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Case Report

A case of papilledema in Camurati-Engelmann disease treated effectively with prednisolone

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Highlights

- To the best of our knowledge, this is the first case in which prednisolone was effective for ophthalmologic symptoms of Camurati-Engelmann disease (CED).
- Optic nerves should be evaluated by brain MRI STIR in addition to ophthalmic follow up in CED.

Abstract. Camurati-Engelmann disease (CED) causes bone pain, muscle weakness, and cranial nerve symptoms due to abnormal thickening of the long bones of the limbs and the cortex of the skull. The pathophysiology of CED is a gain-of-function variant of *transforming growth factor beta 1 (TGFB1)*. The ophthalmological symptoms of CED are usually caused by increased intracranial pressure and optic canal stenosis. Here, we report the case of a patient in whom prednisolone was effective against papilledema caused by CED. In this case, when papilledema was observed in both fundi, the patient showed increased bone pain, fever, and elevated CRP and ALP levels. Brain magnetic resonance imaging (MRI) revealed a high short tau inversion recovery (STIR) signal in both optic nerves, suggesting edematous changes. Prednisolone ameliorated bone pain, fever, and papilledema, resulting in a slight improvement of the visual function of the right eye. Our results suggest that prednisolone may be effective in treating ophthalmologic symptoms in addition to bone pain in patients with CED.

Key words: Camurati-Engelmann disease, *TGFB1*, prednisolone, visual function

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Introduction

Camurati-Engelmann disease (CED, MIM 131300) is characterized by intramembranous cortical thickening and fusiform hypertrophy of the diaphysis of the long bones, resulting in progressive bone sclerosis of the long bones and skull. Bone pain and muscle weakness are the typical symptoms of CED (1). Although its exact prevalence is unknown, more than 300 cases have been reported to date (1).

The inheritance of CED is autosomal dominant and is caused by CED, a gain-of-function variant of the *transforming growth factor B1* gene (*TGFB1*, MIM 190180). Fourteen missense variants have been reported previously (2, 3). In bone, TGFβ1 differentiates and proliferates osteoblast precursors. Furthermore, TGFβ1 suppresses the differentiation and activation of osteoclasts. Therefore, constitutive activated TGFβ1 signals result in systemic bone cortical thickening in CED (1).

Approximately 40% of patients with CED have cranial nerve deficits (1). These symptoms are caused by an overgrowth of the skull base, leading to foraminal stenosis and diminished cranial vault volume, resulting in neurovascular compromise and increased intracranial pressure. Ophthalmic manifestations including blurred vision, papilledema, proptosis, glaucoma, and subluxation of the globe have been observed (1, 4).

Glucocorticoid has been reported as effective in suppressing bone pain and muscle weakness and improving fatigue (3, 5–8). For ophthalmic symptoms, surgical treatment and/or oral acetazolamide were reported to be effective for nerve foramina stenosis and increased intracranial pressure (9, 10). However, to the best of our knowledge, there are no reports on the effectiveness of corticosteroids in treating ophthalmic symptoms of CED.

In the present study, we identified a novel variant of *TGFB1* in a patient with CED. Furthermore, in our patient, prednisolone was effective in treating papilledema and improved visual function.

Case Report

The patient was a 17-yr-old girl born to nonconsanguineous parents; the case had no family history of bone metabolic disease. CED was diagnosed during childhood based on difficulty walking, pain in the lower extremities, and cortical thickening of the diaphysis of the whole-body bone, as determined by radiographs. Due to the COVID-19 pandemic, it became difficult for her to visit the previous hospital, and she was referred to our hospital.

