International Journal of Healthcare Sciences ISSN 2348-5728 (Online)
Vol. 4, Issue 2, pp: (2028-2032), Month: October 2016 - March 2017, Available at: www.researchpublish.com

Deletion of Short Arm of Chromosome No. 4 (4p-)-Wolf Hirschorn Syndrome Seizure Disorder, Control on Levetiracetam

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Abstract: **Wolf-Hirschhorn syndrome (WHS) is a rare chromosomal disorder characterized by dysmorphic features, multiple congenital anomalies, hypotonia, psychomotor retardation and epilepsy.**
Results: 3 year old Saudi female presented with history of generalized tonic-clonic seizures at the age of 8 months. She had lagoopthalmos and other dysmorhic features. Genetic studies showed terminal deletion in short arm of chromosome 4 consistent with the diagnosis of WHS. Phenobarbital was started initially for the treatment of her seizure. Later, she developed atypical absence seizures and valproic acid was started. Liver enzymes were elevated and the seizures remained uncontrolled. Levetiracetam was started and valproic acid discontinued. She had excellent control on Leviteracetam without clear adverse reaction.
Conclusion: Atypical absence seizures are known type of epilepsy occurring in WHS. Valpric acid was reported to the drug of choice. We believe that Leviteracetam is a good alternative especially in cases of valprioc acid intolerance or side effects.

Keywords: **Wolf-Hirschhorn syndrome; status epilepticus; EEG; levetiracetam.**

1. INTRODUCTION

Wolf-Hirschhorn syndrome (WHS) is a rare chromosomal syndrome caused by a deletion of the terminal part of the short arm of chromosome 4 (4p16.3) [1]. It was first described by Copper and Hirschhorn in 1965 [2]. It has an incidence of 1/20,000 – 1/50,000 live births. Affected patients are predominantly females [3].

AGATINO BATTAGLIA and colleagues described Epilepsy in WHS patients in case series published 2008. They reported epilepsy in 93% of their patients. The age of onset was mainly within the first 3 years of life. Most (74%) of the patients had generalized tonic clonic seizures. Other seizure types were tonic spasms, complex partial seizures, clonic seizures and atypical absence which occurred in 33% of the patients between 1 and 6 years of age [4,5].

Epilepsy was well controlled in 81% of patients, mainly with valproate and phenobarbital, and improved with age in all. 55% of patients are currently seizure-free. Seizures stopped at a median age of 4 years 6 months [6,7,8] .

2. CASE REPORT

A 3 years old Saudi girl was first admitted to our hospital at the age of 8 months with febrile status epilepticus.

She is full term, product of consanguineous marriage, uneventful pregnancy, and spontaneous vaginal delivery. No family history of genetic disorders.

She is the third sibling, the first one die at age of 27 days due to neonatal sepsis and septic shock. The second one is healthy female.

She had intrauterine growth restriction, delivered at 38 week gestation. Birth weight 1.5 kg, she was admitted to neonatal intensive care unit (NICU) for 20 days due to low birth weight and dysmorphism, which was not diagnosed at that time.

Her stay at NICU was smooth, feeding through NGT and oral route yet poor sucking, discharged with the mother with weight 1.9 kg

During early infancy she had problem with feeding, frequent vomiting and chocking and failure to thrive and 2 times admission due to aspiration pneumonia

At the age of 8 months, the patient start suffering a frequent difficult to control episodes of unilateral tonic clonic convulsion interchanging sides with secondary generalization. Some of her episodes were associated with eye blinking, up rolling of eyes and lip smacking.

