Genetic considerations in syndromic autism

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Abstract

Autism is a complex disorder that affects a child's ability to think, communicate, interact socially and learn, with onset usually between 18 and 24 months of age. Autism etiology can be identified in 15-20% of individuals. This paper aims to review the current understanding of the etiologies and the multiple pathogenetic pathways likely to lead to the autistic phenotype. Recognition of autism genetic etiology is essential for the correct prognosis and risk of recurrence, early identification and intervention being critical for the patient and for his family. For these reasons, the evaluation strategy should include a multidisciplinary team.

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1. Introduction

Described for the first time by Kanner in 1943, autism (ASD) is a complex disorder that affects a child's ability to think, communicate, interact socially and learn. For most children with autism, symptoms develop gradually, with onset usually between the ages of 18 and 24 months. Currently, the diagnostic criteria for autism are entirely behavioral.

Most frequently, the criteria used for persons diagnosed with autism are those listed in DSM-IV (Diagnostic and Statistical Manual of Mental Disorder) of the American Psychiatric Association (APA, 1994), that includes autistic disorders among the pervasive development disorders (PDD). Specific PDDs, in addition to autistic disorders, include the Asperger syndrome (less frequent then autism), Rett syndrome (typically occurring in females) and childhood disintegrative disorder. According to the DSM-IV, persons diagnosed with autism must have been symptomatic since infancy or childhood and manifest a specified number of deficits that are out of keeping with their development level in each of the following three aspects of behaviour (APA, 1994): qualitative impairment in reciprocal interaction;

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qualitative impairment in verbal and nonverbal communication; a markedly restricted repertoire of activities and interests. Summarizing the data from various studies, about 40% of children with an ASD do not talk at all and another 25%–30% of children with autism have some words at 12 to 18 months of age and then lose them. Others may speak, but not until later in childhood (Johnson, C.P et al., 2004).

Regarding psychiatric nosography, the concept of "syndromic autism", meaning autism associated with other clinical signs, should be promoted because it may help to distinguish patients in need of a multidisciplinary approach and further investigation.

2. Etiological considerations

The etiology of autism is complex, including multiple environmental, genetic and epigenetic factors (Persico, A. M.; Bourgeron, T., 2006). Currently, etiology can be identified in only 15 to 20% of individuals with autism; for all the others the causes remain unknown. The principal non-genetic cause of autism is prenatal viral infection (Piven, J. et al., 1993). Also, prenatal toxoplasmosmosis, rubella (Chess S., 1977), syphilis and varicella (Markowitz, P.I., 1983), perinatal or neonatal trauma, hypothyroidism and maternal alcohol use during pregnancy (Gillberg, C. et al., 1996) have been linked to cases of autism.

In the last years, hoping to better define and categorize the phenotype of autism, investigators have searched for biological correlates as with the core autistic symptomatology. Diverse retrospective longitudinal studies show that most cases of children with autism show changes in head size and brain morphology and describe that approximately 24% of individuals with autism have macrocephaly (Fombonne, E. et al., 1999; Lainhart, J.E. et al., 1997) and 15.1% have microcephaly (Fombonne, E. et al., 1999; Miles, J.H. et al, 2000). It suggests that while some enlargement may take place before birth, an increased rate of growth appears to occur during the early postnatal period (Lainhart, J.E. et al., 1997; Stevenson, R.E. et al., 1997). These statements are supported by magnetic resonance imaging (MRI) studies, which confirm that brain volume in autism is increased (Piven, J. et al., 1997). Early twin studies (compared autistic twins from nonautistic co-twins), showed that some in utero events, also, might predispose a fetus to the development of autism (Folstein, S. et al., 1997). Among the cognitive theories trying to explain autism and the behavioral variability of people with autism, the most common are: the theory of mind ("Theory of mind", Baron-Cohen, S. et al., 1985), the "weak central coherence theory" and the executive deficit theory or "executive functioning" (Ozonoff, S. et al., 1991).

