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Case Report

Corpus callosotomy for drug-resistant epilepsy in a pediatric patient with Waardenburg syndrome Type I

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ABSTRACT

Background: Waardenburg syndrome (WS) is caused by autosomal dominant mutations. Since the coexistence of epilepsy and WS type I is rare, the detailed clinical features and treatment of epilepsy, including surgery, have not been fully reported for these patients. We report the first case of an individual with WS type I, who underwent corpus callosotomy (CC) for drug-resistant epilepsy and obtained good seizure outcomes.

Case Description: A boy was diagnosed as having WS type I and developmental delay based on characteristic symptoms and a family history of hearing loss. He underwent cochlear implantation at 18 months of age. At 4 years of age, he developed epileptic seizures with a semiology of drop attack. Electroencephalography (EEG) showed bilateral synchronous high-amplitude spikes and wave bursts, dominant in the right hemisphere. Based on the multimodality examinations, we considered that ictal discharges propagated from the entire right hemisphere to the left, resulting in synchronous discharge and a clinical drop attack; therefore, CC was indicated. At 9 years of age, he underwent a front 2/3rd CC. At 1 year, the patient became seizure free, and interictal EEG showed less frequent and lower amplitude spike and wave bursts than before.

Conclusion: When patients with WS Type I and cognitive impairment show drug-resistant epilepsy, clinicians should consider a presurgical evaluation.

Keywords: Corpus callosotomy, Drug-resistant epilepsy, Genetic dysmorphic syndrome, Waardenburg syndrome

INTRODUCTION

Waardenburg syndrome (WS) is caused by autosomal dominant mutations with high penetrance. Identified for the 1st time in 1947,[15] it affects approximately 1 in 42,000 individuals.[14] WS is characterized by deafness, pigmentary anomalies, and various defects in neural crest-derived tissues.[14] It accounts for over 1–2% of congenital deafness.[10,14] Based on clinical symptoms, WS has been classified into four subtypes, namely, WS type I to type IV.[11] WS Type I is characterized by hair hypopigmentation (white forelock), pigmentary disturbances of the iris, congenital sensorineural hearing loss, affected first-degree relatives, dystopia canthorum (as major criteria); broad high nasal root, alae nasi hypoplasia, synophrys or medial eyebrow flaring, congenital leukoderma, and prematurely graying hair (as minor criteria); patients meeting two major criteria or one major and two minor criteria should be considered as WS Type I.[5] Cognitive impairment

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is rarely associated with WS Type I, and only two (0.74%) of 270 cases have been reported to have developmental delay.[7] Since the coexistence of epilepsy and WS Type I is rare,[9,14] detailed clinical features of epilepsy and its treatment, including epilepsy surgery, have not been fully reported for these patients.[3,12] Herein, we report the first case of a patient with WS type I who underwent corpus callosotomy (CC) for drug-resistant epilepsy and obtained good seizure outcomes. Written informed consent was obtained from the patient for publication of this case report and all accompanying images.

CASE REPORT

A boy weighing 3126 g at birth, with Apgar scores of 9 and 9, showed total heterochromia in the left eye, dystopia canthorum (W-index: 2.36),[8] and broad nasal root [Figure 1a]. At the age of 1 month, he was diagnosed with congenital sensorineural hearing loss. His mother and grandmother also experienced hearing loss. Based on the previously characterized symptoms and his family history of hearing loss, he was diagnosed as having WS Type I with developmental delay. At the age of 18 months, he underwent cochlear implantation [Figure 1b] and achieved auditory-verbal communication.

At 4 years of age, he developed epileptic seizures with a semiology of drop attack, left upper limb atony, and left eyelid myoclonia, followed by focal to bilateral tonic–clonic seizures (FBTCS). He was diagnosed with epilepsy, and antiepileptic drug (AED) administration initiated. However, despite treatment with optimal AED dosages, including levetiracetam (LEV), valproate (VPA), perampanel (PRP), clobazam (CLB), ethosuximide (ESM), lacosamide, and zonisamide, the intractable seizures persisted.

He was referred to us at 9 years of age. He had severe cognitive impairment (intelligence quotient of 33) and behavioral features of autism spectrum disorder. His epileptic seizures included daily multiple drop attacks, and weekly left eyelid myoclonia followed by FBTCS, despite treatment with multiple AEDs including 1000 mg of LEV, 500 mg of VPA, 4 mg of PRP, 10 mg of CLB, and 500 mg of ESM. His seizures were characterized by repeated appearance and disappearance; if present, they persisted for approximately 2 weeks. Further, following a drop attack, he also experienced a head trauma.

