Spectrum of epilepsy and electroencephalogram patterns in Wolf–Hirschhorn syndrome: experience with 87 patients

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To define the spectrum of epilepsy in Wolf–Hirschhorn syndrome (WHS) better, we studied 87 patients (54 females, 33 males; median age 5.6 years; age range 1–25.6 years) with confirmed 4p16.3 deletion. On the basis of clinical charts, we retrospectively analyzed the evolution of the electroencephalogram (EEG) findings and seizures. Epilepsy occurred in 81 patients (93%) within the first 3 years of life. Sixty out of 81 (74%) had generalized tonic–clonic seizures, which was the only seizure pattern in 32. Tonic spasms occurred in 15 out of 81 (18%), complex partial seizures in 10 out of 81 (12%), and clonic seizures in 6 out of 81 (7%). Seizures were frequently triggered by fever (59 out of 81; 73%), and occurred in clusters in 36 out of 72 (50%). In the same 36 (50%), unilateral or generalized clonic or tonic–clonic status epilepticus occurred during the first 3 years of life. Twenty-seven out of 81 patients (33%) developed atypical absences between 1 and 6 years, accompanied by a myoclonic component involving the eyelids and the hands. Distinctive EEG abnormalities were observed in 73 out of 81 (90%). Epilepsy was well controlled in 65 out of 81 (81%), mainly with valproate and phenobarbital, and improved with age in all. Thirty-two out of 58 (55%) are currently seizure-free. Seizures stopped at a median age of 4 years 6 months. Epilepsy represents a major clinical challenge in WHS; however, it has a good prognosis. Early diagnosis and treatment of atypical absences, subtle and often misdiagnosed, is mandatory.

Epilepsy and intellectual disability are frequent features in chromosomal disorders. In such disorders, epilepsy is usually challenging because it occurs in the context of a pre-existing disability. In addition, whenever chromosomal abnormalities are associated with frequent and difficult-to-control seizures, long-term cognitive outcome can be seriously impaired.[1,2] For these reasons, clinicians should endeavour to characterize the seizure type and/or epilepsy syndrome in persons with chromosomal aberrations. Accurate analysis of epilepsy phenotype not only leads to improved management of patients but also can aid diagnosis. Among chromosomal disorders, distinct epileptic phenotypes have been described in Angelman syndrome,[3] idic(15) or inv dup(15) syndrome,[4] terminal deletion 1p36 syndrome,[5] and ring chromosome 20 syndrome.[6]

Wolf–Hirschhorn syndrome (WHS) is a well-known multiple congenital anomalies/intellectual disability syndrome. Its frequency is estimated as 1 per 50 000 births, with a female predilection of 2:1. The disorder is caused by partial loss of material from the distal portion of the short arm of chromosome 4 (4p16.3).[7] The most striking features of WHS (del 4p) include the typical 'Greek warrior helmet appearance' of the nose (i.e. the high nasal bridge of the nose continuing to the forehead), microcephaly, high forehead with prominent glabella, ocular hypertelorism with large and protruding eyes, epicanthal folds, short philtrum, downturned mouth, micrognathia, and poorly formed ears. All affected individuals have intrauterine and postnatal growth retardation with marked feeding difficulties, congenital hypotonia, and developmental delay/intellectual disability, and most have seizures.[7]

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Epilepsy constitutes a major medical challenge during the first years of life, and occurs in 50 to 100% of patients with WHS.[1] Although about 200 cases have been reported in the literature, there are few published data on the epileptic phenotype, on electroencephalogram (EEG) findings, and, particularly, on the natural history of epilepsy.

In the present paper, we describe the electroclinical features of 87 patients with WHS, in order to obtain better information on the characteristics of epilepsy, including seizure semiology and EEG features, and on its natural history. To our knowledge, this study is the largest report on a detailed analysis of the electroclinical characteristics of epilepsy in this syndrome.

METHOD

We retrospectively studied the electroclinical pattern of 87 patients diagnosed with WHS (54 females, 33 males). The median age at the final visit was 5 years 6 months (from 1 year to 25 years 6 months). Thirty-three of the 87 patients have been followed up by us from 4 months to 21 years.

