Epilepsy in a Child with Wolf-Hirschhorn Syndrome

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SUMMARY

Introduction Wolf-Hirschhorn syndrome (WHS) is a rare chromosomal disorder characterized by facial dismorphy, multiple congenital anomalies, delayed psychomotor development and pharmaco-resistant epilepsy.

Case Outline We present a 5-year-old girl with severe delay in growth and development, microcephaly, mild facial dismorphy and epilepsy. The pregnancy was complicated by intrauterine growth retardation. Generalized muscle hypotonia was observed at birth. First seizures started at age of 9 months as unilateral convulsive status epilepticus (SE), sometimes with bilateral generalization. Seizures were often triggered by fever and were resistant to antiepileptic treatment. Introduction of lamotrigine and valproate therapy led to complete seizure control at the age of 33 months. Electroencephalographic (EEG) finding was typical at the beginning. After transitory improvement between age four and five years, epileptiform EEG activity appeared again at the age of five years, without observed clinical seizures. Magnetic resonance imaging showed diffuse brain atrophy and delay in myelination. Using Multiplex ligation-dependent probe amplification (MLPA) method, we disclosed heterozygote microdeletation of the distal part of the short arm of chromosome 4 (4p16).

Conclusion We present a clinical course of epilepsy in a patient with Wolf-Hirschhorn syndrome. The diagnosis was verified by modern molecular technique. This is the first molecular characterization of a patient with WHS performed in our country.

Keywords: Wolf-Hirschhorn syndrome; status epilepticus; EEG

INTRODUCTION

Wolf-Hirschhorn syndrome (WHS) is a chromosomal dysmorphic syndrome first recognized and described by Copper and Hirschhorn in 1965 [1]. It has an incidence of 1/20,000 – 1/50,000 live births, with higher incidence in females [2]. It is caused by a deletion of the distal part of the short arm of chromosome 4 (4p16.3) [3]. The disorder is sporadic in origin in 85% of cases, while the remaining 15% appear due to balanced translocation in one of the parents [4]. WHS is characterized by microcephaly and characteristic facial dismorphy, often described as "Greek warrior helmet" appearance; a high forehead, prominent glabella, hypertelorism, epicanthal folds, highly arched eyebrows, protruding eyes, short philtrum, and micrognathia. Most patients have additional major congenital anomalies; a cleft lip and/or palate, various eye, heart, bone, urinary and genital tract anomalies [5]. Almost all patients have intrauterine and postnatal growth retardation, generalized muscle hypotonia and mental deficiency. Seizures occur in 50-100% of patients [6].

CASE REPORT

A 9-nine-months old female infant was admitted due to the right-sided clonic status epilepticus (SE). First clinical examination revealed microcephaly and discrete dysmorphic facial features with a high forehead, prominent glabella, hypertelorism, epicanthal folds, micrognathia and prominent eyes. No other anomalies were verified. Severe retardation of longitudinal and ponderal growth was noted (length of 55.5 cm <p0.4; body weight 3.9 kg; <p0.4; head circumference 39 cm <p0.4). She was unable to seat, and had a pronounced generalized hypotonia.

The girl was born at gestational age of 37 weeks with the birth length of 43 cm, body weight of 2000 g and head circumference of 30 cm. Bilateral equinovarus and generalized muscle hypotonia were noted at birth. During the second and the third year of life, the patient suffered of frequent episodes of unilateral tonic, clonic or tonic-clonic SE with side changing followed by occasional generalization. She often had focal clonic seizures of one hand. SE was defined as seizure or series of seizures without regain of consciousness during 30 minutes or longer. Most seizures were provoked by fever and were difficult to control. One of the unilateral left- sided convulsive SE caused permanent left hand paresis.

The first drug treatment was initiated at nine months of age with phenobarbital tablets in maintenance doses of 4 mg/kg/day. The therapy was ineffective and after 3 months carbamazepine suspension was added in daily maintenance doses of 20 mg/kg with a gradual discon-