The patient's height and weight were 160.0 cm and 50.0 kg, respectively. She exhibited frontal bossing, a wide-based waddling gait, dolichostenomelia, arachnodactyly, and joint contractures of the knees, elbows, and wrists. Radiography of the lower limbs showed cortical thickening of the femur, fibula, and tibias (**Fig. 1**). She complained of fatigue. The bone pain persisted, and analgesics were administered regularly. At 18 yr of age, she had left eye (left) amaurosis fugax. Her visual acuity was normal at 1.2 (left) and 1.2 (right eye; right). A decrease in the size of the left internal isopter was also observed (**Figs. 2A, 2B**). Magnetic resonance imaging (MRI) revealed a short tau inversion recovery (STIR) coronal image showing enlargement of the subarachnoid space around the left optic nerve (**Fig. 3A**). There were no abnormalities in the head or neck vessels on MR angiography (MRA). Thereafter, bone pain gradually worsened. Simultaneously, the patient developed visual complaints including blurry left vision and bilateral decreased acuity, particularly in the left eye. Decimal visual acuity (VA) was 0.5 (left) and 0.8 (right) decimal visual acuity Ophthalmoscopy did not reveal bilateral papilledema at 19 yr of age. Computed Tomography (CT) showed the thickening of the entire skull (**Fig. 4A**). The optic canals narrowed bilaterally, and there was no difference in the degree of narrowing between the left and right canals (**Figs. 4B, 4C**). MRA did not reveal ophthalmic arterial stenosis (**Fig. 4D**). The left optic nerve showed high signal intensity on the STIR image (**Fig. 3B**). At 20 yr of age, the patient complained of intermittent fever and increased bone

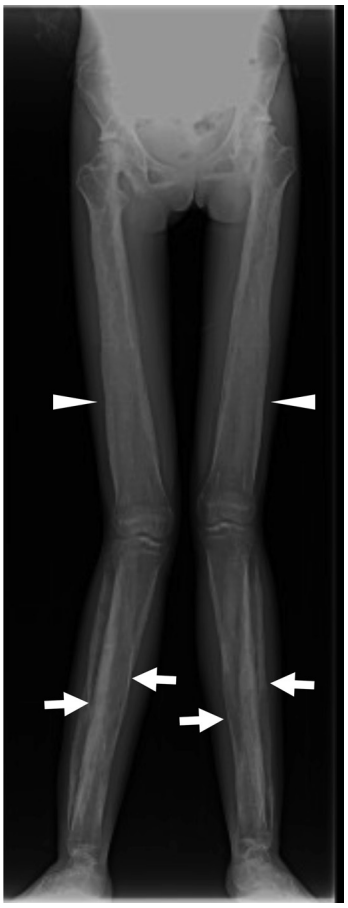

Fig. 1. Radiography of the lower limbs shows cortical thickening of both femurs (arrowhead), fibula (arrow), and tibia (arrow).