All patients had a partial deletion of the short arm of chromosome 4. The proximal breakpoint of the deletion varied from p15.32 to p16.3. Deletion was detected on standard cytogenetics in 44 of the 87 (50.5%) patients, whereas fluorescent in situ hybridization or array comparative genomic hybridization were necessary in the other 43. Sixty-five of the 87 (74.7%) had a pure, de novo, terminal deletion; 21 of the 87 (24.1%) had a derivative chromosome 4 as part of an unbalanced translocation; and 1 of the 87 (0.2%) had a tandem duplication of 4p16.1p16.3 associated with 4p16.3pter deletion.

Clinical details were obtained from an exhaustive questionnaire sent out to the families through their national support groups in the USA and Italy. Families were also requested to send copies of the hospital files. In addition, 42 of the 87 patients were also personally observed by two of us (AB and JCC). All patients received careful physical and neurological evaluation.

The hospital files were retrospectively reviewed to determine seizure history and classification, with specific attention to seizure incidence, types, and frequency, and response to treatment. Epilepsies were classified according to the 1989 recommendation of the International League Against Epilepsy.

Sixty-seven of the 87 patients (77%) were studied with at least one awake and sleep EEG recording. Polygraphic video-EEG recordings were performed while patients were awake and asleep at 15 or 30mm/s on paper, with a 10- or 20-channel EEG apparatus (10–20 system, according to measurements from bony landmarks)[8] with bipolar and referential montages using silver–silver chloride surface electrodes, at the onset of epilepsy and during its course. The results of routine EEG studies performed in other institutions were obtained by chart review.

This study was approved by the institutional review boards of the Stella Maris Clinical Research Institute for Child and Adolescent Neurology and Psychiatry, Pisa, Italy, and of the University of Utah, Salt Lake City, UT, USA.

RESULTS

Clinical findings

All patients showed characteristic craniofacial features, intellectual disability, and generalized hypotonia. Distinct dysmorphic features included 'Greek warrior helmet appearance' of the nose, microcephaly, high forehead with prominent glabella, ocular hypertelorism, epicanthal folds, highly arched eyebrows, short philtrum, downturned mouth, micrognathia, and poorly formed ears. All patients presented developmental delay and different degrees of cognitive impairment, varying from profound–severe (87%) to moderate–mild (13%). No variability in cognitive outcome was ever observed.

None of the 87 patients had a familial history of epileptic seizures. All patients had intrauterine growth retardation, and one-third had transient perinatal distress.

Electroclinical pattern

Seizures/epilepsy affected 81 of the 87 patients (93%). The age of the six patients without seizures ranged between 12 and 16 years.

In almost all individuals seizures started within the first 3 years of life, with a peak incidence at around 6 to 12 months of age.

Seventeen of the 81 patients (21%) had the first seizure within the first 6 months of age (3 out of 17 in the neonatal period); 39 of the 81 (48%) at 6 to 12 months of age; 17 of the 81 (21%) between 12 and 24 months of age; but only 4 of the 81 (5%) between 24 and 36 months of age. In four of the 81 patients (5%) the age at seizure onset was impossible to determine from the clinical history.

Sixty of the 81 patients (74%) had generalized tonic–clonic seizures; in 32 of these 60 (40% of all epileptic patients) this was the only seizure pattern. Other seizure types included tonic spasms in 15 of the 81 (18%), complex partial seizures in 10 of the 81 (12%), and clonic seizures in six out of 81 (7%).

These seizures were frequently triggered by fever (59 out of 81; 73%), even of low degree. Other triggering factors were mainly represented by respiratory or urinary tract infections (11 out of 81; 14%). Tiredness (five out of 81; 6%) and excitement (two out of 81) were also listed by parents, as supposed triggers. In two of the 81 patients, high-degree fever (>38°C) seemed to inhibit seizures.

Seizures occurred in clusters, on occasions lasting about 15 minutes, in 36 out of 72 (50%) patients for whom such information was available. In the same 36 patients (50%), unilateral or generalized clonic or tonic–clonic status epilepticus occurred during the first 3 years of life, despite adequate antiepileptic treatment.

Twenty-seven of the 81 patients (33%) developed atypical absences by age 1 to 6 years, often accompanied by a mild myoclonic component, mainly involving the eyelids and the hands. These seizures were very frequent and long-lasting during the day (Fig. 1). Of note, eyelid myoclonias had been on several occasions misdiagnosed as 'tics' by some of the clinicians who had seen the children previously.

