DOOR syndrome concomitant with non-convulsive status epilepticus and hyperintense cerebellar cortex on T2-weighted imaging

Takayasu Nomura *, Norihisa Koyama, Machiko Yokoyama, Atsuko Awaya, Kenji Yokochi

Department of Pediatrics, Toyohashi Municipal Hospital, Hachiken-nishi, Aotake, Toyohashi, Aichi 441-8570, Japan

Abstract

We report a case study of an 11-year-old Japanese boy with complex partial status epilepticus, a type of non-convulsive status epilepticus, concomitant with DOOR syndrome. To our knowledge, this is the first report of this type of epilepsy concomitant with DOOR syndrome. Magnetic resonance (MR) imaging showed diffuse atrophy of the cerebellar cortex. The cerebellar cortex was hyperintense on T2-weighted imaging. This finding of MR imaging is rare and has been considered pathognomonic for infantile neuroaxonal dystrophy and Marinesco–Sjögren syndrome which are in the entity of metabolic disease. So this lesion may be the result of a metabolic defect occurring in conjunction with DOOR syndrome.

Keywords: DOOR syndrome; Non-convulsive status epilepticus; Cerebellar atrophy

1. Introduction

DOOR syndrome is a very rare syndrome characterized by mental retardation, sensorineural deafness, and dysplastic nails and distal phalanges of the hands and feet. The syndrome is considered to have been first reported in 1970 [1,2], but the acronym DOOR is believed to have been coined in 1975 [3]. To date, only about 30 cases worldwide have been reported. Although the etiology of DOOR syndrome remains largely unknown, decreased activity of 2-oxoglutarate decarboxylase in fibroblasts and white blood cells due to a recessive genetic defect have been implicated, and elevated plasma and increased urinary levels of 2-oxoglutarate have been found in several cases [4,5].

We report on an 11-year-old Japanese boy with DOOR syndrome which may be related to his non-convulsive status epilepticus (NCSE), and hyperintense lesions in the cerebellar cortex revealed on T2-weighted magnetic resonance (MR) imaging. To our knowledge, this is the first report of DOOR syndrome concomitant with this type of epilepsy.

2. Case report

The patient, the first child of nonconsanguineous Japanese parents, was born at term weighing 2715 g after an uneventful pregnancy and delivery. Neither his parents, grandparents nor younger brother had any dysmorphic features. At birth, all of his fingernails and toenails were absent. At 2 months old he showed no response when presented bilaterally with 85 dB stimuli in a brainstem auditory evoked response test. His psychomotor development was delayed; he could not sit independently until 11 months old nor walk unaided before 20 months old. At 3 years 6 months, he achieved a development quotient score of 55 (Postural-Motor area of 48, Cognitive-Adaptive area of 62, and Language-Social area of

* Corresponding author. Tel.: +81 532 33 6111; fax: +81 532 33 6177.
E-mail address: nomura332000@ybb.ne.jp (T. Nomura).
on the revised Kyoto scale of psychological development and was assessed as being mildly behind in his mental development. He was also diagnosed with autism spectrum disorders before the age of 4 years.

At 11 years old, his height (135 cm), body weight (31.3 kg), and head circumference (52.5 cm) were all within normal range. His thumbs were unusually long, and looked like fingers with an extra flexor skin crease because of the presence of an extra phalanx between the proximal and distal phalanges. On each hand, the nails on the middle and ring fingers were hypoplastic and the nail on the little finger was rudimentary, while the nails on his thumbs and index fingers and on all of his toes were absent (Fig. 1A). At age 10, dermatoglyphic investigations revealed arches on all fingertips. Radiological examination revealed tri-phalangeal thumbs and hypoplastic terminal phalanges in all the fingers of each hand but the terminal phalanx of the left ring finger was separated (Fig. 1B).

His seizures first occurred at 2 months of age. Although several anti-epileptic drugs including phenobarbital, clonazepam and carbamazepin excluding phenytoin were administered, the seizures were not suppressed. He had multiple types of seizures; generalized tonic seizure, visual hallucination following generalized tonic-clonic seizure, and unresponsiveness all occurring intermittently within a few minutes. During such periods an interictal electroencephalogram (EEG) showed independent bilateral occipital spikes. Additionally, prolonged seizures typically continuing for a few hours occurred a few times every few months during which he would become dull and emotionally labile laughing or crying regardless of external stimuli. Associated with these ‘mood changes’, unusual movements including twitching of his eyelids, jerking of his extremities and difficulties in standing or walking were observed. Sometimes, an intravenous injection of diazepam (0.5 mg/kg bolus) followed by a continuous infusion of midazolam (1–5 µg/kg/min) was needed to stop these seizures. EEGs taken during these prolonged seizures revealed persistent high-voltage theta and high-voltage delta waves with a 2.5-Hz spike and a wave complex which was focused at the left frontal area (Fig. 2). The spike and wave complex abated following the administration of diazepam. These episodes were diagnosed as complex partial status epilepticus (CPSE) [6]. The abnormal behaviors which occurred during these episodes were interpreted as being caused by impaired consciousness and the motor symptoms were not thought to have originated directly from an epileptic process but instead to have been involuntary movements associated with consciousness disturbance. Continuous infusion of midazolam has been necessary a few times each year.