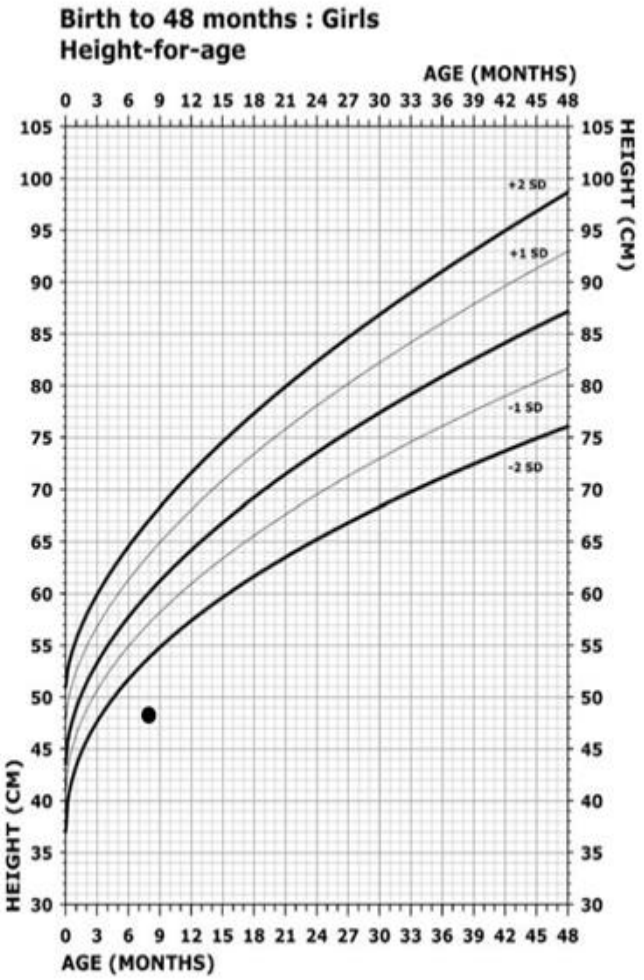
Most her seizures were provoked by fever, these episodes used to be last 30 minutes or longer and difficult to control thus necessate sedation and intubation and ICU admission.

First clinical examination conducted at age of 8 months in our hospital revealed characteristic facial features in form of high forehead, prominent glabella, hypertelorism, epicanthal folds, lagophthalmia, prominent eyes, short philtrum, Greek warrior helmet appearance of the nose, fish shaped mouth and micrognathia.

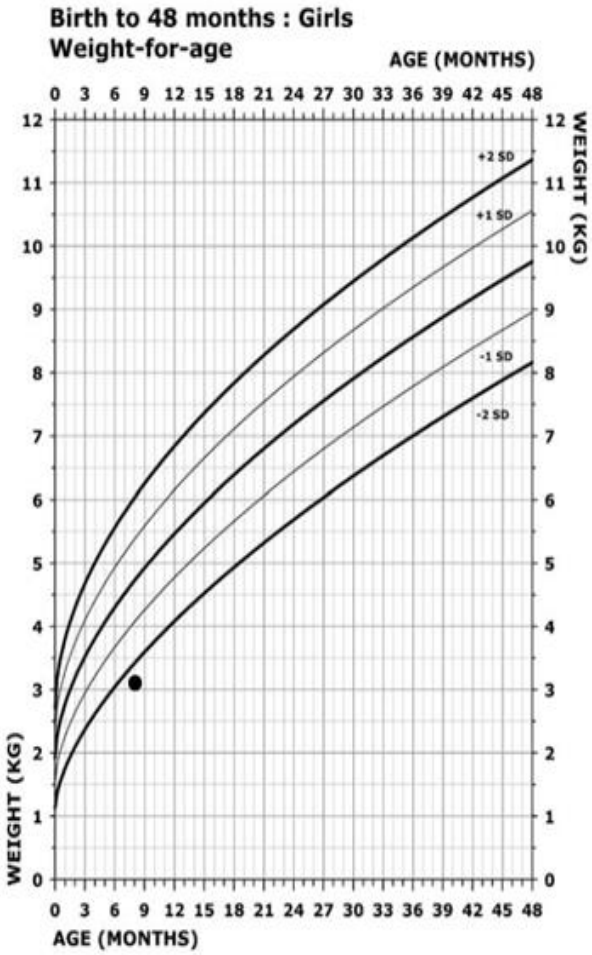
Neurological examination revealed hypotonia, and delayed motor developmental milestones.

