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BRIEF REPORT

Early canakinumab therapy for the sensorineural deafness in a family with Muckle-Wells syndrome due to a novel mutation of *NLRP3* gene

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Abstract

Cryopyrin-associated periodic syndrome (CAPS) is one of the autoinflammatory disorders caused by mutations in *NLRP3* gene. The over-production of interleukin (IL)-1β induced by *NLRP3* gene mutations plays an important role in the pathophysiology of CAPS. We diagnosed 3 patients with CAPS, who were lineal family members having a novel mutation of *NLRP3* gene. The objective of this report is to compare the characteristics of symptoms and differences in the therapeutic responses of them, who had the same mutation. In addition, we aimed to examine the usefulness of cytokine measurement for diagnosis or determination of treatment effect of CAPS. A 5-year-old Japanese boy (proband) came to our hospital because of short stature, reached the diagnosis of Muckle-Wells syndrome (MWS) due to a mutation in *NLRP3* gene, which had not been reported so far (p.G328E, c.G983A). His mother and grandmother harbored the same mutation of *NLRP3*. We measured serum concentrations of cytokines in the proband assessed by flow-cytometric bead array. All of them had episodic skin eruptions with conjunctivitis, hearing loss, and arthralgia, but not periodic fever, cold-triggered episodes, and chronic aseptic meningitis. Only the proband had short stature. Canakinumab therapy led to a prompt relief of symptoms and normalized laboratory data in all patients. Audiograms demonstrated an improved hearing level in the proband, but not two others despite of the same mutation. All cytokines did not show any characteristic findings. Sensorineural hearing loss and itchless rash but not serum cytokine profile deserved attention to the diagnosis and treatment start of CAPS. The early intervention of IL-1β blockade may reduce the chance of complete deafness in patients with CAPS.

Keywords CAPS · G328E · G983A · Hearing loss · IL-1β

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Introduction

Cryopyrin-associated periodic syndrome (CAPS) is one of the inherited autoinflammatory diseases. It arises from the gain-of-function mutation in *NLRP3* gene located on chromosome 1q44, which encodes a protein named cryopyrin [1, 2]. The typical presentation of CAPS consists of periodic fever, urticaria-like rash, arthralgia/arthritis, and congestion of bulbar conjunctivas. This syndrome is classified into three classical phenotypes according to the severity: neonatal-onset multisystem inflammatory disorder (NOMID), Muckle-Wells syndrome (MWS), and familial cold autoinflammatory syndrome (FCAS). The mode of inheritance of CAPS is autosomal dominant with variable penetrance. Somatic mosaicisms occasionally involve the development of NOMID [3, 4]. The pathophysiology of CAPS accounts for the overproduction of interleukin (IL)-1β induced by *NLRP3* gene mutations [5]. CAPS is a rare disease with the estimated prevalence of 1–2 cases for every 1 million inhabitants in the US, and 1 in every 360,000 in French [6]. However, a varied presentation of CAPS may lead to the delayed diagnosis and therapeutic intervention.

The diagnostic triad for MWS are 1) intermittent episodes of fever, headache, urticaria-like rash, and joint pain, 2) progressive sensorineural hearing loss, and 3) secondary (AA) amyloidosis with nephropathy. The morbidity of MWS (63%) was higher than that of FCAS (39%) or NOMID (19%) in the French registry [6]. On the other hand, the number of patients with MWS, FCAS, and NOMID were disparately reported 4 and 8, 6 and 2, and 9 and 8, in Japan [3] and Australia [7], respectively. The distinct morbidity may be explained by the variable presentation, the genotype and/or ethnicity. Recently, the biologic agents for cytokine blockade have become to control the excessive inflammation in patients with CAPS. Nevertheless, the indication of biologics remains unclear, because not only the clinical expression but also the relevant cytokine production and treatment response may be individualized.

We herein report a family of MWS having a novel mutation of *NLRP3* gene, and the efficacy of early canakinumab therapy against the sensorineural deafness.

Materials and methods

Genetic test and cytokine measurement

We extracted genomic DNA from white blood cells of peripheral blood collected from patients in the presence of anticoagulant. DNA was extracted with the use of a Qiamp DNA Blood Mini Kit (Qiagen, Valencia, CA, USA). The PCR reaction was performed in a total volume of 10 μL containing template DNA (80 ng/μL), 10 pmol of each primer, dNTP mixture (200 μM each), 1× Ex Taq buffer (Mg^{2+} plus), and 1 U of Ex Taq polymerase (Takara, Tokyo, Japan). The reaction mixture was overlaid with 10 μl of mineral oil and amplification was performed with a Gene Amp PCR System PC818 (ASTEC, Tokyo, Japan), with an initial denaturation at 95 °C for 2 min followed by 30 cycles of denaturation at 94 °C for 30 s, annealing at 60 °C for 20 s, and extension at 72 °C for 30 s. The PCR products were separated by electrophoresis on a 2% agarose gel and stained with ethidium bromide. For sequencing, 2.5 μl of the PCR products were incubated with 1 μl of illustra ExoProStar (GE Healthcare, Buckinghamshire, UK) first for 20 min at 37 °C and then for 20 min at 80 °C. Sequencing reactions were then performed with the use of a BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems, Thermo Fisher Scientific, Inc., Waltham, MA, USA). After purification with ethanol, the reaction products were applied to an ABI 3500 Genetic Analyzer (Applied Biosystems).