Routine blood and urine laboratory analyses did not indicate any abnormalities. Analysis of urinary organic acids, including 2-oxoglutarate, also indicated no abnormalities. Chromosome analysis revealed he had a normal male karyotype. Ultrasound images of his heart and kidney were normal. MR imaging of the brain at 8 years of age showed diffuse atrophy of the cerebellar cortex. The cerebellar cortex and a part of the subcortical white matter were hyperintense on T2-weighted imaging (Fig. 3). All of these observations were unchanged from a previous examination at 7 years old. Unfortunately, no other neurological images had been obtained prior to these.

3. Discussion

DOOR syndrome is a very rare inherited syndrome, and its etiology has not been fully elucidated. Rajab [5] proposed two types of DOOR syndrome. Type I is characterized by increased 2-oxoglutarate levels in the
urine, early onset of seizures, and a progressive course leading to blindness, deafness and early death. Type II is characterized by the absence of organic acid abnormalities and only a mild neurological involvement. Our case was definitively diagnosed as DOOR syndrome due to the physical features of the patient, and as type II because there were no organic acid abnormalities and the course was mild.

In many of the reported cases of DOOR syndrome, the seizures were either uncontrollable [4,5,7] or critical [4,5]. However, the types of seizure were not precisely described. In the present case, the patient suffered from CPSE, a type of NCSE, which as far as we know has never previously been reported in conjunction with DOOR syndrome. This type of status epilepticus is thought to be unique among the range of epileptic seizures [6]. It can therefore be noted that DOOR syndrome has been found concomitant with NCSE in this case.

Patton [4] reported increased levels of 2-oxoglutarate in the plasma and urine of three patients with DOOR syndrome. The role of 2-oxoglutarate in the pathogenesis of DOOR syndrome has not yet been determined. An increased level of 2-oxoglutarate in urine has also been reported in other patients [5,8]. Surendran et al. [8] demonstrated a deficiency in the E1 component of the 2-oxoglutarate dehydrogenase complex, a catalyzer of 2-oxoglutarate to succinyl CoA, in four patients. Multiple placental cysts on the fetal side of the placenta may be related to the pathogenesis of DOOR syndrome [5]. Increased presence of 2-oxoglutarate in urine and plasma has also been reported for other metabolic disorders such as Zellweger syndrome and glutaric aciduria type II.

With regards to previous reports on MR imaging of the brain of patients with DOOR syndrome, delayed myelination and some loss of the gyral folds were observed in a girl with type I DOOR syndrome [5]. Presence of cavum septum pellucidum and persistent cavum vergae [7], and cerebellar and pontine hypoplasia [9] has also been reported. Cerebellar atrophy has been reported in patients with epilepsy [10]. The cause of the atrophy is controversial because it remains unclear.

Fig. 2. Ictal EEG during NCSE episode at age 8 years. High-voltage theta and delta waves with a 2.5-Hz spike and a wave complex focused at the left frontal area are shown.

Fig. 3. Brain MRI at 8 years of age. Diffuse atrophy of cerebellar cortex and hyperintense lesion of the cerebellar cortex and a part of the subcortical white matter on T2-weighted imaging.
as to whether such cerebellar atrophy results from phenytoin toxicity or the effects of recurrent seizures. So it is unclear whether the cerebellar atrophy of our case has a similar origin as those previously reported [9] or is the result of recurrent seizure or of the etiology of DOOR syndrome itself.

Hyperintense cerebellar cortex visible on T2-weighted imaging is a rare finding and has been considered pathognomonic for infantile neuroaxonal dystrophy [11] and Marinesco–Sjogren syndrome [12] which is in the entity of metabolic disease. So the finding that our case of DOOR syndrome has a similar lesion is very interesting. As with organic acid abnormalities and placental cysts of other patients, the hyperintense cerebellar cortex on T2-weighted imaging of our case may suggest the involvement of DOOR syndrome with metabolic disease. The main role of neuroimaging in NCSE remains that of identifying structural abnormalities such as focal cortical dysplasia, vascular disease, neoplasm and others [13]. As such, interpretation of the cerebellar MR imaging of this case of NCSE is unclear. Accumulation of such images of NCSE patients may be useful to define the etiology of this rare inherited syndrome.

Acknowledgements

We would like to thank Professor Seiji Yamaguchi and Dr. Mitsuru Endo (Shimane University, Japan) for confirming the urine organic acid pattern in our patient. We also thank Dr. Kyoko Hoshino who diagnosed this patient as DOOR syndrome and referred him to us.

References