No other anomalies were verified.

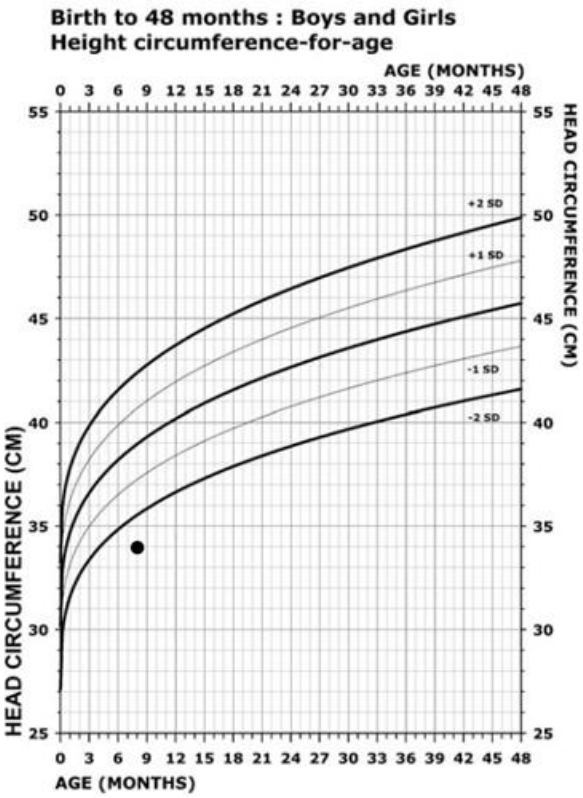
Her body weight, length and head circumference measurements were below the third percentile.



Height for age growth chart for girls from birth to 48 months with WHS



Weight for age growth chart for girls from birth to 48 months with



Head circumference for age growth chart for girls from birth to 48 months

The first drug treatment was initiated at 8 months of age with phenobarbital in maintenance dose of 5 mg/kg/day.

She still compliant on phenobarbitone when she was admitted again to our pediatric ICU at age of 11 months for difficult to control status epilepticus requiring intubation and sedation.

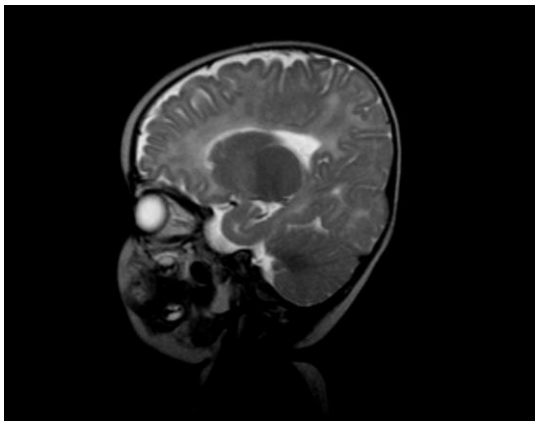
At that time, valporic acid suspension was added in daily maintenance dose of 40 mg/kg/day with a gradual discontinuation of phenobarbital.

A complete control was achieved at 16 months. No adverse effects of antiepileptic drugs were noted. With a corresponding follow up, the patient having gradually increasing liver enzyme AST 223 mmol/l ALT 148 mmol/l

