CASE REPORT

Biopsy-proven multiple sclerosis in an adult patient with atypical craniometaphyseal dysplasia

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SUMMARY

Craniometaphyseal dysplasia (CMD) is a rare condition characterised by progressive, diffuse hyperostosis of cranial and long bones, with compression of cranial nerves, linked to mutations in *ANKH* or *GJA1* genes. Here we describe an adult case with clinical features of CMD, who developed cerebral expansive lesion of undetermined nature. Brain biopsy revealed active demyelinating lesions, consistent with multiple sclerosis. The genetic screening of target genes for CMD (*ANKH* and *GJA1*) resulted negative in this patient. The peculiar clinical association and the negativity of genetic analyses allow to hypothesise that other genetic causes, not already known, are responsible for the combination of these pathological conditions. Future studies aim to identify the genetic causes of CMD, which will be important to further understand the pathogenetic mechanism of this rare and invalidating disease.

BACKGROUND

Craniometaphyseal dysplasia (CMD) is a rare clinical condition characterised by sclerosing osseous dysplasia leading to progressive diffuse hyperostosis of cranial and long bones. The neurological manifestations of CMD are secondary to the progressive obstruction of the physiological course of cranial nerves, frequently leading to blindness and deafness. The diagnosis is based on clinical and radiological features, with observation of diffuse hyperostosis of the cranial bones, metaphyseal widening of long bones with thinned cortex and decreased bone density. In the majority of patients, CMD is linked to autosomal dominant mutations of the *ANKH*

gene in *de novo* cases.¹⁻³ More recently, the autosomal recessive form of CMD was linked to a novel homozygous missense mutation of *GJA1*.⁴ By now, in literature, case reports describing the association between CMD or other craniotubular dysplasias and multiple sclerosis (MS) or other demyelinating diseases of the central nervous system (CNS) are missing.

CASE PRESENTATION

Here we present a case of a male patient who developed in childhood clinical symptoms of a cranio-tubular disease resembling CMD, characterised by short stature, macrocephaly, brachydactyly of the fingers of the hand and hyperostosis of cranial and long bones (figure 1). With development, the patient presented with progressive bilateral blindness secondary to optic nerve compression, treated with surgical decompression of optical ducts, but without any benefit, and bilateral hearing loss due to stenosis of the acoustic duct. Patient's family history is negative for any neurological disease and no other subjects are affected by any cranio-tubular disease. His parents were consanguineous (cousins of second degree) and the patient does not have children. The mother is still alive and healthy, the father deceased several years ago due to cardiac disease.

At the age of 41, the patient presented with protracted dizziness by 2 weeks, with nausea, vomit and difficulty walking. Brain MRI revealed the presence of multiple hyperintense lesions in T2/FLAIR (Fluid attenuation inversion recovery) sequences in the bilateral periventricular white

Figure 1 Brain CT scan showing hyperostosis of cranial bones (A); lower limbs X-ray showing widening of the metaphyses and mild cortical thickening of femurs (B) and tibiae (C).

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Figure 2 First brain MRI scan showing hyperintense lesion (arrow) in the right medium cerebellar peduncle (FLAIR sequence; A)), with gadolinium contrast enhancement (B).

matter and the right medium cerebellar peduncle, characterised by moderate gadolinium contrast enhancement (figure 2). Spinal cord MRI was non-significant. Lumbar puncture resulted normal with absent oligoclonal bands. On suspicion of cerebral demyelinating lesions, the patient was treated with steroid therapy (methylprednisolone intravenous, 1 g per day for 5 days), with progressive amelioration of the symptoms.

Following 6 years of clinical stability without any symptoms, the patient presented with progressive left sensitive hemisyn-drome, characterised by paresthesia and moderate weakness of both limbs. Brain MRI revealed a cystic expansive lesion in the right paramedian frontoparietal region, without significant contrast enhancement (figure 3). On suspicion of a neoplastic lesion, stereotactic brain biopsy was assessed, revealing a demyelinating lesion in active inflammatory phase (figure 4).

OUTCOME AND FOLLOW-UP

The diagnosis of relapsing-remitting MS was confirmed and the treatment with interferon- β -1a weekly was started. He also presented with multiple episodes of transient left limbs pares-thesia, treated with levetiracetam 2 g daily with good response. The subsequent radiological follow-up with brain and spinal cord MRI did not reveal any additional lesion and the patient did not report any adjunctive symptom.

In the clinical suspicion of CMD, the patient underwent screening of known candidate genes. Given parental consan-guinity, we first analysed *GJA1*, which resulted negative for pathogenetic mutations. *ANKH* was then screened, to exclude any *de novo* mutation, but without any significant result.

DISCUSSION

In the case here described, the clinical and radiological features are primarily suspected for CMD. However, the negativity of genetic investigations and some clinical atypias, such as short stature and the absence of prominent metaphyseal flaring, put this diagnosis in doubt. As far as we know, there are no case reports about the association of CMD or other craniotubular diseases with demyelinating diseases of the CNS. It is possible that these two conditions coexist by chance in the patient here described.

However, in this case, the genetic screening of known caus-ative genes resulted negative. It is possible thus to speculate the presence of other, not yet known, genetic causes responsible for this complex clinical picture. Moreover, the mild radiolog-ical signs of this patient could be linked to mutations of other unknown gene with a less severe clinical effect. Further studies will be necessary to improve the knowledge of the pathogenetic mechanisms underlying the disease.

Figure 3 Second brain MRI scan 6 years later showing right posterior frontal lesion (arrow) in axial (A) and coronal (B) FLAIR sections, without contrast enhancement (C).

Figure 4 Brain biopsy showing reduction of cellular count (H&E stain; A), characterised by reactive gliosis (GFAP immunoreaction; B) and increase of CD68 + macrophages, observed also in the perivascular tissue (C).

Learning points

- ▶ Craniotubular disease with clinical features of craniometaphyseal dysplasia can be associated with demyelinating diseases of the central nervous system, such as multiple sclerosis.
- ▶ The screening of known causative genes resulted negative in this case, allowing to hypothesise other possible genetic causes still to be identified.
- ▶ Further studies are needed to improve the understanding of the pathogenetic mechanisms of this rare and invalidating disease.

Contributors JCDiF: clinical evaluation of the patient and clinical diagnosis. GI: histopathological diagnosis. MFB: clinical evaluation of the patient. BC: genetic examination.

Competing interests None declared.

Patient consent Obtained.

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REFERENCES

- 1 Nürnberg P, Thiele H, Chandler D, *et al*. Heterozygous mutations in ANKH, the human ortholog of the mouse progressive ankylosis gene, result in craniometaphyseal dysplasia. *Nat Genet* 2001;28:37–41.
- 2 Reichenberger E, Tiziani V, Watanabe S, *et al*. Autosomal dominant craniometaphyseal dysplasia is caused by mutations in the transmembrane protein ANK. *Am J Hum Genet* 2001;68:1321–6.
- 3 Baynam G, Goldblatt J, Schofield L. Craniometaphyseal dysplasia and chondrocalcinosis cosegregating in a family with an ANKH mutation. *Am J Med Genet A* 2009;149A:1331–3.
- 4 Hu Y, Chen IP, de Almeida S, *et al*. A novel autosomal recessive GJA1 missense mutation linked to Craniometaphyseal dysplasia. *PLoS One* 2013;8:e73576.

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