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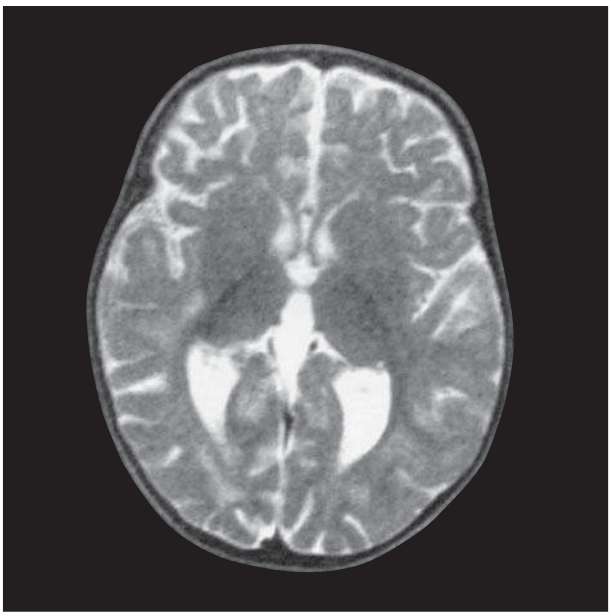

Figure 1. MRI of the brain. Disclosed global brain atrophy and delayed myelinisation.

tinuation of phenobarbital. At the age of 17 months valproate syrup was added in maintenance doses of 25 mg/kg /day with a corresponding blood level of 50.53 μg/ml. Subsequently, the daily doses of valpraote were increased to 30 mg/kg/day. However, she continued to suffer frequent seizures and at 22 months of age carbamazepine was gradually substituted by lamotrigine tablets. Titration of dosage of lamotrigine lasted over a 3-month period. Maintenance doses of 3 mg/kg/day improved seizures control. A complete control was achieved at 33 months. No adverse effects of antiepileptic drugs were noted.

Magnetic resonance imaging (MRI) of the brain was performed at the age of 22 months, showing diffuse global brain atrophy and delayed myelination (Figure 1). X-ray of the left hand at the age of 33 months showed a significant delay in skeletal maturation. At 5 years of age she was reevaluated by performing paediatric and neurological clinical evaluation, EEG and psychomotor development testing. She exhibited severe developmental delay, with score 14 using Brunet-Lezine scale. She had subnormal anthropometric parameters, each of them below the

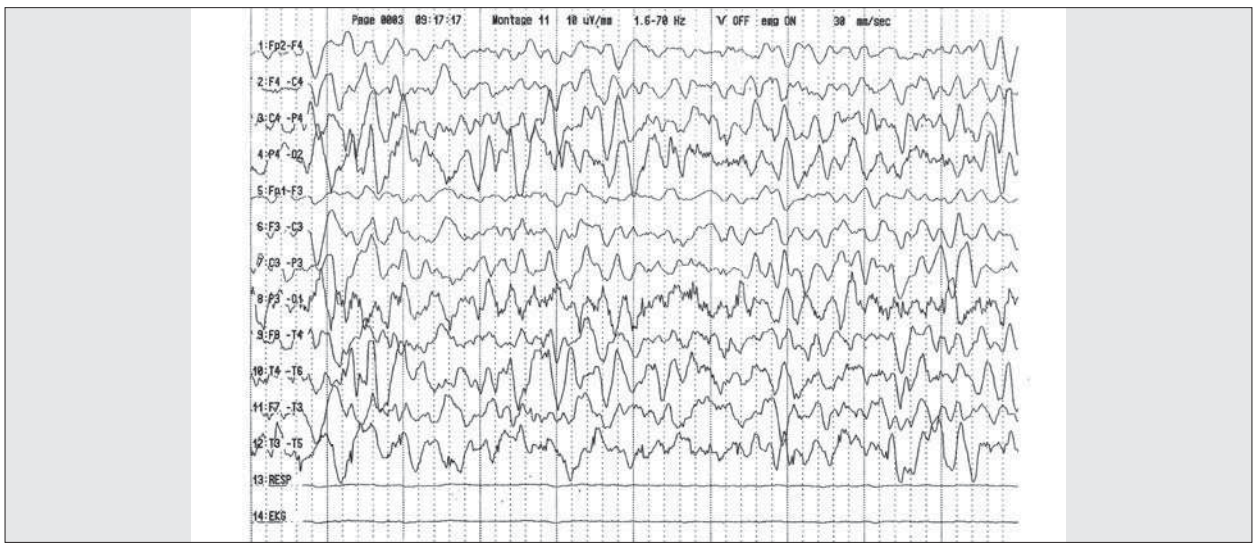

Figure 2. EEG at the age of nine months. Activity of 3-3.5 Hz and occasional spike-wave complexes over the temporo-parieto-occipital regions.

