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Relationship between macrocephaly and autism spectrum disorder in infancy

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Case presentation

An arab four years old boy presented with macrocephaly and autism spectrum disorder (ASD). His father's head circumference was 64 cm (> 97°C) without any significant behavioral problems. Skin lesions suspected of trichilemmomas was visible on the father's face. His mother and two brothers had no macrocephaly or other dysmorphisms. The child was born at full term and all the auxological parameters were higher than the 97°C (weight 4365 g, height 55 cm, head circumference 38 cm) but during the boy's growing up the skull's circumference showed an increasing trend, going well above the 97°C. The child started to walk alone at 18 months and at 14 months he pronounced only a few words in arabic with a successive progressive language regression. At the age of 3 years and 6 months, a diagnosis of autism spectrum syndrome (ASD) was made. At physical examination, macrocephaly was confirmed (CC 57.5 cm, >97°C) while the other auxological parameters where in a lower range and he showed a characteristic habitus with elongated face shape, rounded forehead, downslanting palpebral fissures with hypertelorism, thin upper lip, pointed chin, angled, rotated auricles, no macroglossia, no skin spots and no other pathologic sign. Ophtalmological examination showed pseudopapilledema from papillary drusen. Brain MRI confirmed macrocephaly and excluded intracranial anomalies. A genetic analysis showed a nonsense variant in the PTEN gene in heterozygosity diagnosis of Cowden Syndrome (CS). The same variant was subsequently performed in the child's parents showing the same mutation in the father. The child continued the neurodevelopmental and clinical-dermatological follow-up. The baby's father instead began the oncological follow-up for the risk of developing colon cancer, renal cell carcinoma, papillary and follicular thyroid cancer.

Discussion

Cowden's syndrome is an autosomal dominant disease caused by PTEN gene mutations, in over 80% of cases. Most mutations are de novo but they are inherited in the 10-50% of cases, and therefore genetic analysis and cancer screening must be extended also to positive family members even apparently asymptomatic and without macrocephaly or other signs [1]. Cowden's clinical features include multiple hamartomas in different tissues and high risk of developing benign and

Table 1: Diagnostic criteria for Cowden syndrome.

Revised PTEN Hamartoma tumour syndrome/Cowden syndrome clinical diagnostic criteria	
Major criteria	**Minor criteria**
Breast cancer Endometrial cancer Follicularthyroid cancer Lhermitte-Duclos disease (LDD) (Garbgliooftorna) GI hamartomas or ganglioneuromas Macrocephaly (≥97 percentile: 58 cm for females, 60 cm for males) Macular pigmentation of the glans penis Multiple mucocutaneous lesions Trichilemmomas (≥3, at least one biopsy proven) Acral keratoses (≥3) Mucocutaneous neuromas (≥3) Oral papillomas (≥3)	Autism spectrum disorder Colon cancer Esophageal glycogenic acanthosis (≥3) Lipomas (≥3) Intellectual disability (ie, IQ≤75) Renal cell carcinoma Testicular lipamatosis Papillary thyroid cancer (papillary or follicular variant) Thyroid anomalies (including multiple intracranial development venous anomalies)
Operational diagnosis in an individual (either of the following): 1. Three or more major criteria, but one must include macrocephaly, LDD, or hamartomas; or 2. Two major and three minor criteria.	
Operational diagnosis in a family where one individual is diagnostic for Cowden syndrome or has a PTEN mutation: 1. Any two major criteria with or without minor criteria; or 2. One major and two minor criteria; or 3. Three minor criteria	

malignant tumors: thyroid (68% benign, 3-38% malignant [2]), endometrium (up to 28% [2,3]), breast (81-85% in females [3]), and then kidneys, colorectal and skin's involvement. Other frequent CS's characteristics are macrocephaly, dolichocephaly and behavioural alterations (e.g. ASD in 10-17% of cases) [4]. Another rare sign seen in our patient is the presence of papillary drusen [5]. Clinical manifestations become evident in about 90% of cases between twenties and thirties years and involve the skin with pathognomonic mucocutaneous lesions (e.g. trichilemmomas). The neoplastic risk is precocious around the third life's decade. There is also a rare and benign dysplastic cerebellar gangliocytoma called Lhermitte-Duclos disease. The International Consortium for Cowden (ICC) defined the clinical criteria for the CS that have been subsequently revised by Pilarski R et al. (Table 1) [6]. These criteria are appliable more usefully in the adults than in children because few symptoms are present in pediatric age. A definitive CS's diagnosis is usually got with a genetic positive test. The CS is largely underdiagnosed in the pediatric age because typical clinical signs as the cutaneous ones become evident only in around twenty years old patients and the few signs and symptoms are common to other syndromes. In our case, there was an initial total overgrowth but subsequently the only abnormal auxological value was the head circumference. This finding is sometime present in children with isolated ASD and could be considered a sign of not sufficient importance to start specific investigations [7].

Conclusion

In presence of a child with ASD (or learning disorders) and macrocephaly, the diagnosis of CS has to be considered. However, because the macrocephaly is present in about a quarter of total patients with isolated ASD it is important in these patients not to forget the chance of the presence of CS early manifestations. CS's early diagnosis is essential as it affects the prognosis. It also allows the early identification of other family members who may have the pathogenetic mutation with no clinical manifestations, with the benefit to include them in a tumor screening program. It is also useful to underline that when a child with an ASD, must be always subjected to a genetic evaluation, in order to arrive at early and exceptional diagnoses like in this case.

Declarations

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