Epidemiologic research over the past two decades has demonstrated a significant role for hereditary factors in the etiology of autism. The importance of genetic contributions became clear in the 1980s, when the co-occurrence of chromosomal disorders and rare syndromes with the ASDs were noted (Wassink, T.H. et al., 2001; Blomquist, H. K. et al., 1985). It is estimated that cytogenetically identified lesions are present in 20% of cases (Gillberg, C. et al., 1985), though recent surveys have reported lower frequencies ranging from 3% to 8% (Wassink, T.H. et al., 2001; Marshall, C. R. et al., 2008), although this proportion is higher in dysmorphic populations with mental retardation. It seems that the persons with the fragile X mutation account for one-third to one-half of these (Konstantareas, M.M. et al., 1999).

Among the most common cytogenetic abnormalities in the ASDs, duplications involving the chromosomal region 15q11–15q13 are inherited and account for 1–2% of cases, with maternal interstitial duplications and isodicentric marker chromosomes observed in most cases (Gillberg, C. et al., 1985; Konstantareas, M.M. et al., 1999). All these rates may increase, however, as more sophisticated molecular cytogenetic techniques are applied. It is estimated that the number of genes involved have ranged from at least three to more than fifteen (Wassink, T.H. et al., 2001; Risch, N. et al., 1999). The existence of multiple symptom domains, the spectrum of related disorders and the differential gender distribution across IQs suggest genetic heterogeneity and indicate that autism is likely to be due to multiple genes interacting in variable combinations in additive, multiplicative, epistatic, or as yet unknown fashions.
3. Methodology

This paper aims to review the current understanding of the etiologies and the multiple pathogenetic pathways that are likely to lead to the autistic phenotype. We also want to highlight the importance of genetic factors in the ethiopathogeny of syndromic autism and to emphasize the essential role of the geneticist in investigating and diagnosing autism spectrum disorders. We selected five cases in which autism has been described as one of the possible manifestations and was diagnosed by specific genetic investigations in our department. In all cases, the diagnosis of autism was making by a psychologist or a neuropsychiatrist. Parents wanted to know what are the characteristics of the autism evolution in their child in the case of diagnose of a genetic syndrome that associates various malformations or the risk of developing certain diseases along the life. Also, they requested genetic counseling and calculation of the risk of recurrence in offsprings, except for one case, in witch the mother was already pregnant and was recommended for prenatal diagnosis. The selected cases show a genetic heterogeneity associated with ASD. Genetic counseling regarding the disease (ASD) or risk of recurrence is different for each case, the particularity of it being given by the genetic anomaly involved in the etiopathogenesis of the syndrome.

4. Results

The first case that we want to present is a 13 year-old boy with severe impairments in cognitive and adaptive functioning and distinctive fenotype. Based on the clinical exam, we performed karyotype from a peripheral blood sample and chromosomal analyses showed 47,XY, +21 [see fig. 1 (a)]. Intellectually, he showed functions in the medium range of mental retardation with an IQ of 45. Also, he had always experienced a significant degree of social dysfunction, characterized by the inability to form empathic, affectionate, and reciprocal relationships with others.

The second case is a 7-year-old boy that was born at 38 weeks gestation to a 32 year-old mother and 35 year-old father. Fenotype is marked by facial dimorphic (flat nasal bridge, large philtrum, narrow high arched palate), central hypotonia, brisk deep tendon reflexes, normal sensory neurological examination and cranial nerves, psychomotor and speech delay, repetitive/compulsive tendencies. Fluorescent in situ hybridization analysis revealed: 22q13 deletion. Aberrant social skills with strict adherence to routine were significant by 7 years of age, prompting further evaluation for an ASD by a multidisciplinary team.

The third case is a 9 year-old boy that was born at forty weeks gestation; the pregnancy was uncomplicated and delivery was normal. His parents noted an unusual cry. The clinical diagnosis of Cri-du-chat Syndrome was suggested after the following features: low birth weight, slow weight gain, cat-like cry, head circumference below 10th percentile, hypotonia, hypertelorism, epicanthic folds, downward sloping fissures, low set ears, and micrognathia, hypospadias, syndactily. We performed karyotype and the results showed 46,XY,del(5)(p13) [see fig. 1 (b)]. We also noted some problems on behavioral traits in this subject that included autism spectrum disorder, attention-deficit, hyperactivity disorder, and unmanageable behavior including aggression, tantrums, irritability, and self-destructive behavior. The patient’s mother, aged 41, is pregnant (16 weeks of gestational age), and in this case we recommended prenatal genetic diagnostic.