Distinctive EEG abnormalities were observed in 73 of the 81 (90%) patients. These included the following: (1) frequent, ill-defined, diffuse or generalized or with variable predominance over both hemispheres, high-amplitude, sharp element spike/wave complexes at 2 to 3.5Hz, occurring in long bursts (lasting up to 25 s), activated by slow-wave sleep (Fig. 2) (these abnormalities were also seen in the few patients with no seizures; Fig. 3); (2) frequent high-amplitude spikes–polyspikes/wave complexes at 4 to 6Hz, over the posterior temporo-parieto-occipital regions, often triggered by eye closure (Fig. 4); (3) slow background activity; (4) poverty of the usual rhythmic activities both over the rolandic regions and over the posterior third of the head, on eye closure; (5) the sleep spindles, well recognizable in most patients, were hardly recognizable in a minority (Fig. 5).

Of note, the fast spike–polyspike-wave complexes at 4 to 6Hz, triggered by eye closure, over the posterior temporo-parieto-occipital regions were also seen in the few patients with no seizures, in those who experienced only one or three seizures during the first three years of life, and in those who had been seizure-free for several years, and were not affected by antiepileptic treatment.

Interictal EEG was normal in eight of the 81 (10%) patients.

Long-term outcome

Epilepsy was well controlled in 65 of the 81 (81%) patients. Control was achieved by monotherapy in 17 of the 81 (21%) and polytherapy (two or three antiepileptic

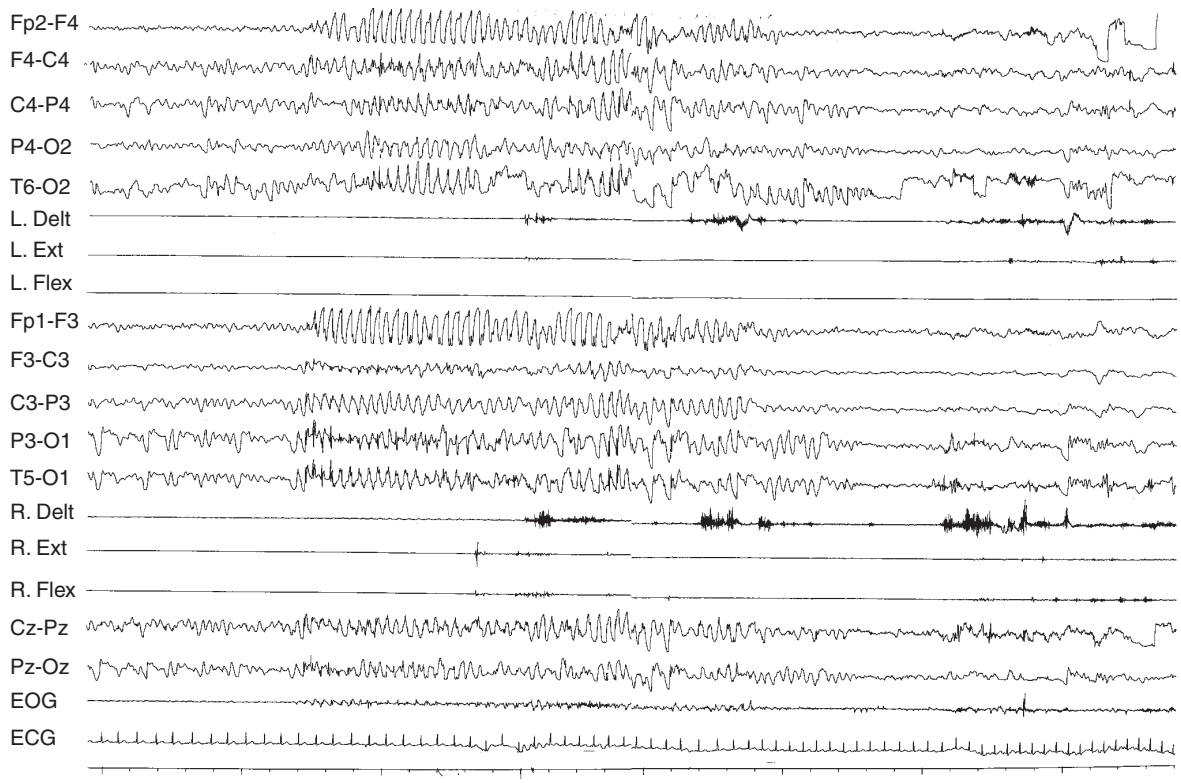

Figure 1: Patient 15, at 3 years of age. Awake electroencephalogram (EEG) showing an atypical absence characterized by diffuse rhythmic 2.5 to 3Hz spike-wave, ill-defined complexes, reaching up to 300μV, lasting 19s. This child had 15 such episodes, lasting up to 25s, during a 50-min EEG polygraphic recording. Amplitude 150μV/cm; speed 1s/1.5cm.

