Case Report

Chiari Type I Malformation Caused by Craniometaphyseal Dysplasia

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Craniometaphyseal dysplasia is a rare genetic condition characterized by progressive thickening of bones in the skull and metaphyseal abnormalities in the long bones. This disorder often causes progressively symptomatic cranial nerve compression, but in rare cases foramen magnum stenosis may lead to quadriplegia. Chiari I malformation with craniometaphyseal dysplasia is extremely rare. The authors report on a 25-year-old woman with myelopathy due to Chiari I malformation along with craniometaphyseal dysplasia. There are only four previous case reports of this condition. The authors present here the fifth case report of this rare condition and summarize its characteristics.

Key words: craniometaphyseal dysplasia, Chiari malformation, cervicomedullary compression

Case Report

Patient history. A 25-year-old woman presented to our department with progressive quadriplegia over a 2-year period. She had had a normal delivery with a birthweight of 3,000g. Skeletal abnormalities were noted at birth; however, further diagnostics were not performed at that time. By 3 years of age, she had strabismus and amblyopia and was diagnosed with CMD at a national hospital. She experienced hearing loss by age 7, vertigo and tinnitus by age 13 and had surgery for facial nerve palsy when she was 21 years old. Gradually, she began suffering from neck pain, headache, nausea, and numbness of the hands, so she visited our hospital. She had no significant perinatal or family history.

Physical examination. On examination, she was able to walk without any support and had mild muscle weakness (MMT 4/5). She also had some sensory disturbance of her hands. All her extremities showed spasticity and hyperreflexia. The physical
examination revealed bossing of the forehead with bitemporal narrowing. She had vertigo, nausea and sleep apnea syndrome but no ataxia nor dysphasia. Other systems were clinically normal.

**Laboratory findings.** Laboratory findings were as follows: Ca, 9.3 mg/dl (reference range, 8.2–10.4 mg/dl); P, 5.4 mg/dl (reference range, 4.5–6.7 mg/dl); calcitonin (CT), 31 pg/ml (reference range: <100 pg/ml); parathyroid hormone (PTH), 43 pmol/L (reference range: 1.3–7.5 pmol/L); bone alkaliphosphatase, 51.1 U/l; urine NTx 45.9 nMBC.

**Imaging.** Plain radiographs of the cranial bone revealed increased bone density, hyperostosis and sclerosis of the calvarium, skull base and other bones (Fig. 1). The patient underwent magnetic resonance imaging (MRI), on which we identified Chiari I malformation and compression of the medulla (Fig. 2). Computerized tomography (CT) showed extreme thickness of the skull (Fig. 3). We diagnosed her as having Chiari I malformation with cranimetaphyseal dysplasia. Because of the severity of her disease and the risks associated with surgery, she has chosen to remain under careful observation at this time.

**Discussion**

 CMD is a rare genetic disorder of bone remodeling caused by a failure of osteoclasts, and determined by an autosomal dominant or recessive inheritance [4]. The dominant and mild form of this disorder is due to a gene abnormality in chromosome region 5p15.2–p14.1. This abnormality is located in the ankylosis (ANK) gene which encodes a protein involved in the transport of pyrophosphate into the bone matrix [5]. On the other hand, clinical features of autosomal recessive CMD with the gene abnormality located in chromosome region 6q21–22, the function of which is not yet known, are typically more severe than those of the autosomal dominant form [7]. The penetrance of CMD is close to 100%, and males and females are equally affected. CMD is so rare that epidemiology has not yet been established, so the exact occurrence rate is unclear.

CMD is often detected within the first few weeks of life because breathing or feeding problems occur due to choanal stenosis [8–11]. Its prominent clinical symptoms are characterized by certain facial features. Patients typically have a wide nasal bridge, paranasal bossing, wide-set eyes (ocular hypertelorism) with an increase in bizygomatic width, and a prominent mandible [4]. A long skull shape (dolichocephaly) resulting from fronto-occipital hyperostosis has also been reported. Progressive thickening of craniofacial bones continues throughout life as in our case. As a result, it often narrows the cranial foramina and rarely includes the foramen magnum. If this condition is not treated, compression of the cranial nerves can lead to disabling conditions such as facial palsy, blindness, or deafness [12]. Furthermore, associated Chiari I malformation can sometimes lead to severe headaches and myelopathy [4].