The forth case is a 4 ½ year-old boy diagnosed with Cornelia de Lange Syndrome (CDL) [see fig. 1 (c)]. His evolution showed many respiratory infections, congenital diaphragmatic hernias and mild hearing loss. We noted some behavioral problems, which include: medium intellectual disability, relatively poor expressive communication, prominent self-injurious behavior, hyperactivity and “autistic-like” behaviors.

In the last case, we present a 7 ½ year-old female diagnosed with Sotos syndrome. The main clinical features are represented by macrocrania without megalencephaly (based on CT scan), dolichocephaly,
prominent forehead, apparent hypertelorism, high arched palate, disproportionately large hands and feet, poor fine motor control. Concerning behavioral traits, main problems included: poor enunciation, limited vocabulary, short, nearly unintelligible sentences, poor coordination, 2 years cognitive delay, attention deficit, emotional outbursts, autistic behavior and drooling.

Fig. 1. (a) Autism & Down Syndrome (karyotype – 47,XY,+21); (b) Autism & „Cri du chat” syndrome (phenotype features and karyotype); (c) Autism & CDL syndrome (phenotype features).

5. Discussion

Studies on genetic syndromes associated with autism can provide genetic markers or uncover very relevant events, and are very important for the definition of autism subgroups in future molecular research. In our cases, the specific phenotype with dysmorphic clinical examination was essential in order to identify the cause of manifestations and to perform the proper genetic testing. It is essential for parents to understand that the evolution and prognosis of ASD are assessed according to associated congenital anomalies. The importance of genetic diagnosis lies in the fact that it can explain the clinical features and evolution in each case, on the one hand, and on the other hand, it is essential to providing genetic counselling and recurrence risk calculation. Reports of early social or language deficits, delays, or regressions should be addressed promptly and thoroughly to specialists. Birth of a child with autism is a tragedy for any family. Physicians must pay attention to the psychological concerns of the family because identifying a genetic cause of the disease amplifies the psychological impact of a diagnosis. They need to be prepared to inform the parents of individuals with autism about the benefits of psychological counselling and possibly psychotherapy. To avoid placing additional stress on the family, we should not delay investigation of abnormal development. In present, although there are various screening tests for autistic behaviors, there is no definitive medical or biological test for autism. These specific causes and others must be investigated when the family history or examination suggests them, but in most individuals the cause of the autism remains unidentifiable at present (Filipek, P.A. et al., 2000). Because testing may be useful for genetic counselling but rarely leads to a meaningful change in the affected child’s management, we recommend limiting extensive testing to those with a suspicious family or medical history, mental retardation, or dysmorphology and to families who wish to have additional children, as different genetic disorders have different recurrence risks.

6. Conclusions

Numerous complementary strategies are currently being employed to attempt to determine autism disease causes. The symptoms and deficits may be associated in a variety of forms, levels of intensity or severity, the impairment of various functions (eg. cognitive), behavior or skills and abilities may differ substantially from one individual to another. The complexity of the etiology of autism and presence of a wide variety cytogenetic abnormality are providing us with extremely valuable information about the role
played by the medical geneticist in autism and collaboration with psychiatrists, particularly in the low functioning individuals with dysmorphic features. Recognizing a genetic condition is vital because it may alter treatment or therapy options and is critical not only to the individual patient but also for the entire family. Diagnosing a genetic condition also enables health care providers to both estimate the chance of recurrence in other family members and discuss the availability of diagnostic testing for other family members. We consider that a routine metabolic screening study or chromosomal analysis should be performed in the presence of autistic regression or suggestive clinical findings. Such recognition and understanding will help clinicians implement syndrome-specific treatments of patients identified with a genetic cause of autism spectrum disorder.

References