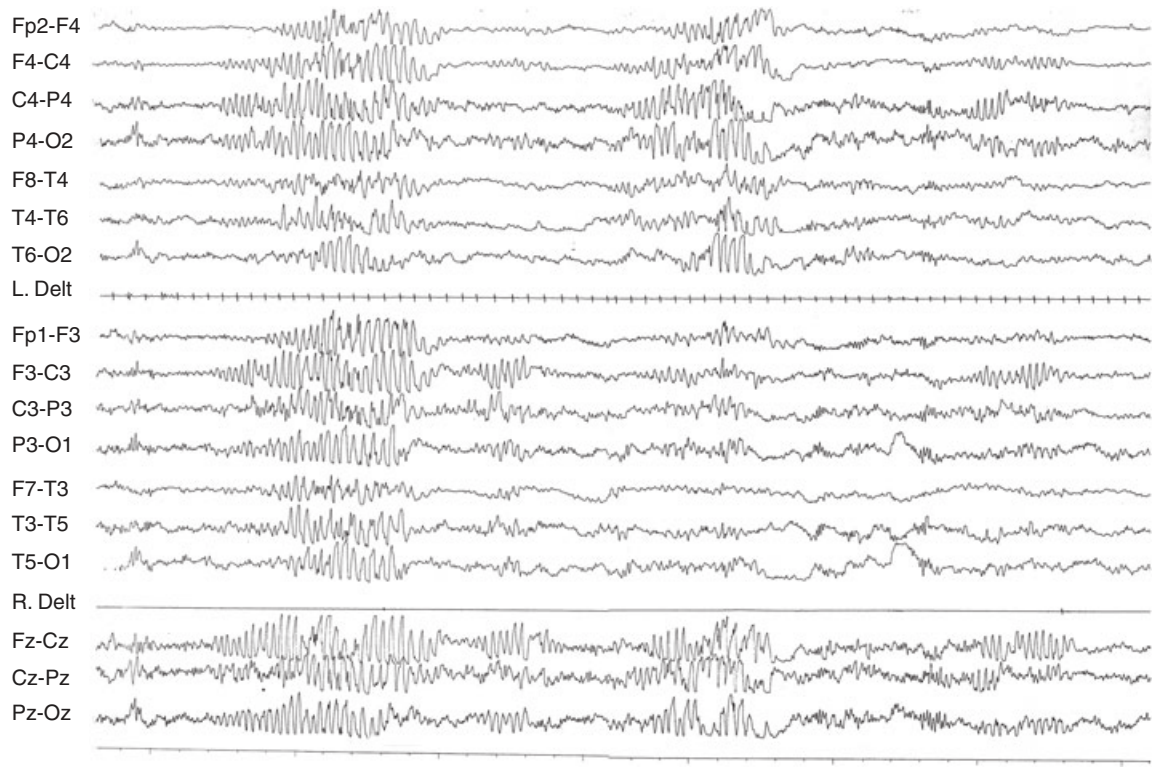

Figure 2: Patient 2, at 4 years 10 months of age. Slow wave sleep. Electroencephalogram showing frequent, ill-defined, diffuse, high-amplitude (up to 450μV) sharp element spike-wave complexes at 3 to 3.5Hz, lasting 8s. Amplitude 150μV/cm; speed 1s/1.5cm.

drugs) in 48 of the 81 (60%). Phenobarbital was the most effective drug against tonic–clonic seizures, whereas valproate alone or associated with ethosuximide succeeded in treating the atypical absences. Only in nine of the 81 patients (11%) did atypical absences require the combination of valproate, ethosuximide, and a benzodiazepine to be controlled.

Epilepsy improved with age in all patients. Thirty-two of the 58 (55%) individuals for whom information is available are seizure-free at present. Seizures stopped at a median age of 4 years 6 months (between 1y 9mo and 13y).

DISCUSSION

The present series is, to our knowledge, the largest sample of patients with WHS to date, with the longest follow-up ever reported, allowing a better delineation of epilepsy phenotype and its evolution in this terminal microdeletion syndrome. Our results highlight that epilepsy is a significant and potentially treatable feature in patients with WHS.