Magnetic resonance imaging (MRI) performed after removal of the cochlear implant magnet showed no obvious abnormal findings (he underwent replacement of cochlear magnetic implant after the MRI) [Figure 1c]. 18F-fluorodeoxyglucose-positron emission tomography demonstrated hypermetabolism in the right frontal lobe and parietal lobe [Figure 1d]. (123)I-iomazenil (IMZ) single-photon emission computed tomography demonstrated decreased IMZ uptake in the right parietal lobe in a late image [Figure 1e].

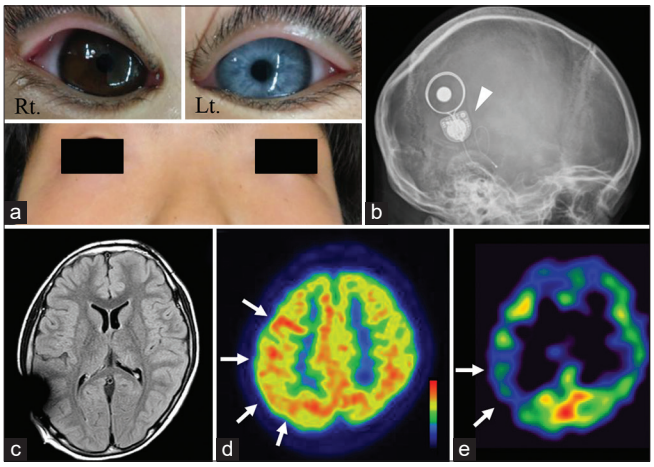

Figure 1: (a) Photograph showing total heterochromia in the left eye, dystopia canthorum, and broad nasal root. (b) Plain head radiograph demonstrating the cochlear implant device for congenital sensorineural hearing loss (arrowhead). (c) Magnetic resonance images with a fluid-attenuated inversion recovery sequence revealing no obvious abnormal findings. (d) 18F-fluorodeoxyglucose-positron emission tomography depicting hypermetabolism in the right frontal lobe and parietal lobe (white arrows). (e) (123)I-iomazenil (IMZ) single-photon emission computed tomography showing decreased IMZ uptake in the right parietal lobe in a late image (white arrows).

On video electroencephalography (EEG), ictal EEG showed bilaterally synchronous high-amplitude spikes and wave bursts, dominant in the right hemisphere. Six seconds after spike burst appearance, the EEG exhibited a mild attenuation when the patient experienced a drop attack [Figure 2a]. Another ictal EEG showed background activity attenuation, followed by continuous poly spike-and-wave activities from the parieto-occipital region at C4 and P4 of the International 10–20 EEG system. During epileptiform discharges, the patient experienced an atonic seizure in the left upper limb and left eyelid myoclonia [Figure 2b].

From multimodal examinations, we considered that ictal discharges originating from the entire right hemisphere abruptly propagated to the left hemisphere, resulting in synchronous discharge on both sides and a clinical drop attack; thus, a Stage II evaluation placing a chronic subdural electrode on the entire right hemisphere was deemed complicated, while placing a chronic subdural electrode was considered too invasive for a 9-year-old boy with severe cognitive impairment. Therefore, we focused on the drop attack as main symptom and decided to perform a CC.

The patient underwent a front 2/3 CC. The cochlear implant magnet was removed again and replaced by a nonmagnetic titanium plug by an otolaryngologist just before the CC, and a new magnet was inserted after the postoperative MRI was performed the next day. After CC,