We measured serum cytokine concentrations in the proband during the treatment course. Multi-target streaming protein quantitative technology (BD-Pharmingen Cytometric Bead Array; BD Biosciences, Franklin Lakes, NJ, USA) was used to analyze the serum levels of interleukin (IL)-2, -4, -6, -10, tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ), following the manufacturer's instructions. The lower detection limits for IL-2, IL-4, IL-6, IL-10, and TNF-α; and IFN-γ are 2.6, 2.6, 2.5, 2.8, and 2.8; and 7.1 pg/mL, respectively. Serum levels of IL-18, IL-17, and IL-1β were determined using enzyme-linked immunosorbent assay kits (IL-18: Medical & Biological Laboratories, Co., Ltd., Nagoya, Aichi, Japan, IL-17 and IL-1β: R&D systems, Minneapolis, MN, USA) according to the manufacturers' protocols. The lower detection limits for IL-18, IL-17 and IL-1β are 12.5, 15, and 1 pg/mL, respectively.

Results

Patient 1 (Proband)

A 5-year-old Japanese boy was hospitalized for the investigation of short stature and elevation of serum C-reactive protein (CRP) levels. His height was 98.0 cm (−2.3 SD). The short stature had been already investigated in a former hospital. The secretion of his growth hormone was within normal limits. Elevated levels of serum CRP (6.0 mg/dL), increased erythrocyte sedimentation rate (22 mm per hour), and iron deficiency anemia (hemoglobin [Hb] 9.7 g/dL, MCV 59.8 fL, ferritin 15.5 ng/mL) were observed.

He had repeated urticaria-like rash since three-month-old, and it regressed spontaneously in a few days each time. In addition, he suffered from periodic pains of ankle and knee joint since age 4 years. The arthralgia persisted for a few days,

and disappeared spontaneously. At the first visit to our hospital, he had urticaria-like rashes without pruritus in upper limbs and hip (Fig. 1). He had bulbar conjunctivitis and mild local heat in the painful ankle joints. Other physical findings were unremarkable. Results of hematological examinations were as follows: leukocytes, 17.06×10^9/L; Hb, 9.9 g/dL; platelet count, 606×10^9/L; D-dimer, 0.8 mg/L (reference range [rr]: 0–1 mg/L); alanine aminotransferase (ALT), 8 U/L (rr: 5–43 U/L); aspartate aminotransferase (AST), 22 U/L (rr: 12–34 U/L); ferritin, 8.5 ng/mL (rr: 25–280 ng/mL); lactate dehydrogenase (LDH), 211 U/L (rr: 115–217 U/L); CRP, 5.21 mg/dL (rr: 0–0.25 mg/dL); procalcitonin, 0.15 ng/mL (rr: 0–0.05 ng/mL). The urinary β_2-microglobulin (U-β_2MG) levels were elevated, 8.06 mg/L (rr: < 0.29 mg/L). Urine and feces were negative for occult blood. MRI findings of the legs revealed synovial fluid in talocrural joint but no hypertrophy of synovial membranes. The auditory test revealed sensorineural hearing impairment, especially at higher test frequencies (Fig. 3a). Head MRI showed no abnormality. These findings raised a diagnosis of CAPS. Other differential diagnoses included autoinflammatory disease such as hyper IgD syndrome, TNF receptor-associated periodic syndrome, Blau syndrome, or juvenile idiopathic arthritis. A genetic test identified a novel mutation in *NLRP3* gene located on chromosome 1q44, p.G328E, c.G983A (supplementary figure).

After the diagnosis of CAPS, MWS, subcutaneous injection of canakinumab (2 mg/kg/dose, every 8 weeks) was started. We used the treatment with canakinumab alone, because canakinumab has been shown to be effective as a single agent [8]. Anti-inflammatories such as methotrexate were not an essential treatment, and these agents were not so effective [9]. These symptoms promptly disappeared, and then hearing ability (Fig. 3b) and anemia improved. He smoothly grew taller after the canakinumab therapy (data not shown). There were no adverse events. In our case, his parents were not short stature, and his endocrinological examinations showed no abnormalities. Moreover, we have never administered glucocorticoids before. Musculoskeletal symptoms including short stature are one of manifestations of CAPS [13], thus we believe that the disease itself causes his short stature.