The prevalence of epilepsy was 93%, well in keeping with previously reported data.[9–13] In most patients (90%), epilepsy started within the first 2 years of life, but only seldom in the neonatal period. As previously reported, seizures were frequently triggered by low-degree fever, usually secondary to respiratory or urinary tract infections.[12]

First seizures were usually generalized tonic–clonic; in 40% this represented the only seizure pattern. Thirty-three per cent of the epileptic patients developed atypical absences by age 1 to 6 years, often accompanied by a mild myoclonic component, mainly involving the eyelids and the hands. Our percentage was lower than previously reported in smaller samples,[12,13] showing the relevance of large series in the study of the natural history. Other seizure types, rarely observed, included tonic spasms and complex partial and clonic seizures. We did not find any correlation between deletion size and seizure types, severity, and age at onset, which were randomly distributed among the entire sample.

Epilepsy constitutes one of the main medical challenges in individuals with WHS, particularly during the early years, with unilateral or generalized clonic or tonic–clonic status epilepticus occurring in half the patients despite adequate antiepileptic treatment. However, epilepsy outcome is usually favorable, and in just over half of our patients for

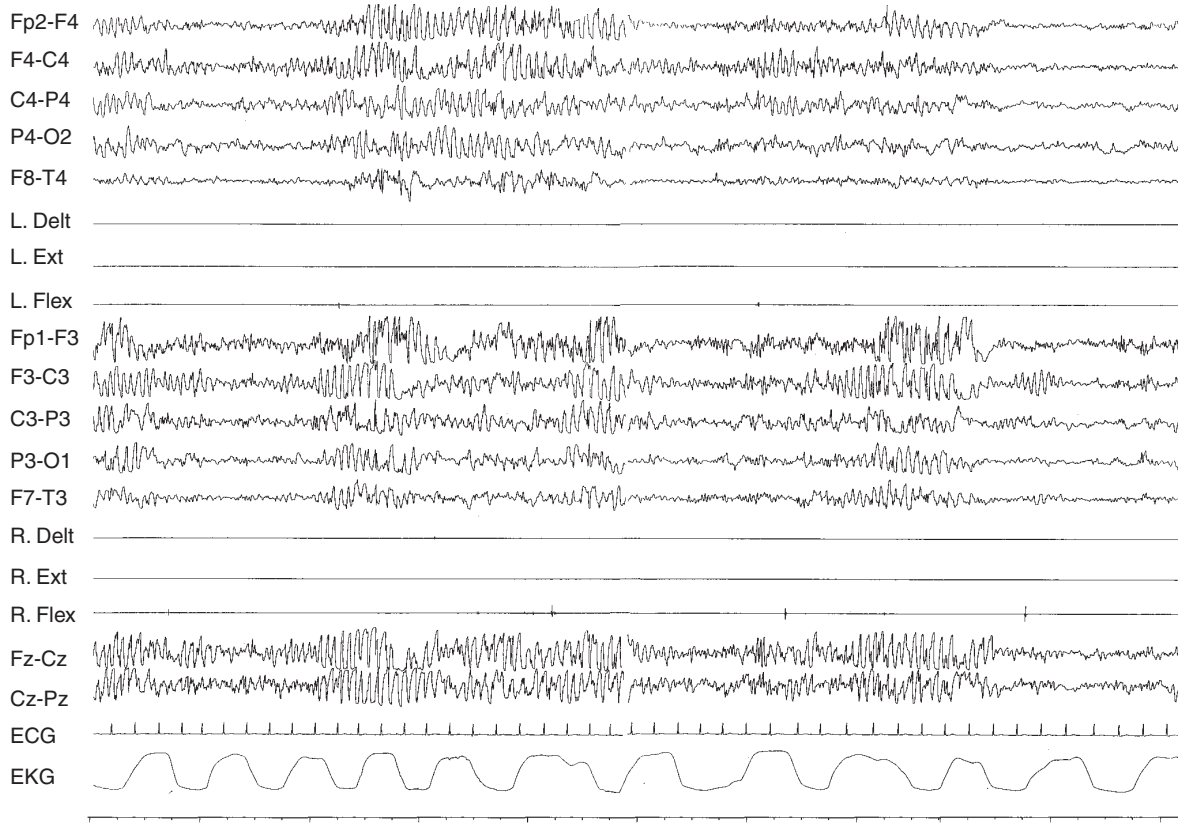

Figure 3: Patient 27, at 8 years of age. Slow wave sleep. Electroencephalogram showing frequent, ill-defined, diffuse, high-amplitude (over 200μV) sharp element spike-wave complexes at 3 to 3.5Hz, lasting up to 12s. The patient, at present 14 years of age, has never had any seizures. Amplitude 100μV/cm; speed 1s/1.5cm.

whom accurate data were available seizures stopped between ages 1 year 9 months and 13 years.