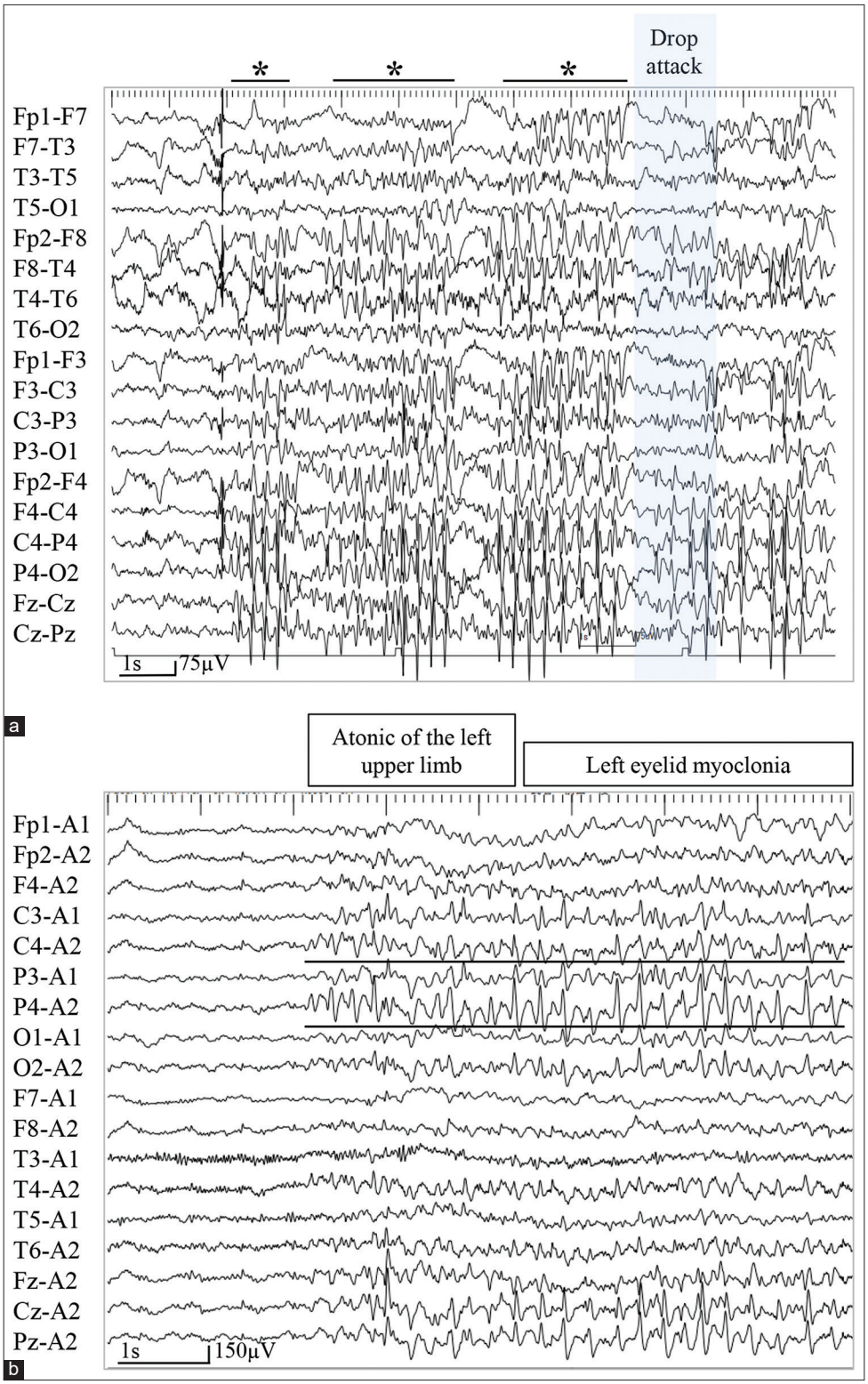

Figure 2: (a) On video electroencephalogram (EEG), ictal EEG showing bilaterally synchronous high-amplitude spike and wave bursts, right hemisphere dominant (Asterisks). Six seconds after the appearance of spike bursts, the EEG shows a mild attenuation when the patient shows a drop attack (blue box). (b) Another ictal EEG revealing background activity attenuation, followed by continuous poly spike-and-wave activities from the parieto-occipital region at C4 and P4 of the International 10–20 EEG system (black lines). The patient experienced an atonic seizure of the left upper limb and left eyelid myoclonia during epileptiform discharges.

Table 1: Cases presenting epilepsy associated with Waardenburg syndrome Type I.

No.	Reference	Age (epilepsy onset)	Sex	Classification of seizure type	EEG findings	Image findings	Developmental delay	Drug at evaluation of outcome	Surgery	Outcome
1	Cantani *et al.*, 1989	2.5 years	F	N/A	Diffuse abnormalities in the left temporal region	N/A	+	N/A	-	N/A
2		4 months	N/A	Generalized onset	Bilaterally synchronous spike-wave complexes	N/A	+	PB	-	N/A
3	Suzuki *et al.*, 2018	5 months	M	Generalized onset	No abnormal findings	Delayed frontal lobe myelination in MRI	+	VPA	-	Seizure free (2 years after medication)
4	Present case	4 years	M	Generalized onset	Bilaterally synchronous spike and wave bursts, right hemisphere dominant	Hypermetabolism in the right frontal lobe and parietal lobe in PET, decreased IMZ uptake in the right parietal lobe in a late image in SPECT	+	LEV, VPA, PRP, CLB, ESM	CC	Seizure free (1 year after surgery)