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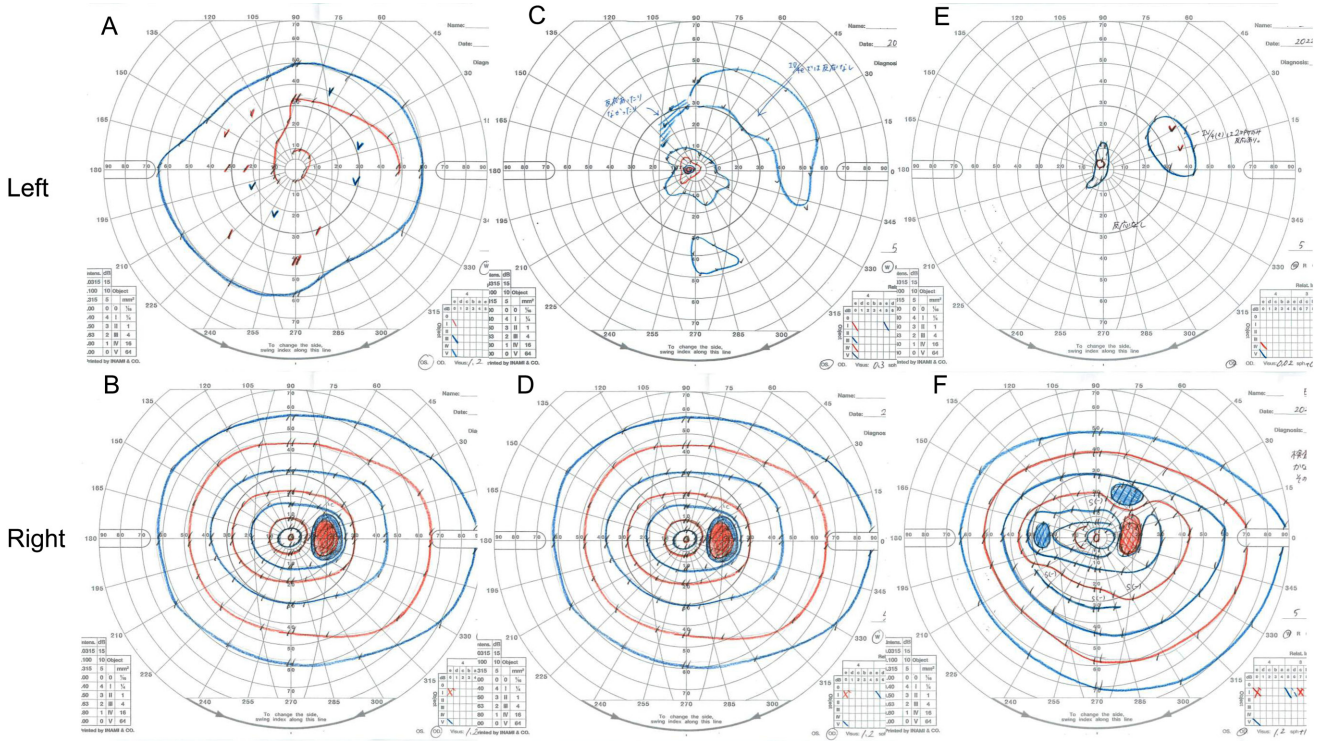

Fig. 2. (A), (B) Visual field testing in the right and left eyes showed no internal isopter desensitization at 18 yr of age. (C) At 20 yr of age just before prednisolone administration, left visual field testing showed decreased internal isopter sensitivity, and (D) right visual field testing showed an enlarged Marriott's blind spot. (E) At 2 mo after prednisolone administration, left visual field testing showed no change of decreasing internal isopter sensitivity, while (F) right visual field testing showed a slight improvement in the expansion of the Marriott blind spot.