Our data confirm that phenobarbital is the most effective drug against tonic–clonic seizures, whereas valproate alone or in combination with ethosuximide succeeds in treating atypical absences in most patients.

The electroclinical picture appears to be very similar to that described as severe myoclonic epilepsy of infancy or Dravet syndrome.[14] However, in WHS patients the epilepsy has a favorable outcome, and no cognitive decline is observed. According to the classification of epilepsies and epileptic syndromes (1989 recommendation of the International League Against Epilepsy), WHS patients could be categorized under undetermined epilepsies.[15]

In keeping with previously reported data, EEG recordings were abnormal from early on,[12] even in those patients with no seizures. In the medical literature little is known about the EEG findings in large WHS series, nor about their evolution. Our data show that patients with WHS have distinctive EEG features, outlasting seizures and not necessarily related to them, which are even detectable in individuals with no seizures. As already stated on the basis of a smaller study,[12] we feel that this observation could be highly relevant to improved medical management of such patients, avoiding unnecessary treatment. Of note, some of the patients in our sample were still receiving antiepileptic drugs, despite being seizure-free for several years, owing to the continuing EEG abnormalities. We would suggest withdrawing antiepileptic drugs in individuals who have not experienced seizures for 2 to 5 years.[16,17]

Contrary to what has been stated elsewhere,[13,15] but in agreement with Laan and Vein,[18] we believe that WHS EEG features look different from those reported in Angelman syndrome. In fact, the fast spike–polyspike-wave complexes triggered by eye closure over the posterior brain regions in WHS are not observed in individuals with Angelman syndrome, in whom the abnormalities detected posteriorly are slower and less well defined;[19] the anteriorly prominent large-amplitude slow activity seen in Angelman syndrome[19] is not observed in WHS; finally, the distinct fast-bursting cortical myoclonus of Angelman syndrome[20] has never been detected in WHS.