M: Male, F: Female, N/A: Not available, PB: Phenobarbital, LEV: Levetiracetam, VPA: Valproate, PRP: Perampanel, CLB: Clobazam, ESM: Ethosuximide, CC: Corpus callosotomy

the frequency of drop attacks gradually decreased. Seven months after the CC, the drop attack disappeared. One year after CC, the patient became seizure free. Interictal EEG at 1 year after CC showed less frequent and lower amplitude asynchronous spike and wave bursts, right hemisphere dominant, than before surgery [Figure 3]. Throughout the 2 years of postoperative follow-up, he remained seizure free and under treatment with 300 mg of LEV, 500 mg of VPA, 6 mg of PRP, 10 mg of CLB, and 500 mg of ESM. Further, his hearing ability through the cochlear implant showed no noticeable changes after CC.

DISCUSSION

WS has been reported to be caused by mutations in six genes: *PAX3, MITF, EDN3, EDNRB, SOX10,* and *SNAI2*,[6,11] and the WS type I is mostly caused by loss-of-function mutations in the *PAX3* gene.[6] In our case, the patient was clinically classified as having WS type I without genomic examination.

Epilepsy is one of the most common findings in genetic dysmorphic syndromes and more than one-third of these patients have drug-resistant epilepsy.[2] However, it is rare for epilepsy to coexist with WS type I, probably because WS Type I is characterized by defects in neural crest-derived tissues. To date, only three epileptic patients with WS Type 1 have been reported [Table 1].[3,12] Suzuki *et al.*[12] reported a 5-month-old boy who developed an attack of generalized seizures. After sodium VPA administration, the seizure stopped at 3 years of age. They speculated that epilepsy was due to delayed myelination caused by gene mutations,[1,4,13] and that seizures might stop as immature myelination gradually develops.[12] Cantani *et al.*[3] reported two epileptic patients with diffuse EEG abnormalities. Although they did not demonstrate the epileptogenesis of these patients,

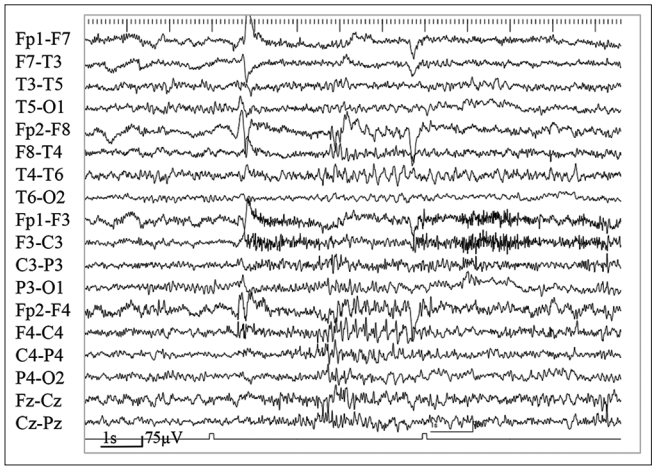

Figure 3: Interictal electroencephalogram showing right hemisphere dominant less frequent and lower amplitude asynchronous spike and wave bursts than before corpus callosotomy.

cortical involvement was highly suspected, considering that both patients had developmental delay. The present case is also complicated by severe cognitive impairment and it is considered that additional disorders of the cerebral cortex are involved in the epileptogenesis.

In the present case, seizure became drug resistant. We considered that, with multimodal examination, ictal discharges originating from the right entire hemisphere propagated to the left, resulting in synchronous discharge and a clinical drop attack, leading to an indication for CC. This hypothesis was later supported by the postoperative seizure outcomes and EEG findings. Here, we describe the first case of a WS Type I patient who underwent CC for drug-resistant epilepsy and achieved seizure freedom. To the best of our knowledge, this is the first case of CC in a cochlear implant recipient. If a patient is a cochlear implant recipient, such as in the present case, a multidisciplinary team of neurosurgeons, otolaryngologists, and speech-language hearing therapists is necessary to ensure the patient receives maximum benefit from the intervention.

CONCLUSION

When patients with WS Type I and cognitive impairment show drug-resistant epilepsy, clinicians should consider a preoperative evaluation.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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