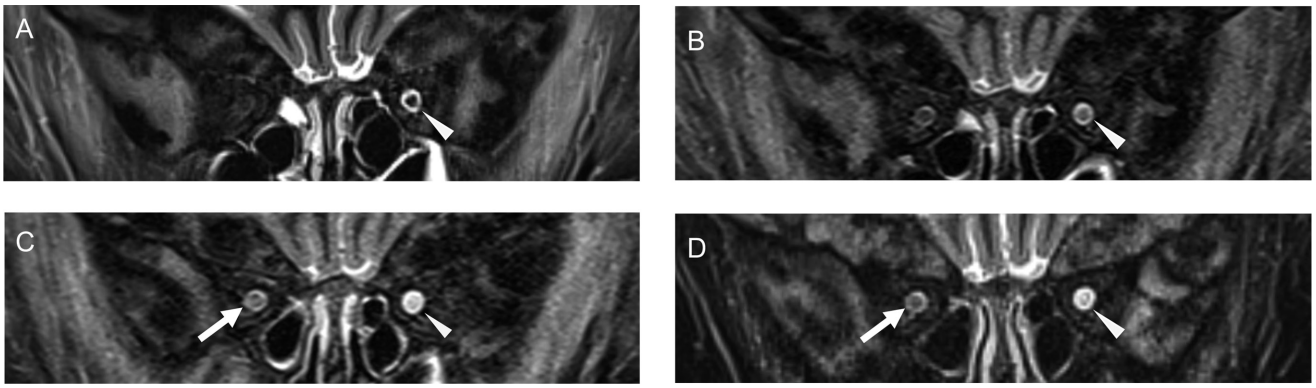

Fig. 3. (A) STIR coronal image showed no abnormal signals on the bilateral optic nerve at the age of 18 yr and 4 mo. The subarachnoid space around the optic nerve is observed as a high-signal area predominantly on the left side (arrowhead). (B) The left optic nerve was slightly hyperintense at 19 yr and 5 mo of age (arrowhead) before prednisolone treatment. (C) The left optic nerve showed marked hyperintense (arrowhead), and the right optic nerve become mild hyperintense (arrow) at 20 yr old just before the administration of prednisolone. (D) After 12 wk of prednisolone treatment, the high signal intensity in the right optic nerve was slightly improved (arrow), but the left optic nerve did not change (arrowhead).

pain. Furthermore, she was always awake 2–3 times during the night because of bone pain.

The left visual acuity further deteriorated [0.2 (left) and 1.2 (right)] at 4 wk later. Ophthalmoscopy revealed optic atrophy on the left side and papilledema (**Figs. 5A, 5B**). Visual field testing revealed an enlarged Marriott's blind spot in the right eye and decreased internal isopter sensitivity in the left eye (**Figs. 2C, 2D**). On MRI, the left optic nerve showed markedly high intensity, and the right side showed slightly high intensity, suggesting edematous changes in the optic nerve or optic neuritis (**Fig. 3C**). Blood examination showed an elevated white blood cell count, C-reactive protein (CRP, 4.2 mg/dL), and ALP-IFCC (530 IU/L,

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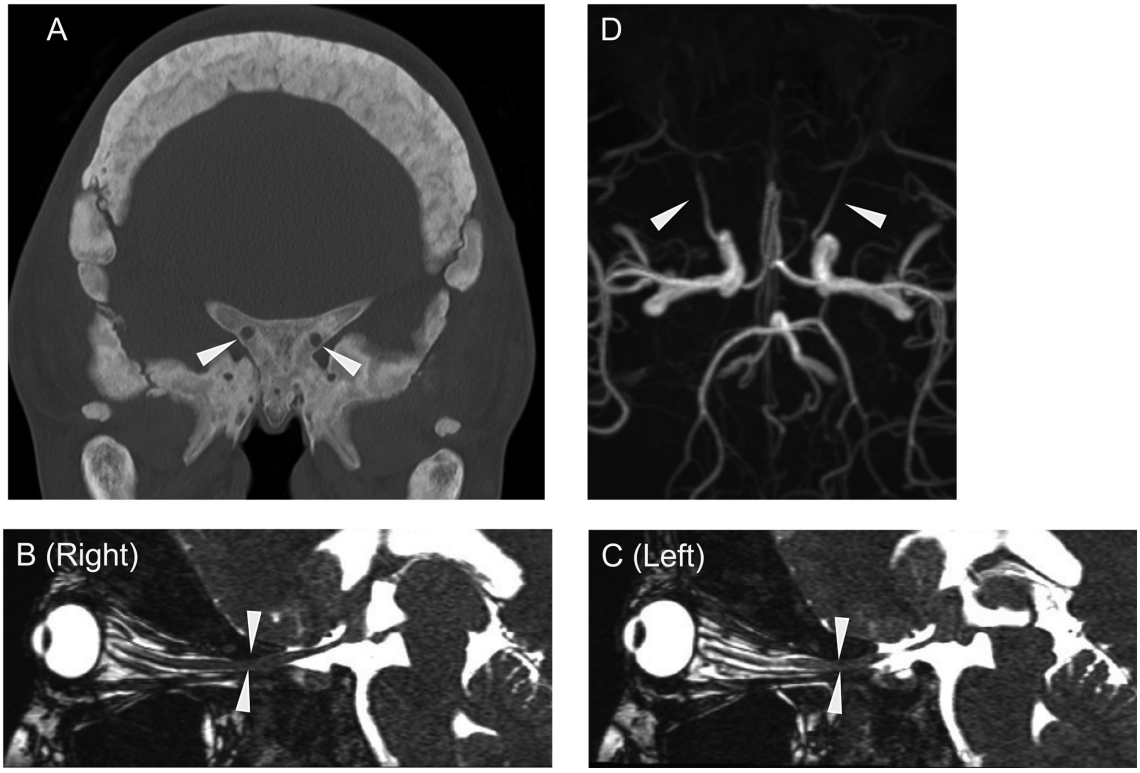