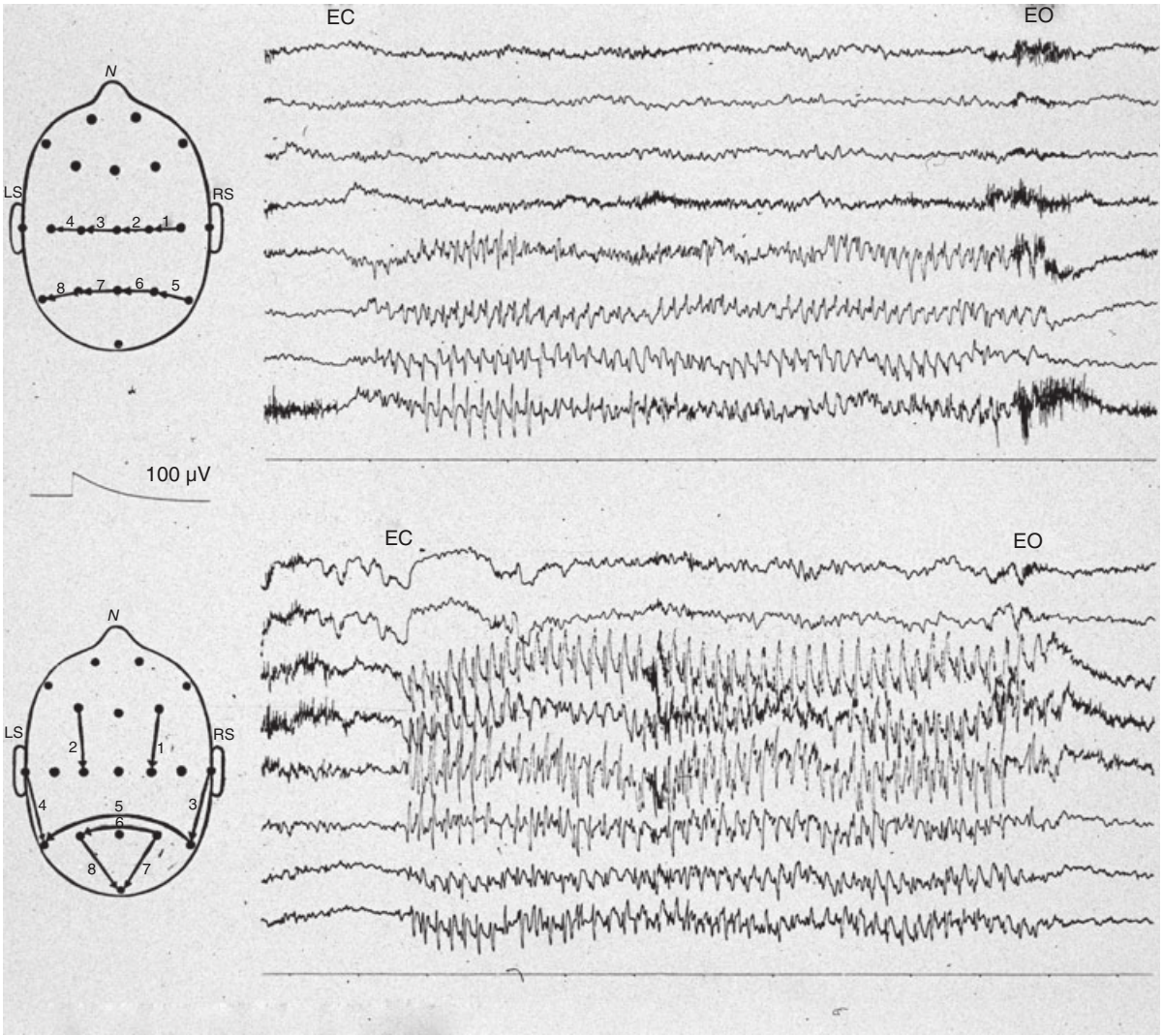

Figure 4: Patient 1, at 10 years 3 months of age. Awake electroencephalogram showing high-amplitude spike–polyspike-wave complexes at 4 to 6Hz, over the posterior temporo-parieto-occipital regions, triggered by eye closure and blocked on eye opening. The patient still shows these paroxysms, at age 28 years, having been seizure-free since 3 years of age. She has been off medication since 7 years of age.

The pathophysiological mechanisms of epilepsy and EEG abnormalities in WHS remain unknown. The $GABA_A$ receptor gene was initially thought to be a good candidate gene for epilepsy in WHS. However, this gene maps to 4p12–p13,[21] proximal to the locus involved in the syndrome. The use of molecular techniques in different patients allowed the identification of a critical region, 2 megabases (Mb) from the telomere.[22] One gene in this region, *WHSC1*, is partly or fully monosomic in all individuals with WHS.[23] *WHSC1* and its murine ortholog (*Whsc1*) are widely expressed in many tissues that are key to the pathogenesis of the core WHS characteristics.[24] Further studies of cryptic terminal deletions in two individuals with the core characteristics indicated that additional genes contributing to the core phenotype should reside telomeric to *WHSC1*, between 1.2 and 1.9Mb from the telomere.[25] About 10 genes are predicted to lie in this region (WHSCR2). Among them, *LETM1*, encoding a putative member of the EF-hand family of Ca^{2+}-binding proteins, involved in Ca^{2+} signaling and/or homeostasis, has been proposed as a candidate gene for seizures and neuromuscular problems in WHS.[26–28] However, the observation that six of our patients with terminal deletions encompassing *LETM1* never had seizures, along with the recent observations by South et al.,[29] suggest that seizures are likely caused by hemizygosity not only of *LETM1*, but also of other genes within the terminal 1.9Mb of 4p. *LETM1*

