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Case report

A patient with DiGeorge syndrome with spina bifida and sacral myelomeningocele, who developed both hypocalcemia-induced seizure and epilepsy

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ABSTRACT

DiGeorge syndrome – a component of the 22q11 deletion syndrome – causes a disturbance in cervical neural crest migration that results in parathyroid hypoplasia. Patients can develop hypocalcemia-induced seizures. Spina bifida is caused by failure of neurulation, including a disturbance in the adhesion processes at the neurula stage. Spina bifida has been reported as a risk factor for epilepsy.

We report, for the first time, the case of a patient with DiGeorge syndrome with spina bifida and sacral myelomeningocele, who developed both hypocalcemia-induced seizures and epilepsy. The patient had spina bifida and sacral myelomeningocele at birth. At the age of 13 years, he experienced a seizure for the first time. At this time, the calcium concentration was normal. An electroencephalogram (EEG) proved that the seizure was due to epilepsy. Antiepileptic medications controlled the seizure. At the age of 29, the patient's calcium concentration began to reduce. At the age of 40, hypocalcemia-induced seizure occurred. At this time, the calcium concentration was 5.5 mg/dL (reference range, 8.7–10.1 mg/dL). The level of intact parathyroid hormone (PTH) was 6 pg/mL (reference range, 10–65 pg/mL). Chromosomal and genetic examinations revealed a deletion of TUP-like enhancer of split gene 1 (*tuple1*)—the diagnostic marker of DiGeorge syndrome. Many patients with DiGeorge syndrome have cardiac anomalies; however, our patient had none.

We propose that the association among DiGeorge syndrome, spina bifida, epilepsy, cardiac anomaly, 22q11, *tuple1*, and microdeletion inheritance should be clarified for appropriate diagnosis and treatment.

1. Introduction

DiGeorge syndrome (Online Mendelian Inheritance in Man (OMIM), #188400) is a congenital disorder that is mainly caused by deletion of chromosome 22q11.2. Patients can exhibit various anomalies, such as parathyroid hypoplasia, thymic hypoplasia, and cardiac outflow tract defects, due to a disturbance in cervical neural crest migration into the derivatives of the pharyngeal arches and pouches.[1] Patients with DiGeorge syndrome can develop hypocalcemia-induced seizure due to parathyroid hypoplasia. Spina bifida is caused by failure of neurulation, including a disturbance in the adhesion processes at the neurula stage.[2] Spina bifida has been reported as a risk factor for epilepsy.[3] There have been some case reports of DiGeorge syndrome with spina bifida and subsequent meningocele or myelomeningocele.[4–7] However, spina bifida has not been described as a complication of DiGeorge syndrome in standard textbooks of pediatrics[8] or endocrinology,[9] though both developed neural migration and adhesion disturbance.

Here, we report the case of a patient with DiGeorge syndrome with spina bifida and sacral myelomeningocele, who developed both hypocalcemia-induced seizures and epilepsy. We discuss the possible association between these anomalies and their symptoms.

1.1. Case report

The patient was male and was born with spina bifida and sacral myelomeningocele in Japan in 1969. At the age of 7 months, he underwent surgery for sacral myelomeningocele. In 1982, at the age of 13 years, he experienced a seizure for the first time. At this

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time, the calcium concentration was normal. On electroencephalogram (EEG) examination, the seizure was found to be caused by epilepsy. Antiepileptic medications controlled the seizure. In 1998, at the age of 29, the patient's calcium concentration began to reduce and dropped to 8.3 mg/dL (reference range, 8.7–10.1 mg/dL). In 2005, at the age of 36, this concentration reduced to 7.1 mg/dL. In 2009, at the age of 40, the patient began to experience seizures approximately once a month. In August 2009, he visited the emergency department of our hospital because he experienced generalized seizure. At this time, his calcium concentration was 5.5 mg/dL. The level of intact parathyroid hormone (PTH) was 6 pg/mL (reference range, 10–65 pg/mL). The parathyroid glands were not detected on neck echograms and enhanced computed tomography (CT) scans. Chromosomal and genetic examinations revealed a deletion of TUP-like enhancer of split gene 1 (*tuple1*). Tuple1 is a putative transcriptional regulator isolated from DiGeorge syndrome critical region on the human chromosome 22q11[10] and is a diagnostic marker of DiGeorge syndrome.[11] On the basis of these results, we established the diagnosis of DiGeorge syndrome. On treatment with the active form of vitamin D at a dose of 2 μg/day, the patient's calcium concentration was normalized and the seizures disappeared.

At the age of 40, the patient had severe mental retardation. Head CT did not reveal enlargement of the cerebral ventricles or any other anomalies. The patient's height was 146 cm and his weight, 66.0 kg; thus, his body mass index (BMI) was 31.0 kg/m^2. The face had the typical appearance associated with DiGeorge syndrome; low-set ears and telecanthus. The thyroid gland could not be seen on neck echograms and enhanced CT scans, though the thyroid hormones were within normal limits. He had repeatedly suffered from respiratory and urinary tract infections since birth. Systemic skin candidiasis was also observed. No cardiac anomalies were detected by cardiac echography and enhanced CT. The plasma concentration of brain natriuretic peptide (BNP) was 5.8 pg/mL (reference range, 0.0–18.4 pg/mL). CT revealed sacral spina bifida. The patient also had a progressive urethral fissure and stricture. He had no family history of facial abnormalities, repeated infection, seizures, or cardiac anomalies. His mother was not an alcoholic when she was pregnant with him.