The diagnosis of CMD is based on clinical and radiographic findings [1], although blood tests are sometimes helpful because serum alkaline phosphatase and parathyroid hormone can be elevated [13], osteocalcin is usually decreased [14], and the blood calcium and phosphate concentrations are within normal limits [15]. Sequence analysis of the ANK gene detects mutation in approximately 90% of patients with CMD [16]. Differential diagnoses include metaphyseal dysplasia, craniodiaphyseal dysplasia, frontometaphyseal dysplasia and osteopathia striata with cranial sclerosis.

Individuals with typical autosomal dominant CMD have a normal life expectancy [4], while patients with the severe forms of CMD can expect a reduced life expectancy as a result of compression of the foramen magnum [3, 9]. Treatment consists primarily of surgery to reduce compression of cranial nerves, the brain stem and the spinal cord at the level of the foramen magnum [3, 9, 10]. Day et al. were the first to report a good surgical outcome of a CMD patient who also had the Chiari I malformation and compression of the medulla [4]. The cause of Chiari malformation associated with CMD is not clear, but its increased internal pressure may play an important role in herniation of the cerebellum. With our current report, there are only 5 case reports [3, 9, 10] of this condition. Table 1 is a summary of the 5 cases. Spastic quadriplegia beginning as a young adult is the typical clinical symptom. Two cases had a large syrinx which contributed to motor paralysis. The 4 cases with foramen magnum decompression surgery had good outcomes. Our patient, however, had neither a syrinx nor severe symptoms, so she declined our recommended surgical intervention and opted for continued
Fig. 1  Plain skeletal radiographs.  A, plain radiographs of the cranial bone revealed increased bone density (white arrow); B, spinal bone density of spine was increased; C, bony deformities and increased bone density were observed.
observation. Garvia reported that an increase in the cranial vault thickness may result in extremely high pressure of the dural sinuses and thus an increase in intracranial pressure [6]. The indication and timing for surgical intervention are controversial in patients with mild myelopathy, because FMD for this kind of patient potentially has a high risk of deterioration due to surgery and the high recurrence rate.

The Chiari malformation, which is defined as a cerebellar tonsil extension below the foramen magnum, was first described in 1891 by Chiari [19]. Many patients with Chiari malformation have no signs or symptoms and do not need treatment. However, some patients with Chiari malformation will have gait disturbances, numbness and tingling of the hands and feet, dizziness, dysphasia, and sometimes life-threatening problems. It is important to closely follow patients with mild symptoms so as not to miss the best timing for surgery [20]. Symptomatic Chiari I malformation with craniometaphyseal dysplasia is extremely rare, but it is important to survey cervical spine MRIs if patients have symptoms such as gait disturbance, numbness, dizziness, dysphasia and hyperreflexia.
Table 1 Patients’ demographic of CMD and Chiari I malformation

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Age</th>
<th>Gender</th>
<th>Symptom</th>
<th>Syrinx</th>
<th>Surgery</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day et al.</td>
<td>1997</td>
<td>15y</td>
<td>F</td>
<td>headache, spastic quadriplegia</td>
<td>Yes</td>
<td>Yes</td>
<td>Improve</td>
</tr>
<tr>
<td>Sewell et al.</td>
<td>2008</td>
<td>35y</td>
<td>F</td>
<td>cough, headache, neck stiffness, thoracic back pain, arm paraesthesia</td>
<td>Yes</td>
<td>FMD</td>
<td>Improve</td>
</tr>
<tr>
<td>Cai et al.</td>
<td>2008</td>
<td>11m</td>
<td>M</td>
<td>spastic quadriplegia</td>
<td>No</td>
<td>Yes</td>
<td>Improve</td>
</tr>
<tr>
<td>Garvia et al.</td>
<td>2011</td>
<td>6y</td>
<td>M</td>
<td>headache, loss of visual acuity</td>
<td>No</td>
<td>Yes</td>
<td>Improve</td>
</tr>
<tr>
<td>This study</td>
<td>2013</td>
<td>25y</td>
<td>F</td>
<td>headache, neck pain, nausea, arm numbness, spastic quadriplegia</td>
<td>No</td>
<td>No</td>
<td>–</td>
</tr>
</tbody>
</table>

CMD, craniometaphyseal dysplasia; FMD, foramen magnum decompression; CVE, cranial vault expansion.

References