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Delayed Diagnosis of Chromosome 22q11.2 Deletion Syndrome Due to Late-Onset Generalized Epilepsy

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Dear Editor,

A 36-year-old man presented with the sudden loss of consciousness. Eyewitnesses reported that he had abruptly collapsed and became rigid with hyperextension of both his arms and legs. His consciousness returned after a few minutes, but he remained detached for several minutes. He also complained of intermittent involuntary twitching of both arms and legs that had first appeared 1 year previously. However, he had no history of seizure, obvious cognitive impairment, or psychiatric disorder. He also denied a history of recurrent infections.

A physical examination revealed a short stature, fullness of the eyelids, a broad nasal bridge, and malar flatness (Fig. 1A). The initial blood investigations revealed hypocalcemia, with a total serum calcium level of 6.1 mg/dL (normal range: 8.8−10.5 mg/dL) and a calcium-ion level of 0.79 mmol/L (normal range: 1.05−1.35 mmol/L). The subsequent workup showed raised serum phosphorous (4.8 mg/dL, normal range: 2.5−4.5 mg/dL) and an inappropriately low level of parathyroid hormone (<5 pg/mL; normal range: 10−65 pg/mL). His total 25-hydroxy vitamin D and thyroid stimulation hormone levels were within the normal ranges, as was his serum magnesium level (1.6 mEq/L, normal range: 1.5−2.5 mEq/L). His spot urine calcium level was 6.1 mg/dL, while his 24-hour urine calcium level was 95 mg (normal range: 170−180 mg/24 hours). An electrocardiogram showed prolongation of the QT interval. He underwent 24-hour video-electroencephalography (EEG) for the differential diagnosis, which showed a nearly continuous fast background rhythm and interictal activity consisting of bifrontal symmetrical spike-and-wave discharges (Fig. 1B).

The presence of hypoparathyroidism and distinctive facial features resulted in a clinical suspicion of chromosome 22q11.2 deletion syndrome. Additionally, abdominal computed tomography showed an atrophied right kidney and a compensatory hypertrophied left kidney (Fig. 1C). A fundoscopic examination performed by an ophthalmologist revealed macular atrophy of the left eye. Although echocardiography revealed no cardiac or aortic-arch anomalies, and none of his family members had any symptoms suspicious of chromosomal deletion syndrome, chromosome 22q11.2 deletion was confirmed by fluorescence *in situ* hybridization (Fig. 1D). The patient was treated with calcium carbonate, calcitriol, and valproate, after which his hypocalcemia recurred intermittently; however, there were no symptoms suggestive of seizure.

Chromosome 22q11.2 deletion syndrome is the most common microdeletion syndrome in humans that is clinically variable.[1,2] The variations in the signs and symptoms of this syndrome have resulted in different features being described as separate conditions, such as DiGeorge syndrome and velocardiofacial syndrome.[3] Its various phenotype expressions make diagnosis difficult.

Hypocalcemia is one of primary features of chromosome 22q11.2 deletion syndrome, and it generally improves during infancy due to hypertrophy of the parathyroid glands.[4] However, there have been several reports of late-onset hypocalcemia associated with this syndrome,[5]