2. Discussion

Here, we report, for the first time, the case of a patient with DiGeorge syndrome with spina bifida and sacral myelomeningocele, who developed both hypocalcemia-induced seizures and epilepsy.

DiGeorge syndrome is a component of the chromosome 22q11.2 deletion syndrome and the most common microdeletion syndrome in humans, with an incidence of 1 in 4000.[12] The chromosome 22q11.2 deletion syndrome includes DiGeorge syndrome, velocardiofacial syndrome, and CATCH-22 syndrome (cardiac defects, abnormal facies, thymic hypoplasia, cleft palate, and hypocalcemia).[1] Therefore, patients with DiGeorge syndrome can present various features.

Neural tube defects, including spina bifida, have a multifactorial etiology encompassing both genetic and environmental components. With a birth incidence of approximately 1 in 1000, these defects are the second most common type of birth defects after congenital heart defects.[13] Neural tube defects are of 2 types: (a) spina bifida occulta – a bony defect of the spine covered by normal skin – is a mild form of spina bifida and is often asymptomatic, and (b) open spina bifida – also known as spina bifida cystica or myelomeningocele – is a severe form and often accompanies anencephaly or Arnold-Chiari malformation.[13]

There have been some case reports of DiGeorge syndrome with spina bifida and subsequent meningocele or myelomeningocele.[4–7] Nickel reported cases of 3 unrelated patients with chromosome 22q11 deletion syndromes—2 with velocardiofacial syndrome and 1 with DiGeorge syndrome—who had neural tube defects.[7] This author recommended that for all children with neural tube defects and congenital heart defects, cytogenetic and molecular studies should be performed to detect chromosome 22q11 deletions. However, in a follow-up study of 295 patients with spina bifida, Nickel and Magenis concluded that 22q11 deletion is an infrequent cause of neural tube defects.[14] Nevertheless, to the best of our knowledge, this study by Nickel and Magenis has been the only one to examine the association between neural tube defects and 22q11. Another study may reveal a positive association between neural tube defects and the DiGeorge syndrome, since both developed neural migration and adhesion disturbance.

There have been some studies on spina bifida and epilepsy. Okuroeska studied the cases of 86 patients with myelomeningocele: a standard EEG obtained in the waking state revealed that 53 patients (62%) showed generalized changes—19 (79%) had thoracic myelomeningocele; 28 (53%), lumbar myelomenigocele; and 6 (66%), sacral myelomeningocele.[3] Clinical practitioners should be aware of the association between myelomeningocele and epilepsy. However, Yoshida et al. reported no association between myelomeningocele and epilepsy; they found only myeloschisis – the most severe neural tube defect – to be associated with epilepsy.[15] The association between spina bifida and epilepsy should be further explored. González and Bautista reported that patients with DiGeorge syndrome without spina bifida can develop epilepsy with abnormalities on an EEG.[16] Thus, clinical practitioners should also be aware of the association between DiGeorge syndrome itself and epilepsy.

Neonatal hypocalcemia due to parathyroid hypoplasia is one of the primary features of DiGeorge syndrome.[8] However, in our patient, hypocalcemia was late onset, and there have been another reports of late onset hypocalcemia in DiGeorge syndrome.[17,18] The neonatal hypocalcaemia in DiGeorge syndrome generally improves over the 1st year of life as the parathyroid glands hypertrophy. Therefore, for those who survive, few older patients require ongoing calcium supplementation.[17] We infer that hypocalcemia become evident when hypertrophy cannot compensate hypoplasia.

In Japan, the cardiovascular manifestations of DiGeorge syndrome, especially tetralogy of Fallot, have received particular attention,[1] and there have been several reports regarding associated cardiovascular anomalies.[19–21] Roberts et al. reported that in humans and mice, the *tuple1* gene is expressed at a critical point during the development of the cardiac outflow tract and the neural crest.[22] Lu et al. identified 22q11 deletion in 14 of 84 (16.7%) patients with sporadic tetralogy of Fallot, and *tuple1* deletion in 13 of these 14 (92.9%) patients with 22q11 deletion.[23] Choi et al. reported that 44 of 61 (72.1%) patients with *tuple1* deletion exhibit congenital heart defects.[24] However, although our patient was Japanese and had *tuple1* deletion, he did not exhibit any cardiac anomalies. Maternal inheritance of 22q11 microdeletion has been reported as a risk factor for tetralogy of Fallot.[25,26] Therefore, in our patient, the 22q11deletion may have been paternally inherited or occurred sporadically. Further studies should be performed to determine the association among 22q11, the *tuple1* gene, and cardiac anomalies.

In conclusion, we propose that the association among DiGeorge syndrome, spina bifida, epilepsy, cardiac anomalies, 22q11, *tuple1*, and microdeletion inheritance should be clarified for appropriate diagnosis and treatment of DiGeorge syndrome.

Conflict of interest

None.

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