Fig. 4. (A) Coronal CT image (bone window) showed markedly thickening of the whole skull, including around the optic canal (arrowheads). (B, C) There is bony thickening and narrowing of the bilateral optic canals. The degree of narrowing was not different on the right and left (arrowheads). (D) Bilateral ophthalmic arteries were well visualized by MRA (arrowheads).

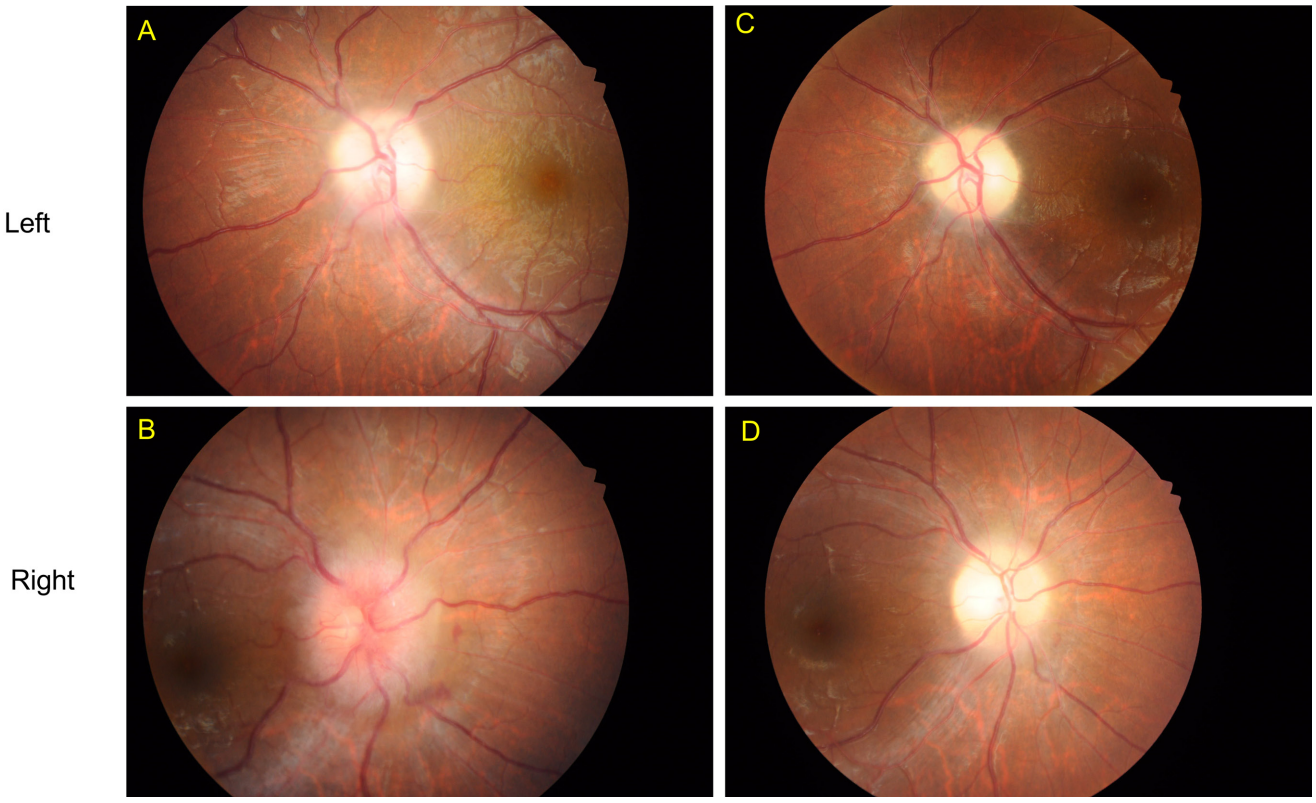

Fig. 5. (A), (B) Ophthalmoscopy revealed bilateral papilledema at 20 yr of age just before prednisolone administration. Right papilledema was more severe than left papilledema. (C), (D) Eight weeks after prednisolone administration, ophthalmoscopy revealed improvement of papilledema.

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reference range 38–113). Ophthalmoscopy did not show typical funding-related findings of optic neuritis, such as redness and swelling of the optic nerve, which are thought to be caused by increased intracranial pressure. Therefore, isosorbide (1.2 mg/kg/d) was administered. However, her ocular symptoms did not improve, and isosorbide was discontinued 7 days after initiation because of adherence.

To reduce bone pain, oral prednisolone (0.5 mg/kg/d) was started. After one wk, the bone pain dramatically reduced, and analgesics were discontinued. The patient was not awake at night because of bone pain. Body temperature also decreased to the normal range, CRP was negative, and ALP levels were reduced. After two wk, the right papilledema improved and the right visual acuity was preserved (1.2), but the left visual acuity did not improve (0.2). Treatment of prednisolone (0.25 mg/kg/d) was continued. Eight weeks after the initiation of prednisolone treatment, her left visual acuity further deteriorated (0.03). Ophthalmoscopy revealed bilateral papilledema (**Figs. 5C, 5D**). The visual field test showed similar left internal isopter desensitization, and the expansion of the Marriott blind spot improved slightly on the right side (**Figs. 2E, 2F**).

