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Case report

A patient with ossification of the yellow ligament and ventriculomegaly with 22q11.2 deletion syndrome undiagnosed until adulthood

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ABSTRACT

A 44-year-old female developed mild gait disturbance. She had a history of a ventricular septum defect, deafness, epilepsy, schizophrenia and cataracts. Magnetic resonance imaging showed ventriculomegaly of the brain and lower thoracic spinal stenosis due to ossification of the yellow ligament (OYL). She was diagnosed as having 22q11.2 deletion syndrome (22q11.2DS) by chromosome analysis, and OYL was suspected to be a secondary symptom due to hypoparathyroidism. This is the first report of 22q11.2DS with OYL and ventriculomegaly. Since the present patient was not diagnosed until adulthood, we emphasize that we should keep this common but heterogeneous congenital disease in mind.

1. Introduction

22q11.2 deletion syndrome (22q11.2DS) is the most common chromosomal microdeletion disorder, which exhibits multiple symptoms including congenital heart disease, congenital anomalies, cognitive delay, immunodeficiency and hypoparathyroidism. Among chromosomal abnormalities, 22q11.2DS frequently shows congenital heart disease or cognitive delay next to Down syndrome [1]. Here, we report an adult case of 22q11.2DS with ossification of the yellow ligament (OYL) and ventriculomegaly.

2. Methods and results

2.1. Case report of ossification of the yellow ligament and ventriculomegaly with 22q11.2 deletion syndrome

A 44-year-old female developed gait disturbance at age 41. At age 44, she complained of pain in her back and lower limbs. Although she started rehabilitation, her gait disturbance and pain did not improve. Biochemical examination of blood revealed hypocalcemia (serum calcium level, 4.8 mg/dl). She started to take 1.5 μg/day alfacalcidol and 5 g/day calcium lactate, and was referred to our department for further examination. Then, it became clear she had multiple medical histories. She had a ventricular septum defect (cardiac VSD) at birth, which closed naturally. She developed deafness in her left ear in her high school days. She fell unconscious at home, and she has taken valproic acid (VPA) 400 mg/day and carbamazepine (CBZ) 100 mg/day since then. At age 32, when she was hospitalized, auditory hallucination and delusions appeared, and she was diagnosed as having schizophrenia, however, no antipsychotic drug was prescribed. After she turned 44, she had cataract surgery on her right eye. She exhibited juvenile behavior. She graduated from high school from a special class for handicapped students and had not done well at school. There was no relevant family history.

Neurological examination revealed external eye findings including upslanting palpebral fissures, hypertelorism and hooded eyelids. She had a left eye cataract. She complained of pain in her back and legs, but we could not clearly determine specific pain areas because of her vague complaint due to her immaturity. Mild muscle weakness was noted in both the iliopsoas and quadriceps femoris muscles. Patellar tendon reflexes were decreased. However, ankle reflexes were increased and bilateral Babinski's reflexes were noted. Bilateral superficial sensation was diminished from her thighs to her toes. Bilateral position sense of the lower limbs was also diminished and Romberg's sign was positive. She could walk by using a 4-point walker. The mini-mental state examination score was 23 and the full scale intelligence quotient score of the Wechsler adult intelligence scare-third edition was 53.

As to laboratory findings, the serum calcium level 7.8 mg/dl (serum albumin, 4.0 g/dl), the serum phosphorus level 5.5 mg/dl, and the platelet count 127,000/μl. Thyroid function was within the normal range (thyroid stimulating hormone, 3.58 μIU/ml; free-T3, 2.45 pg/ml; free-T4,

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1.30 ng/dl). Intact parathyroid hormone (PTH) was also within the normal range but low (9.52 pg/ml), and urinary calcium was 18.7 mg/dl (normal value: 3.6–31.2 mg/dl). Head MRI showed bilateral ventricular dilatation (Figure 1, A and B). The third ventricle might be slightly dilated. Spinal MRI showed lower thoracic spinal stenosis due to OYL at the height of the 11-12th thoracic vertebrae (Th11-12) (Figure 1, C and D).

