Delayed Diagnosis of Potocki-Shaffer Syndrome in a Woman with Multiple Exostoses and Mental Retardation

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Key Words

11p11 deletion · Epilepsy · *EXT2* · Mental retardation · Potocki-Shaffer

Abstract

We describe the case of an adult patient affected by multiple exostoses, severe mental retardation, epilepsy and facial dysmorphisms with a deletion of ~2.3 Mb on chromosome 11p11.21, correlated to Potocki-Shaffer syndrome (PSS). PSS is a rare contiguous gene deletion syndrome, mainly characterized by multiple exostoses and bilateral parietal foramina. Mental retardation and craniofacial dysmorphisms have often been reported, too. Although the patient showed many signs of PSS since early childhood, the diagnosis was suggested only when we examined her at adult age. This case highlights how frequently rare diseases remain undiagnosed till adulthood and is an excellent example of the need for a timely and correct diagnosis.

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Potocki-Shaffer syndrome (PSS; OMIM 601224) is a rare contiguous gene deletion syndrome due to haploinsufficiency of the 11p11.2 region. It is mainly characterized by multiple exostoses and bilateral parietal foramina. Intellectual disability and craniofacial dysmor-

phisms have also often been reported [Wuyts et al., 1999; Brémond-Gignac et al., 2005; Swarr et al., 2010]. Other common features include CNS, cardiovascular, ocular and genitourinary tract abnormalities as well as hearing loss [Wakui et al., 2005; Swarr et al., 2010].

It has been well-established that hemizygosity of different regions of 11p is associated with different phenotypic characteristics [Swarr et al., 2010]. For example, the *EXT2* gene, which maps in the 11p11.2 region, is associated with hereditary multiple exostoses [Ligon et al., 1998]. The *ALX4* gene, which maps proximal to *EXT2*, is correlated to ossification defects of the skull [Wu et al., 2000]. Therefore, the clinical phenotype is largely correlated to the size of the deletion.

Case Report

Here, we report on an adult Italian patient affected by PSS. The proband is a 34-year-old woman, the second child of healthy, non-consanguineous parents, born at term after an uneventful pregnancy with weight, length and head circumference values within normal parameters. Her developmental milestones were markedly impaired. At the age of 33 years she was referred for severe mental retardation. The woman presented epilepsy with absences resistant to antiepileptic drugs. At that time she did not speak and she had facial dysmorphisms including a high forehead, laterally sparse eyebrows, upslanting palpebral fissures, hypoplastic alae nasi, short philtrum and thin lips (fig. 1).

Fig. 1. Facial features of the patient. Of note are the high forehead, laterally sparse eyebrows, upslanting palpebral fissures, hypoplastic alae nasi, short philtrum and thin lips.

Results and Discussion

The G-banded karyotype on cultured lymphocytes of the proband has been interpreted to be 46,XX. On the basis of the presence of mental retardation and dysmorphisms we performed an array-CGH analysis using the CytoChip 575-kb resolution BAC array (BlueGnome, Cambridge, UK), according to the recommendations of the manufacturer. Data were analyzed using the BlueFuse for microarrays software package (BlueGnome). The analysis identified a deletion of ~2.3 Mb on chromosome 11p11.21, bridging from clone RP11-70A9, at position 43,973,845 bp, to clone RP11-164L18, at position 46,299,625 bp (fig. 2), according to the human genome NCBI Build 36.1 version (hg18). Parental karyotypes were not available. Radiographs of extremities performed after the cytogenetic diagnosis at age 34 disclosed exostoses in the distal region of the right femur and in both tibiae. The

Fig. 2. Array-CGH results revealed a 2.3-Mb deletion on chromosome 11p11.21 (red line).

patient complained of knee pain; however, the exact nature and location of her pain were not determinable as her communication skills were extremely poor due to the severe intellectual impairment. Skull X-ray was not available.

The deleted 11p segment included approximately 10 genes, 2 of which, such as *EXT2* and *ALX4*, have been correlated to specific clinical features. FISH analysis was not performed because the cytogenetic material had run out and the family decided to stop the investigations. However, the genotype-phenotype correlation was clear enough for the diagnosis of PSS.

So far, 46 patients from 31 families affected by PSS have been described [Francke et al., 1977; Gustavson et al., 1984; Lorenz et al., 1990; Shaffer et al., 1993; McGaughan et al., 1995; Bartsch et al., 1996; Potocki and Shaffer, 1996; Wuyts et al., 1999, 2004; Hall et al., 2001; Yamamoto et al., 2001; Chien et al., 2003; Brémond-Gignac et al., 2005; Chuang et al., 2005; Wakui et al., 2005; Romeike and Wuyts, 2007; Almind et al., 2009; Swarr et al., 2010]. The clinical phenotype of PSS is extremely heterogeneous, from normal development and intelligence to severe developmental delay and other abnormalities, including

WAGR syndrome, due to the size of the deletion. Approximately 33% of patients presented epilepsy [Swarr et al., 2010]. Recently, medical recommendations have been proposed for the evaluation and the care of children affected by PSS, which include a full skeletal survey and monitoring of the exostosis, which sometimes may evolve in malignancy. A screening for strabismus and nystagmus, an evaluation for hearing loss and for developmental-behavioral problems should be performed, too [Levenson, 2010; Swarr et al., 2010]. However, considering the small number of patients analyzed by Swarr et al. [2010] and the short period of their examination, it is difficult to establish appropriate medical practices.

The present case highlights how frequently rare diseases remain undiagnosed till adulthood. In fact, although the patient showed many signs of PSS since early childhood, the diagnosis was suggested only when we examined her at adult age. Probably the diagnosis was made so late because of the poor socio-economic status of the family.

In conclusion, this is an excellent example of the need for a timely and correct diagnosis in childhood, which is very important regarding prognosis and management.

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