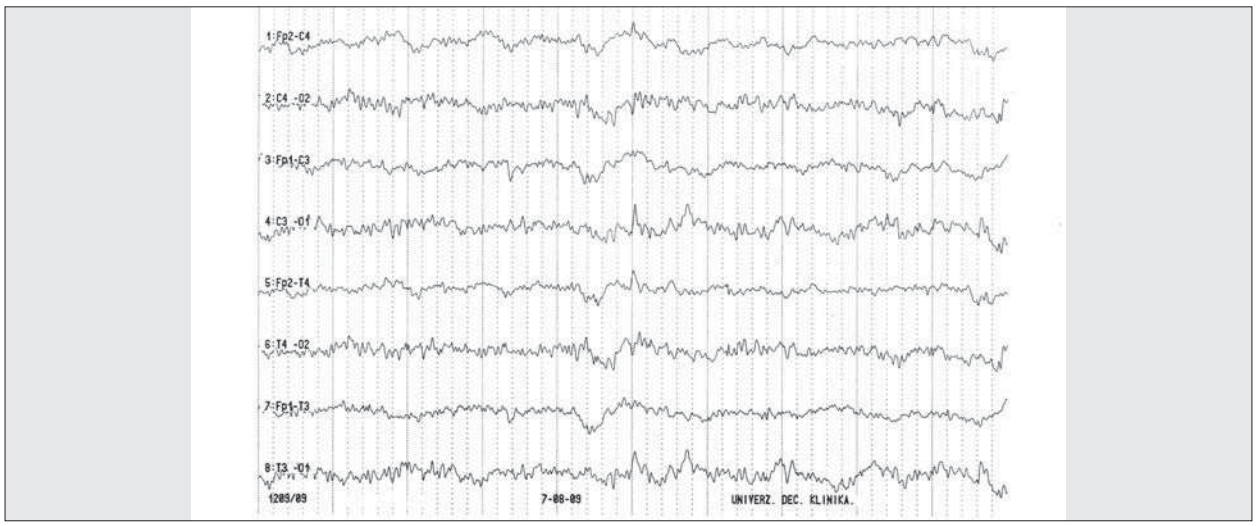

Figure 3. EEG at the age of four years. Rare sharp wave.

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3rd percentile; height 86.5 cm (average -19.3 % for age and sex), weight 7.8 kg (-36.1%) and head circumference 42cm (-16.8%).

The first electroencephalographic (EEG) finding performed at the age of 9 months showed 3-3.5 Hz activity and occasional spike-wave complexes over the temporo-parieto-occipital regions (Figure 2). EEG recorded at the age of 21 months revealed rare spike-wave complexes and slow delta-wave activity with predominance over the right side. At the age of four years EEG disclosed a rare sharp wave (Figure 3), while at the age of five years it demonstrated unilateral or bilateral spikes-polyspike and wave complexes and theta waves over the temporo-parieto-occipital regions (Figure 4).

Cytogenetic analysis revealed a normal female karyotype (46, XX). Molecular analysis of subtelomeric chromosomal regions by Multiplex ligation-dependent probe amplification (MLPA) method revealed heterozygote deletion of 4p16 (Figure 5). This analysis was performed using SALSA MLPA kit P036-E1 and SALSA MLPA kit P070-B1 (MRC Holland). The same test was performed in both parents and no chromosomal aberration was found indicating "de novo" origin of the deletion in our patient.

Informed consent for genetic testing and case publishing was obtained from both parents.

DISCUSSION

Wolf-Hirschhorn syndrome is relatively well described clinical entity. However, until recently, published data were deficient in detailed information about clinical course of epilepsy and EEG findings [7, 8]. The largest series of patients, published by Battaglia et al. [8], shows that seizures usually occur during the first three years of life, mostly as generalized tonic-clonic type. At later course, tonic spasms, complex partial seizures and clonic seizures appear. Atypical absences could be verified in 1/3 of children between age one and six years. Seizures are often provoked by fever [8, 9]. At the age of nine months our patient had unilateral convulsive SE, as the first epileptic event. By the age of 33 months, she had frequent unilateral convulsive SE with side alternation. She had only 2 generalized seizures. According to Battaglia et al. [8], generalized tonic-clonic seizures are the most common type, which is in contrary with clinical course of epilepsy in our patient. Half of their patients had unilateral or generalized clonic or tonic-clonic SE occurring during the first three years of life. Kagitani-Shimono et al. [9] reported that all of their patients had SE. Our patient had frequent seizures provoked by fever, which is consistent with other reports [8, 9]. Despite phenobarbital and later combination of valproate and carbamazepine, seizures