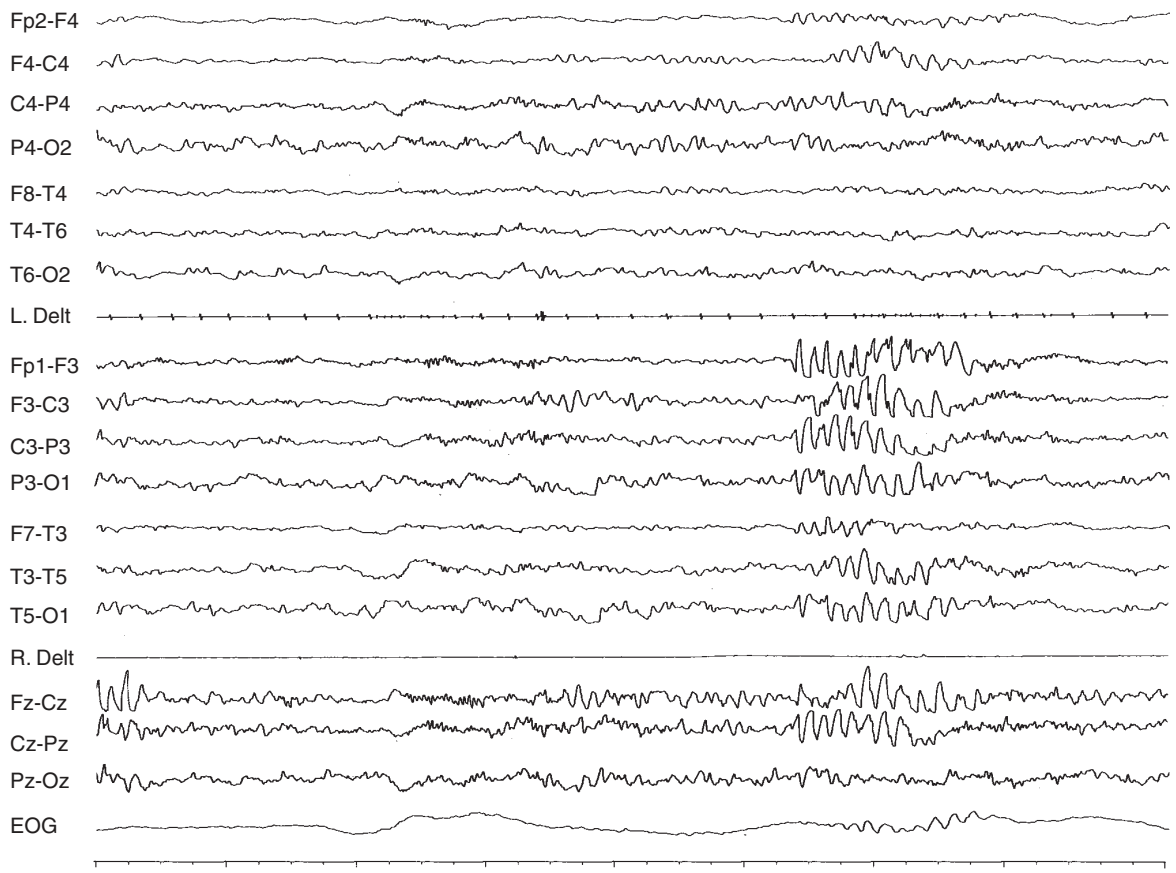

Figure 5: Patient 2, at 4 years 10 months of age. Slow wave sleep. Electroencephalogram showing well-defined sleep spindles over the fronto-central regions, better formed in the left hemisphere. A paroxysm similar to that shown in Figure 2 is also present, over the left hemisphere. Amplitude 150μV/cm; speed 1s/1.5cm.

might still be the only candidate gene for the WHS-distinctive EEG abnormalities (Fig. 3). *WHSC2* is ubiquitously expressed and might have a possible transcriptional role.[30] However, more work is needed to identify the function of *LETM1*, *WHSC1*, and *WHSC2* both in normal development and in individuals with del 4p, and to characterize any remaining genes in the WHS critical region.

Recently, array comparative genomic hybridization has shown an unexpectedly high frequency of unbalanced translocations, possibly explaining the complexity of the WHS phenotype, with the presence of trisomic material associated with the deleted segment.[31]

CONCLUSION

Our observations confirm that epilepsy represents a major clinical challenge in individuals with WHS. However, prognosis is good both for seizure control by the usual pharmacotherapy and for epilepsy outcome. Clinicians should be aware of the WHS distinct electroclinical phenotype, paying particular attention to the correct and early diagnosis of atypical absences associated with mild myoclonias, because they can be subtle and misdiagnosed, particularly in younger children. Deletion 4p16 should be considered in patients presenting with a history of early febrile and non-febrile convulsive seizures, preceding atypical absences, if associated with developmental delay/intellectual disability, hypotonia, and distinct craniofacial dysmorphisms.

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