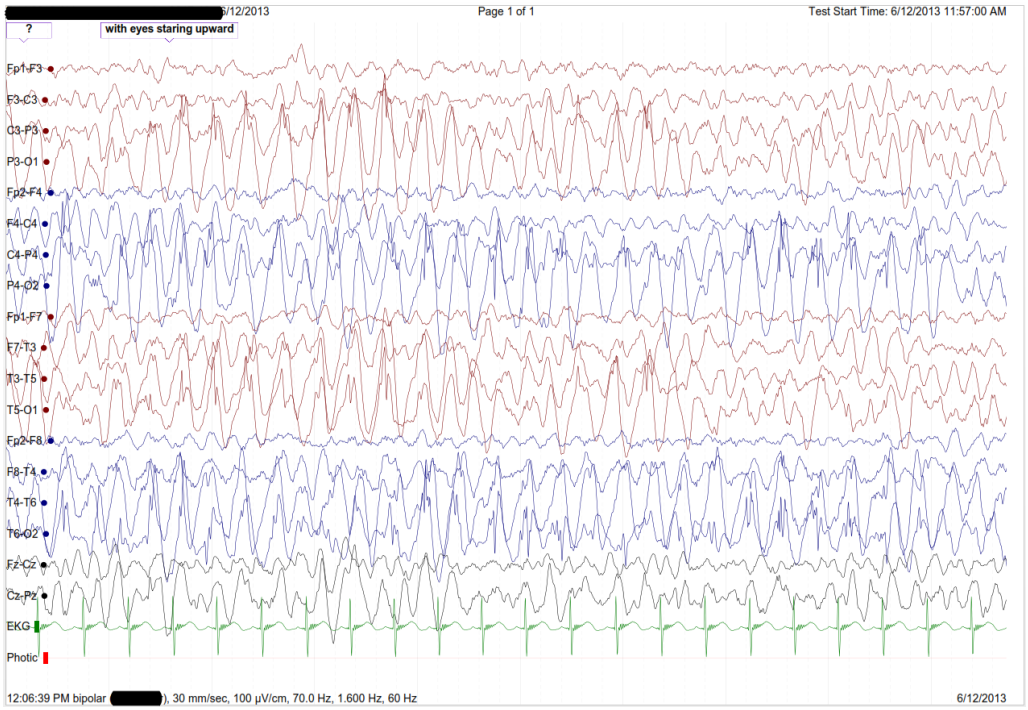
Subsequently, the daily doses of valproate were gradually decreased and substituted by Levetiracetam solution. Maintenance doses of 20 mg/kg/day improved seizures control.

Now she is 3 years, her last EEG is better. She is seizure free after levetiracetam treatment

Magnetic resonance imaging (MRI), T2 sagittal view of the brain done at age 8 months showed delayed myelination and thinning of corpus collosum.



The first electroencephalographic (EEG) finding performed at the age of 8 months showed bi-occipital ictal discharges.



Cytogenetic analysis revealed a normal female karyotype (46, XX).

Fluorescence in situ hybridization revealed 46XX, del (4)(p16), and confirmed the diagnosis of Wolf-Hirschhorn syndrome. The cytogenetic analysis from the mother and the father were both normal.

Informed consent for genetic testing and case publishing was obtained from both parents. But they refuse taking any photographs of the child because they do not want to be recognized although all confidentiality guarantees were offered to them.

3. DISCUSSION

A case series with the largest sample size of patients with WHS reported on 2008, with the longest follow up clearly delineate the epilepsy phenotype and its evolution. It was high lightened that epilepsy is significant and potentially treatable [4,5].

The prevalence of epilepsy was 93%, well in keeping with previously reported data. 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 [5,10]

Thirty three percent 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. [10]

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 over half of the reported cases seizures stopped between ages 1 year 9 months and 13 years. [5,6]

The most recent available data data confirm that phenobarbital is the most effective drug against tonic–clonic seizures, whereas valproate succeeds in treating atypical absences in most patients. [5,7]

In a publication of Battaglia et al. [4], 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. [11] found that Na-bromide is the most effective drug in prevention of status epilepticus.

Our patient achieved a good control of her seizures on valporic acid as monotherapy, but due to unavoidable side effects, valporic acid get tapered down and levetiracetam added gradually with full control of her seizures at the age of 16 months. This could be also a result of natural course of epilepsy in patients with WHS which need to be further studied.

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