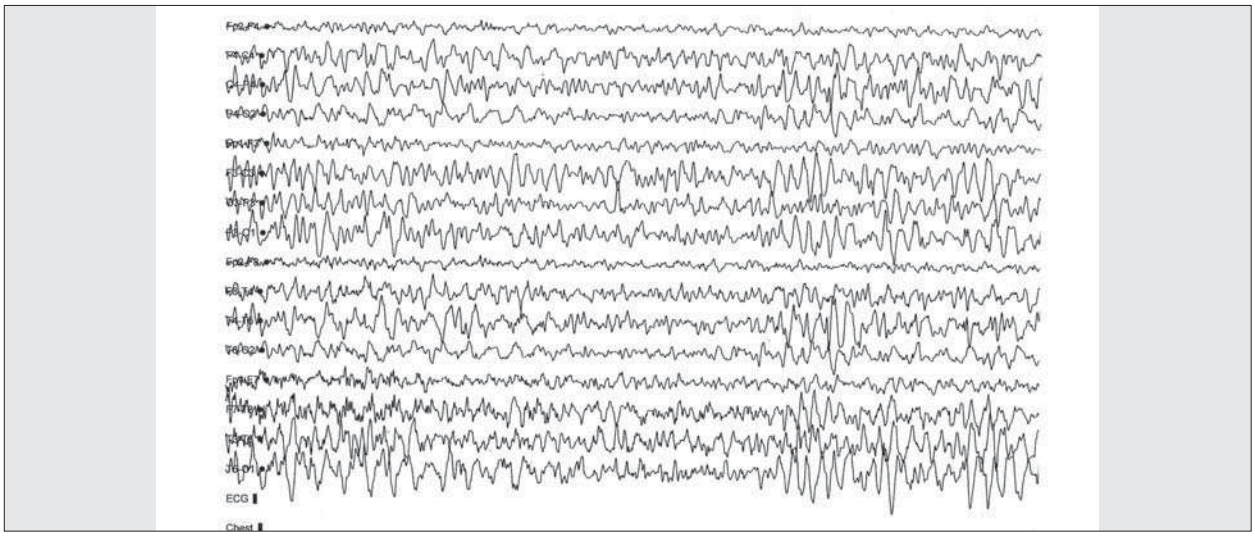

Figure 4. EEG at the age of five years. Spikes-polyspike, waves complexes and theta waves over the temporo-parieto-occipital regions, unilateral or bilateral.

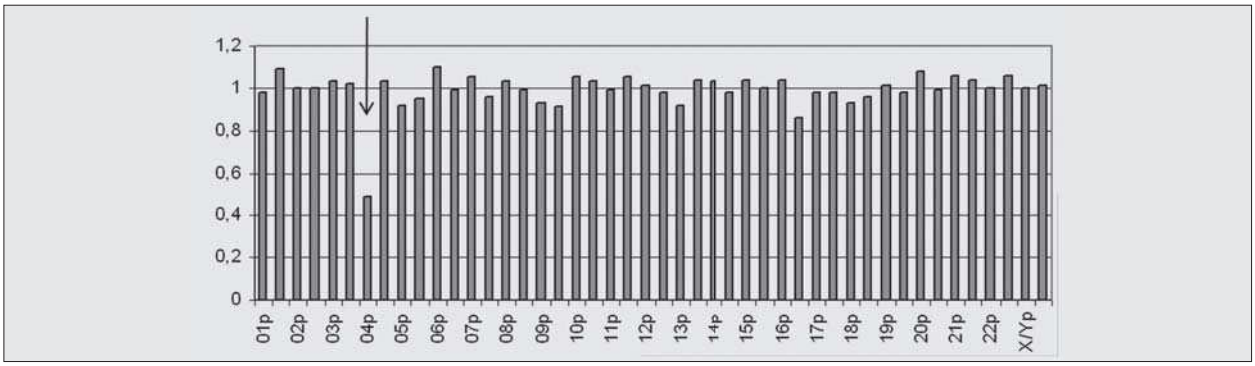

Figure 5. MLPA electropherogram of the sample with the diagnosis of WHS. Axis Y represents probe-height ratios. Height ratio of 4p16 probe is below cut-off value (0.65) showing deletion (indicated by arrow), with other probes having normal height ratio.

were resistant to therapy. Kagitani-Shimono et al. [9] and Battaglia et al. [10] found resistant SE in 6 of 11 and in one of 10 presented cases, respectively. After one episode of SE our patient developed permanent paresis of the left hand, which has already been reported in some cases [9, 11].

In a publication of Battaglia et al. [8], seizure control was achieved in 55% of cases, with average of 4.5 years. Phenobarbital was the most effective drug in the management of tonic-clonic seizures, whereas valproate as monotherapy or in combination with ethosuximide was the most effective for atypical absences. Kagitani-Shimono et al. [9] found that Na-bromide is the most effective drug in prevention of SE. Full seizure control of our patient was achieved at age of 33 months using the combination of valproate and lamotrigine. This could be also the result of natural course of epilepsy in patients with WHS.