We suspected 22q11.2DS from her medical histories and clinical symptoms, and it was confirmed by chromosome analysis (the FISH method) (Figure 1, E). Her parents have no chromosomal abnormality of chromosome 22. We judged that her gait and sensory disturbances were due to the lower thoracic spinal stenosis. Laminectomy for the Th11-12 vertebrae was performed, and she was transferred to a rehabilitation hospital. However, after rehabilitation, her gait remained the same. A ventriculoperitoneal shunt cannot be performed yet because of her psychiatric symptoms.

This study was approved by our institutional review board, and informed consent was obtained from the patient.

3. Discussion

Chromosomal analysis revealed that our patient has a de novo deletion of 22q11.2. Approximately 93% of probands have a de novo deletion of 22q11.2 and the other 7% have inherited the 22q11.2 deletion from a parent [2]. 22q11.2DS shows various symptoms including combinations of congenital heart defects, chronic infection, nasal regurgitation, hypernasal speech, hypocalcaemia, feeding difficulties, developmental and language delays, behavioural traits and learning disabilities [1]. Typical symptoms lead to diagnosis in infancy or childhood. However, patients with only mild symptoms are sometimes not noticed in childhood. In adolescence and adulthood, some symptoms such as behavioral abnormalities, psychiatric illness, hypocalcemia or learning difficulties can lead to the diagnosis of 22q11.2DS [1]. The presence of characteristic facial features can assist with identification at any age, however, the opportunity for diagnosis might be missed when typical craniofacial and other typical congenital features including cardiac or palatal abnormalities are absent [1].

Our patient had a history of cardiac VSD, hearing loss and a cataract, and she was immature and emotionally unstable. Moreover, the facial features of our patient are characteristic of 22q11.2DS. However, since she lacked palatal abnormalities and physicians did not recognize the facial features of this syndrome, her phenotype did not suggest 22q11.2DS. Other characteristic features in our patient were OYL and ventriculomegaly. Symptoms including scoliosis, clubbed feet, polydactyly and craniosynostosis have been reported as skeletal abnormalities of 22q11.2DS [3]. Cervical spine abnormalities, such as platybasia, fusion and/or block, anomalous dens, C2 swoosh or increased motion, have been reported previously [1]. However, there has been no report clearly mentioning OYL with 22q11.2DS so far, and thus this is the first case of 22q11.2DS with OYL and ventriculomegaly together. We presumed the OYL was a secondary complication of hypocalcemia due to hypoparathyroidism. Hypoparathyroidism is generally known as a common complication of 22q11.2DS, and OYL is a frequent complication of hypoparathyroidism. In this case, we presumed that the epilepsy and cataract were also secondary complications of hypocalcemia, and it was assumed that the hypocalcemia and low PTH value were due to hypoparathyroidism, which is known to be a general complication of 22q11.2DS.

Regarding the gait disturbance, we initially judged the cause was not ventriculomegaly but sensory ataxia and pain, because it was clear that OYL at the height of Th11-12 compressed the posterior spinal cord, and her position sense disturbance was also obvious. However, the postoperative process makes us suspect that her gait disturbance is due to gait apraxia caused by ventriculomegaly and that the gait disturbance is