Twelve weeks after the initiation of prednisolone treatment, the STIR signal of the right optic nerve improved slightly but that of the left optic nerve did not change (**Fig. 3D**). CRP levels remained negative, and alkaline phosphatase (ALP)-IFCC levels remained low (222 IU/L).

The genetic analysis was approved by the Institutional Review Board of Jichi Medical University (approval number 21-153). The protein-coding region exon and its boundary region with the intron (up to 10 bases inside the intron) of only *TGFB1* were analyzed by targeted next-generation sequencing using the hybrid capture method (MiSeq system. Illumina). The identified variant of *TGFB1* was confirmed by Sanger sequencing using the Genetic Analyzer 3130 sequencer (Life Technologies, Carlsbad, CA, USA). A novel heterozygous variant of p.Cys223Tyr was identified. Sanger sequencing confirmed the presence of this variant (**Fig. 6**). ClinVar and gnomeA were not registered in this study. *In silico* analysis using PolyPhen-2, SHIFT, PROVEAN, and Mutation testing revealed that this variant was pathogenic. Furthermore, this amino acid position is a hot spot in CED. Therefore, p.Cys223Tyr was thought to be the cause of the patient's CED.

Discussion

In this case, we identified a novel variant (p.Cys 223Tyr) of *TGFB1*. Currently, 14 *TGFB1* variants have been reported in CED (2, 3); 8 of the 14 variants are located between amino acids 218 and 225 (2). In particular, codon 223 contains five amino acid substitutions (p.Cys223Arg, p.Cys 223Ser, p.Cys223Gly, and p.Cys223Trp) associated with CED (2). In our case, p.Cy223Tyr was also identified, which may have been

