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A characteristic EEG pattern in 4p-syndrome: case report and review of the literature

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Abstract Deletions on the short arm of chromosome 4 cause Wolf-Hirschhorn syndrome (WHS) and Pitt-Rogers-Danks syndrome (PRDS). WHS is associated with severe growth and mental retardation, microcephaly, a characteristic facies and congenital malformations. The PRDS phenotype is similar to WHS but generally less severe. Seizures occur in the majority of WHS and PRDS patients. Sgrò et al. [17] described a stereotypical electroclinical pattern in four unrelated WHS patients, consisting of intermittent bursts of 2–3 Hz high voltage slow waves with spike wave activity in the parietal areas during drowsiness and sleep associated with myoclonic jerks. We report a patient with PRDS and the typical EEG pattern and review 14 WHS patients with similar EEG findings reported in the literature.

Conclusion Awareness and recognition of the characteristic electroclinical findings in Wolf-Hirschhorn syndrome and Pitt-Rogers-Danks syndrome might help in the early diagnosis of such patients.

Key words EEG · Epilepsy · Pitt-Rogers-Danks syndrome · Seizures · Wolf-Hirschhorn syndrome

Abbreviations AS Angelman syndrome · FISH fluorescence in situ hybridisation · PRDS Pitt-Rogers-Danks syndrome · WHCR Wolf-Hirschhorn syndrome critical region · WHS Wolf-Hirschhorn syndrome

Introduction

Wolf-Hirschhorn syndrome (WHS) is a well-known chromosomal disorder caused by partial deletion of the short arm of chromosome 4 [7, 19]. It is characterised by severe growth and mental retardation, microcephaly and a characteristic facies with prominent glabella and hypertelorism referred to as the “Greek helmet” appearance. Additional findings include skeletal anomalies (66.6%), facial clefts (46.6%) and cardiac defects (33.3%) [1]. Pitt-Rogers-Danks syndrome (PRDS) overlaps WHS as it shares some features like microcephaly, growth and mental retardation, but is generally less severe with only moderate mental deficiency and absent skeletal, cardiac or clefting anomalies [16]. The facies is characteristic with prominent eyes and a short philtrum, but can also resemble the WHS phenotype. In 1996, Clemens et al. [5] discovered that PRDS is also caused by 4p deletions and it has been suggested since that WHS and PRDS are just different forms of expression of essentially the same syndrome [20],

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although this is not unequivocally accepted [14, 15]. Seizures occur in 50%–100% of WHS [5, 18, 4] and 80% of PRDS [14] patients, but the electroclinical findings have been reported in only a few cases [1, 5, 6, 12, 8, 17]. In 1995, Sgrò et al. [17] described a stereotypic electroclinical pattern in four unrelated WHS patients that seemed to be characteristic for WHS.

In this report, we present a girl with a 4p deletion, the phenotypic features of PRDS and the same typical electroclinical pattern outlined by Sgrò et al. [17].

Case report

Our patient was born at term to healthy non-consanguineous parents (father 32, mother 30 years old). Intrauterine growth retardation had already been noted on ultrasound examination and birth weight (2460 g), length (46 cm) and head circumference (33.5 cm) were all below the 10th percentile. Analysis of G-banded chromosomes from peripheral blood lymphocytes at a 400 band level gave normal results (46,XX). The child was presented to us at 13 months of age because of persistent growth failure and developmental delay. Weight and height were below the 3rd percentile, she was unable to sit and demonstrated peculiar wringing hand movements. Dysmorphic features included relative macrocephaly (50th percentile), a triangular face with prominent eyes, hypertelorism, micrognathia and dysplastic ears. At this point, Silver-Russell syndrome was considered to be the most likely diagnosis.

At 3.2 years of age she was reevaluated. Weight and height were still below the 3rd percentile; she had started walking 6 months earlier and could speak a few words. Her developmental level corresponded to 18 months. MRI demonstrated a delay in myelination and prominent sulci in the frontal cortex suggestive of cerebral atrophy. Her facial appearance had changed somewhat and now showed the typical features of PRDS (Fig. 1). The stereotypic hand movements had disappeared but she had developed epilepsy. The parents had noted seizures for the first time at the age of 18 months. They were described as spasms with brisk elevation of the arm with a tonic phase lasting some seconds accompanied by marked eye opening and a fixed gaze. These attacks occurred more frequently at the end of the day, when the child was tired or had fever. The myoclonia could become very significant causing the child to fall and during some periods, sleep was seriously disturbed by frequent awakenings. The frequency of seizures was quite variable, occurring for 2–3 days, then reappearing after several days or weeks. After the introduction of valproate the frequency of generalised myoclonic seizures diminished and a significant improvement in motor and coordination skills was noted.

Electroencephalography

A total of three EEGs were recorded on a Delcam Digital EEG instrument with a time constant of 1 s, without high filter during acquisition. Gain was 100 µVolt/cm with a paper speed of 30 mm/s.

A first EEG at 2.5 years demonstrated short periods of 2–3 Hz high voltage slow waves, appearing during drowsiness, without a particular localisation. Clusters of generalised discharges without clinical manifestations were also noted. A second registration at 2.11 years showed intermittent stereotyped 2–3 Hz high voltage slow waves with spike wave activity over the centro-occipital areas during drowsiness and sleep (Fig. 2). In video-EEG recordings, the high-voltage spike-wave bursts were frequently associated with myoclonic jerks (extension of arms, eye opening). A third EEG at 4.1 years still displayed the particular bursts of 2–3 Hz localised over the centro-occipital area with diffuse generalised discharges during sleep. However no clinical manifestations were noted.

Cytogenetics and fluorescent in situ hybridisation

Chromosomes for standard G-banding analysis were prepared from the patient’s peripheral blood lymphocytes according to standard methods. The karyotype was (again) normal (46,XX) at a 400 band level. Fluorescence in situ hybridisation (FISH) using a cosmid probe specific for the Wolf-Hirschhorn critical region (WHCR) at 4p16.3 (D4S96, Oncor) and a control cosmid probe specific for 4p11–15 (D4S174, Oncor), which lies outside the WHCR, was performed as described [10]. While the signal of the control plasmid D4S174 was detected on both chromosomes 4, the signal of D4S96 was absent on one of them (Fig. 3). This finding indicates a microdeletion of the WHCR and thus confirmed the clinical diagnosis of WHS/PRDS. The parents karyotypes were normal by conventional cytogenetic analysis (400 bands). FISH was not performed.

Discussion

Although detailed reports on EEG findings in association with 4p deletions are sparse, the distinct EEG abnormalities in our patient have been described in a few patients with WHS. In Table 1 the EEG results of 14 similar cases published in the literature are summarised. Some EEG descriptions are not very detailed and every

![Fig. 1 Patient at 3.2 years with typical features of PRDS: triangular face with prominent eyes, small nose, short philtrum, and micrognathia](image-url)