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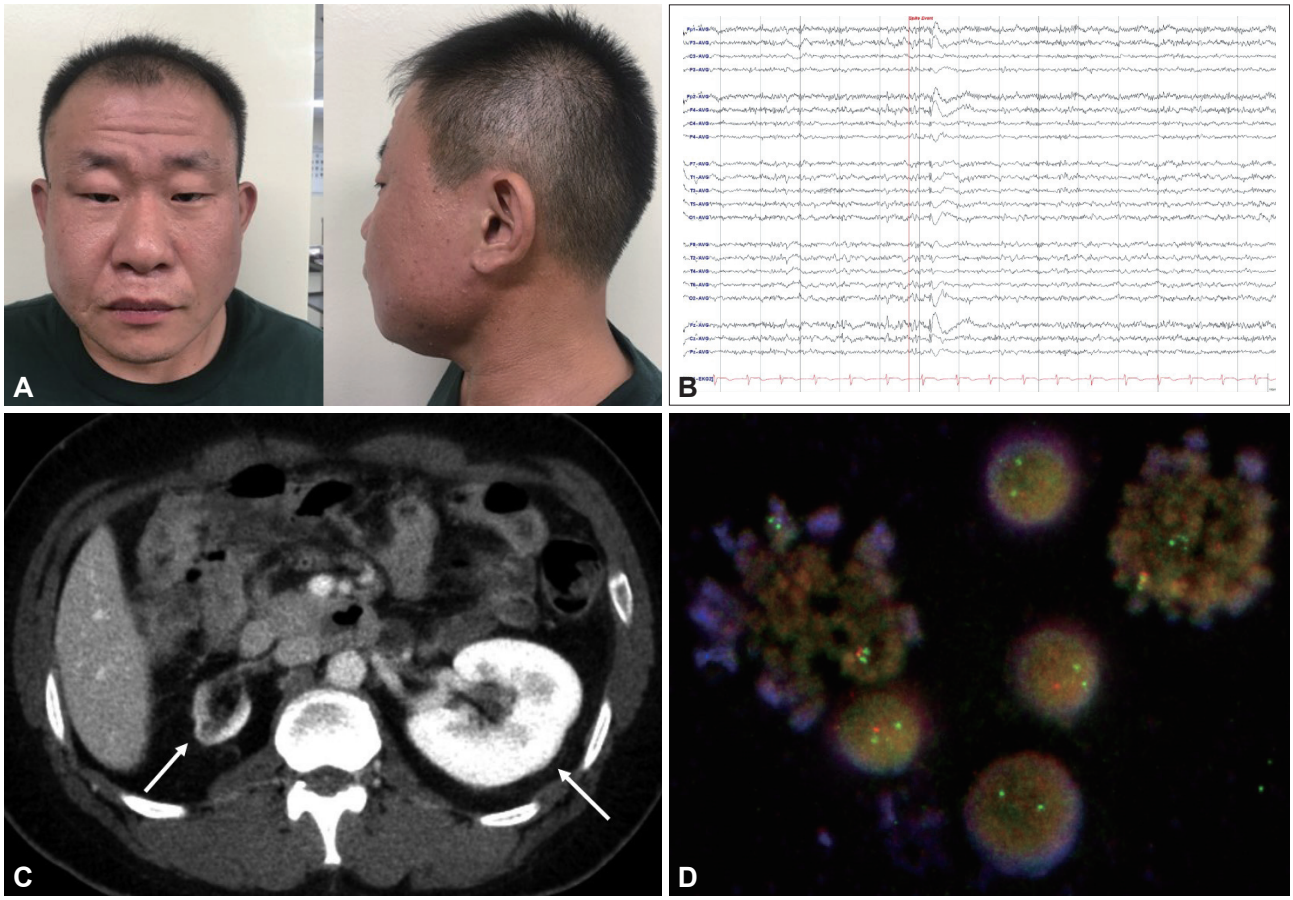

Fig. 1. Clinical features and laboratory findings of 22q11.2 deletion syndrome. A: Dysmorphic facial features of the patient, including of fullness of eyelids with short palpebral fissures, malar flatness, broad nasal bridge, broad nasal tip and protuberant ears. B: The EEG showed a nearly continuous fast background rhythm. Interictal activity consisted of bifrontal symmetrical spike-and-waves. C: Abdominal computerized tomography scan revealed atrophied right kidney and compensatory hypertrophied left kidney (arrows). D: A two-color metaphase (Vysis) after FISH with a dual TUPLE1 red spectrum/ARSA green spectrum probe. The normal 22 chromosome had two red signals meanwhile the deletion 22q11.2 chromosome had one red signal. FISH: fluorescence *in situ* hybridization.

and there are a few case reports of chromosome 22q11.2 deletion syndrome with late-onset hypocalcemia and seizure. Hypocalcemia in chromosome 22q11.2 deletion syndrome, hypocalcemia could enhance the neuronal excitability, and so the physician should treat electrolyte imbalances. However, the correction of hypocalcemia does not always result in complete seizure control.[6] In addition, there have been a few reports on the tendency of patients with chromosome 22q11.2 deletion syndrome to display a predisposition to genetic generalized epilepsy.[7] The clinical pattern of seizures and the age at onset also vary in this syndrome, and so antiepileptic therapy should be considered.

Our patient experienced an acute onset with brief loss of consciousness, and EEG revealed interictal epileptiform discharges emanating bilaterally from the frontal regions. These findings suggest that our patient had generalized epilepsy. A particularly interesting observation was that the administration of valproate induced repeated hypocalcemia whereas seizure was not observed. This suggests that the seizures that can occur in this syndrome are not only due to hypocalcemia.

In conclusion, the phenotypes that appear in chromosome 22q11.2 deletion syndrome may vary widely, and the symptoms may be different in each case. The present case demonstrates that if generalized epileptic seizure occurs in an adult, chromosome 22q11.2 deletion syndrome should be considered as a possible rare cause that may require antiepileptic drug treatment.

Author Contributions

Conceptulization: Tae-Joon Kim, Sang-Kun Lee. Investigation: Eung-Joon Lee, Seon-Kyung Lee. Supervision: Tae-Joon Kim. Writing—original draft: Seon-Kyung Lee, Kyoung-Hyun Kwun. Writing—review & editing: Eung-Joon Lee.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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