Typical EEG finding of patients, first described by Sgro et al. [11], include: burst of 2-3.5 Hz high voltage slow wave with spike-wave complexes, generalized or unilateral or over posterior regions, activated by sleep, and spike-polyspike wave complexes of 4-6 Hz over the temporo-parieto-occipital regions often triggered by eye closure and slow background activity [7, 8, 12, 13]. First EEG findings of our patient showed 3.5 Hz slow waves with spike-wave complexes over the temporo-parieto-occipital regions. During the later course, EEG revealed slow activity with predominance over the right side, as a consequence of SE. EEG records improved after the achievement of seizure freedom. Epileptiform discharges reappeared at age of five, however no seizures were noted. A transitory improvement of EEG is rarely described in publications. Battaglia et al. reported this phenomenon in one of 10 described patients [10].

Molecular characterization of WHS showed that LETM1 gene, which is involved in signal pathway and homeostasis of Ca^{++} could be responsible for seizures [14]. A categorization of the severity of WHS phenotype has been proposed, correlating well with extent of 4p deletions [3]. Accordingly, small deletions not exceeding 3.5 Mb are usually associated with a mild phenotype without major malformations. Taking into consideration phenotypic characteristics, as well as the submicroscopic size of deletion in our patient, she probably belongs to this subgroup of patients.

Although they may be of different length, 4p deletions that include 4p16.3 region are the basis of WHS [3]. Our patient was analyzed using two MLPA kits, each containing a different probe for 4p16.3 region. By this approach, we showed that two loci (FLJ20265 gene and ZNF141 gene) of 4p16.3 region were deleted in this girl, most probably as a part of the same submicroscopic deletion. Between these two genes, two main candidate genes (WHSC1 and LETM1) for WHS are located, with LETM1 proposed as a candidate gene for the seizures.

We present a patient with resistant SE, severe growth and developmental delay and discrete facial dismorphy, as a part of WHS. Frequent unilateral SE resistant to therapy was the main challenge in her management during the first three years of life. Complete seizure control was achieved using combination of valproate and lamotrigine. EEG finding was typical at the beginning. After transitory improvement between age four and five years, epileptiform EEG activity reappeared at the age of five years, without observed seizures. Due to nonspecific clinical presentation and normal karyotype, a definitive diagnosis of WHS was established using the MLPA analysis. To the best of our knowledge, this is the first molecular characterization of patient with WHS performed in our country. This molecular technique proved to be very useful diagnostic tool in a case with unclassified mental retardation with normal cytogenetic finding. Early recognition of this syndrome could help in proper solving of various medical problems of these children, as well as in adequate therapy.

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Епилепсија код детета са Волф–Хиршхорновим синдромом

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КРАТАК САДРЖАЈ

Увод Волф–Хиршхорнов синдром (ВХС) је редак хромозомски поремећај који се одликује дисморфијом лица, вишеструким конгениталним аномалијама, успореним психомоторним развојем и фармакорезистентном епилепсијом.

Приказ болесника Приказујемо петогодишњу девојчицу са значајним заостајањем у расту и развоју, микроцефалијом, благом дисморфијом лица и епилепсијом. Трудноћа је била компликована интраутерусним заостајањем у развоју. Генерализована хипотонија мускулатуре утврђена је на рођењу. Појаве једностраних конвулзивних епилептичких напада, понекад са секундарном генерализацијом, имала је од деветог месеца након рођења. Напад је често изазивала повишена температура и били су резистентни на терапију. Комбинација ламотригина и валпроата довела је до потпуне контроле напада у узрасту од 33 месеца. У почетку је електроенцефалографски (ЕЕГ) налаз био типичан за ВХС. После пролазног побољшања ЕЕГ налаза између четврте и пете године, епилептиформне промене су се без видљивих конвулзија поново јавиле када је имала пет година. Налаз магнетне резонанције указао је на дифузну атрофију мозга и успорену мијелинацију. Применом молекуларне методе вишеструког умножавања проба које је зависно од лигације доказана је хетерозиготна суптеломерна делеција хромозома *4p16*.

Закључак Дијагноза ВХС код приказане девојчице с епилепсијом постављена је коришћењем савремене молекуларне технике, што је први пут урађено у нашој земљи.

Кључне речи: Волф–Хиршхорнов синдром; епилепсија; електроенцефалографија (ЕЕГ)

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