and continued to grow in the following years [28,29]. The rate in rural areas has risen more slowly but, nevertheless, is above 25% [30]. Concern over an overall rise in CS has been expressed also in Latin America [30].

In addition, pitocin induction of labor has steadily increased throughout the last two decades, both in industrialized and in developing countries. In the US, for example, the percentage of induced labor grew from 9.5% in 1990 to 22.1% in 2004 [31–33].

Heritability and gene-environment interactions in ASDs

ASDs are among the most heritable neurodevelopmental disorders, with some studies suggesting a heritability of 60–90% among monozygotic twins [7,15], even if other more conservative estimates place the range of heritability between 37% and 67%, suggesting also higher concordance rates between dizygotic twins than had been previously found [34]. In any case, all these findings imply a greater role for multiple gene-environmental interactions, leading to a wide inter-individual heterogeneity of the disorder [4,34].

These complex interactions of genetic and environmental risk factors call for a pivotal role of epigenetic mechanisms, which can allow the environment to modulate gene expression and, thus, to shape the phenotype [35]. It is therefore likely that epigenetic alterations might contribute to the development of a considerable percentage of ASD cases [36]. Particularly, during the last decade, evidence has accumulated suggesting that the offspring of older parents might present with an increased risk of developing autism [37]. There are several possible age-related biologic mechanisms through which increasing maternal and/or paternal age could affect fetal brain development, possibly leading to autism, including the interaction of chromosomal changes and epigenetic alterations associated with advancing parental age [37].

The existence of interactions between genetic and environmental factors in ASDs is also suggested by the fact that unaffected siblings present with less pre- and perinatal complications than their affected siblings; but, at the same time, they show also more complications than control subjects [17]. Therefore, individuals with ASDs may possibly react differently to the same environmental stimuli and may have less tolerance to prenatal hits compared to their siblings or controls. Such different response to environment might be linked to specific characteristics of the person with ASDs. In addition to that, also studies of animal models have suggested that genetic defects, which lead to synaptic malfunction, may alter the sensitivity to the environment and, therefore, increase autistic-like behaviors [37,38]. However, even if these observations in animal studies appear to be convincing, other possible explanations cannot be completely excluded. For example, the larger rate of complications in ASD subjects, compared to their siblings, might simply be due to a higher exposure to the hypothetical causative factor(s) of the person who will later develop ASDs.

Perinatal and obstetric risk factors

Obstetrical and delivery factors, as well as neonatal exposures, have been the focus of a significant amount of epidemiologic research on the possible risk factors for autism [6,17,18]. Preterm and very preterm delivery, low and very low birth weight, multiple birth, cesarean delivery, breech presentation, preeclampsia, obesity and/or diabetes in pregnancy, and use of assisted reproductive technology for conception are among the most well-studied perinatal factors that have been implicated as risk factors for ASDs [6,39,40]. In recent years, there has been also a progressive postponement of the age of procreation, and advanced maternal age has been associated with an increased risk of ASDs [6,39]. The