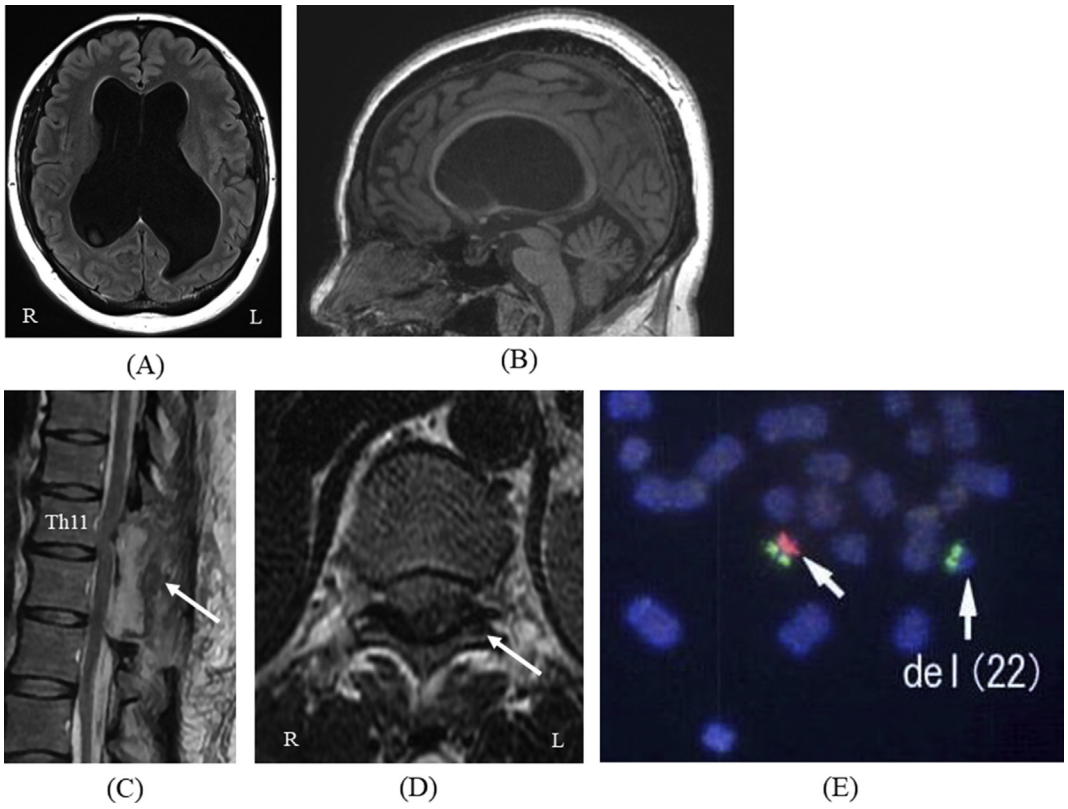

Figure 1. (A) and (B): Head MRI showed ventricular enlargement of the brain. (C) and (D): Spinal MRI showed lower thoracic spinal stenosis due to ossification of the yellow ligament (OYL) at the height of the 11-12th thoracic vertebrae (arrow). The stenosis was more marked at the height of the 11th thoracic vertebra on the left side than on the right side (arrow). (E): FISH analysis of blood metaphase lymphocytes from the patient. The blue ovals are chromosomes. The red signal shows the 22q11.2 lesion, and green signals show the 22q13 lesion. She had a chromosomal deletion on chromosome 22q11.2 (white arrows).

associated with her psychiatric alterations. Although we suspected impairment of cerebrospinal fluid circulation associated with 22q11.2DS, we could not obtain consent for cerebrospinal fluid examination. Elucidation of the pathomechanism underlying ventriculomegaly in 22q11.2DS requires further studies. In addition, her psychiatric symptoms and medical history of schizophrenia might be due to the ventriculomegaly because cerebral atrophy or ventricular enlargement is shown in 54% of cases of schizophrenia involving 22q11.2DS (22q11.2DS-Sz), as previously reported [4].

4. Conclusion

We describe a patient with 22q11.2DS undiagnosed until adulthood, and this is the first report of 22q11.2DS with OYL and ventriculomegaly. In cases having some characteristic symptoms, 22q11.2DS should always be considered for early diagnosis, and we should be careful as OYL or ventriculomegaly could be a complication.

Declarations

Author contribution statement

All authors listed have significantly contributed to the investigation, development and writing of this article.

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Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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