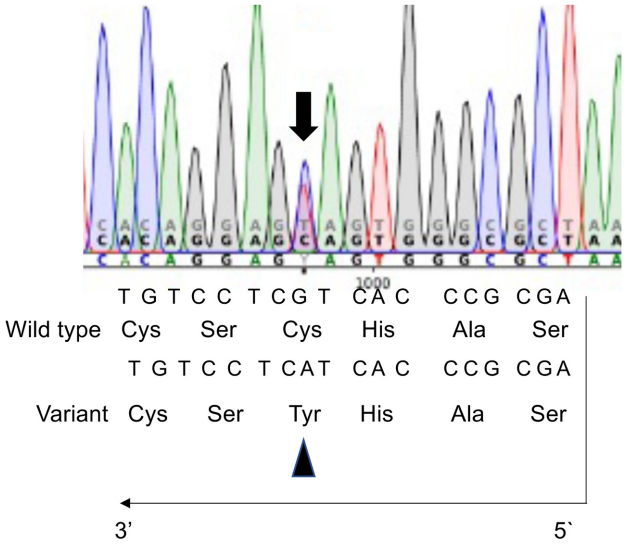

Fig. 6. In this patient, a heterozygous missense variant was present in exon4 of *TGFB1*, resulting in p.Cys223Tyr. T and C bases were present (arrow). The sequence was the reverse strand.

the cause of CED.

Oral administration of prednisolone reduced bone pain, as reported previously (3, 5–8). In some cases, the administration period is as long as 10 yr (6). However, there have been cases in which increased pain has been observed after discontinuation of prednisolone because of the side effects of glucocorticoids (11). Therefore, appropriate monitoring and dose adjustments for glucocorticoids are required. In addition to glucocorticoids, since there have been cases in which losartan was effective for bone pain, a combination of low-dose glucocorticoids and losartan may also be considered (6, 11).

To the best of our knowledge, there are no reports on the effectiveness of corticosteroids for papilledema in patients with CED. The subarachnoid space around the left optic nerve was enlarged in the early stages. Enlargement of the subarachnoid space around the optic nerve indicates increased intracranial pressure (12) and the STIR signal is stronger on the left side than on the right. Therefore, the left optic nerve might have been chronically damaged, causing irreversible changes due to locally increased intracranial pressure. Chronically increased intracranial pressure may cause microvessel perfusion disturbances on the left side, which cannot be identified using magnetic resonance imaging or MRA.

When the patient's left visual acuity worsened, her left optic nerve showed a markedly high intensity on MRI, and the right side showed a slightly high intensity. It was not possible to determine whether the lesion was an edematous change or optic neuritis based on MRI findings alone. Fundus findings revealed papilledema with no redness or swelling of the optic nerve, which is characteristic of optic neuritis. Therefore, isosorbide was administered; however, it was ineffective.

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Considering the exacerbation of bone pain, exacerbation of inflammatory findings in blood tests, and the possibility of increased intracranial pressure due to bone inflammation, prednisolone was administered.

However, the exact mechanism underlying the effect of prednisolone on papilledema has not yet been determined. TGFβ1 is expressed ubiquitously and regulates a broad range of biological processes, including cell proliferation, cell survival, cell differentiation, cell migration, and production of extracellular matrix (13). Regarding inflammation, overexpression of TGFβ1 in mouse skin showed significant skin inflammation (14). TGFβ1 has also been reported to be involved in the development of inflammation in rheumatoid arthritis (14). Furthermore, *in vitro* studies showed that corticosteroids downregulate *TGFB1* mRNA expression (15, 16). In this context, we hypothesize that constitutive activation of the TGFβ1 cascade may lead to inflammation of the whole bone and contribute to the progression of bone diseases in CED. Indeed, ALP elevated.

This study had several limitations. First, bone metabolic markers other than ALP, such as osteocalcin and type I procollagen-N-propeptide, were not measured. Furthermore, serum ALP levels were not measured over time before prednisolone administration. Therefore, it may be insufficient to follow the course of bone inflammation. Second, there was no objective index for evaluating pain intensity.

In conclusion, prednisolone is effective for treating papilledema in patients with CED. Our findings require further evaluation of patients with CED and accompanying ophthalmic symptoms.

Conflict of interests: The authors have nothing to declare.

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