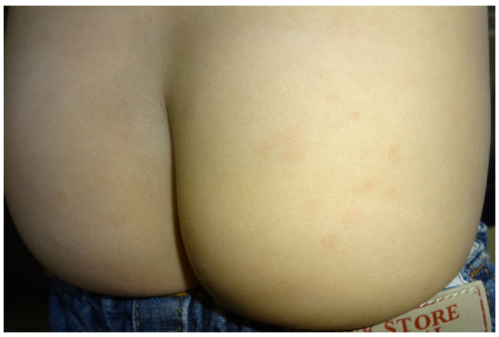

Fig. 1 Urticarial rashes in his hip. These rashes were also seen in his upper rims, and not accompanied by itching

We examined the serum cytokine levels before the initial administration of canakinumab, and every 8 weeks just before the administration of canakinumab. The undetectable levels of serum IL-1β levels before the treatment increased to the range of 8.2–42.6 pg/mL after canakinumab therapy. IL-18 levels increased from 561.1–749.5 pg/mL to 453.4–1223.3 pg/mL (rr: < 257.8 pg/mL) after the therapy. Serum IL-2, IL-4, IL-6, IL-10, IL-17, IFN-γ, and TNF-α levels were stably higher than healthy controls during the observation period (data not shown).

Patient 2

A 36-year-old Japanese female, the proband's mother (Fig. 2), had repeated urticaria-like rash without pruritus, pains of ankle and knee joint, bulbar conjunctivitis, and hearing difficulty, but not periodic fever since childhood, same as the proband. Her body height was 149.0 cm (−1.9 SD). She had received glucocorticoid and methotrexate under the diagnosis of juvenile idiopathic arthritis since age 12 years. Treatment with glucocorticoid and methotrexate was not so effective for CAPS patients [9]. Thus her symptoms had persisted, and serum CRP levels had been persistently positive. The flaring episodes repeated with progressive hearing impairment (Fig. 3a). The blood tests revealed leukocytes, 13.95×10^9/L; Hb, 10.9 g/dL; platelet count, 422×10^9/L; ALT, 11 U/L; AST, 13 U/L; ferritin, 17.5 ng/mL; LDH, 150 U/L; CRP, 6.06 mg/dL; procalcitonin, 0.08 ng/mL. The identified same mutation of *NLRP3* as the proband's, determined the diagnosis of CAPS, MWS (supplementary figure). After the start of subcutaneous administration of canakinumab (150 mg/dose, every 8 weeks), her major symptoms such as rash, arthralgia, and bulbar conjunctivitis promptly improved without adverse events. In addition, her serum CRP level became negative for the first time. However, her hearing ability did not change (Fig. 3b).

Patient 3

A 60-year-old Japanese female, the proband's grandmother (Fig. 2), also had repeated urticaria-like rash in her back and upper limbs, painful ankle and knee joints, conjunctivitis, hearing difficulty since childhood. Her height was 146.2 cm (−1.7 SD). Her hearing impairment was more severe than two others (Fig. 3a). The blood tests revealed as follows: leukocytes, 9.6×10^9/L; Hb, 12.3 g/dL; platelet count, 305×10^9/L; D-dimer, 0.9 mg/L; ALT, 10 U/L; AST, 14 U/L; LDH, 177 U/L; CRP, 7.21 mg/dL. She received the diagnosis of MWS (supplementary figure), because of the symptoms, family history, and genetic test. Canakinumab therapy (150 mg/dose, every 8 weeks) controlled the symptoms but not improved hearing ability, although no adverse events occurred (Fig. 3b).

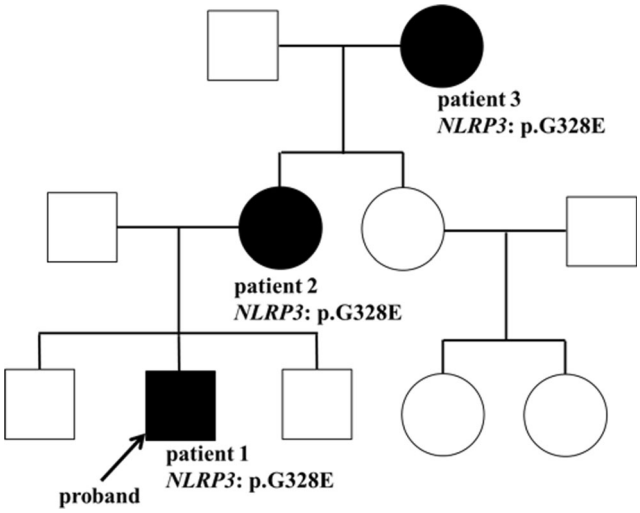

Fig. 2 Genealogy of the family. It shows symptoms of MWS in proband's maternal family, and the same gene mutations were found in symptomatic persons

Discussion

The split response of canakinumab to hearing ability was notable in the family members having the genotype and phenotype of MWS. The novel mutation of *NLRP3* could explain the sharing expressions of 3 patients, although it remains unknown whether absent fever is characteristic for the genotype. The drastic effects of canakinumab on hearing ability of the proband emphasized the significance of early IL-1β blockade to prevent the complete deafness in patients with CAPS.

Cryopyrin serves as a scaffold for assembly of the inflammasome complex. Pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) stimulate the formation of inflammasome and activation of caspase-1, and it leads to the production of IL-1β [5, 10]. In patients with CAPS, the formations of inflammasome are augmented without stimulation. The inflammation is mediated by excessive production of IL-1β in CAPS patients [5, 10, 11]. The persistent inflammation due to higher circulating levels of IL-1β explains the variable expressions of CAPS, such as periodic fever, urticaria-like rashes, and arthralgias. Additionally, affected patients develop sensorineural hearing

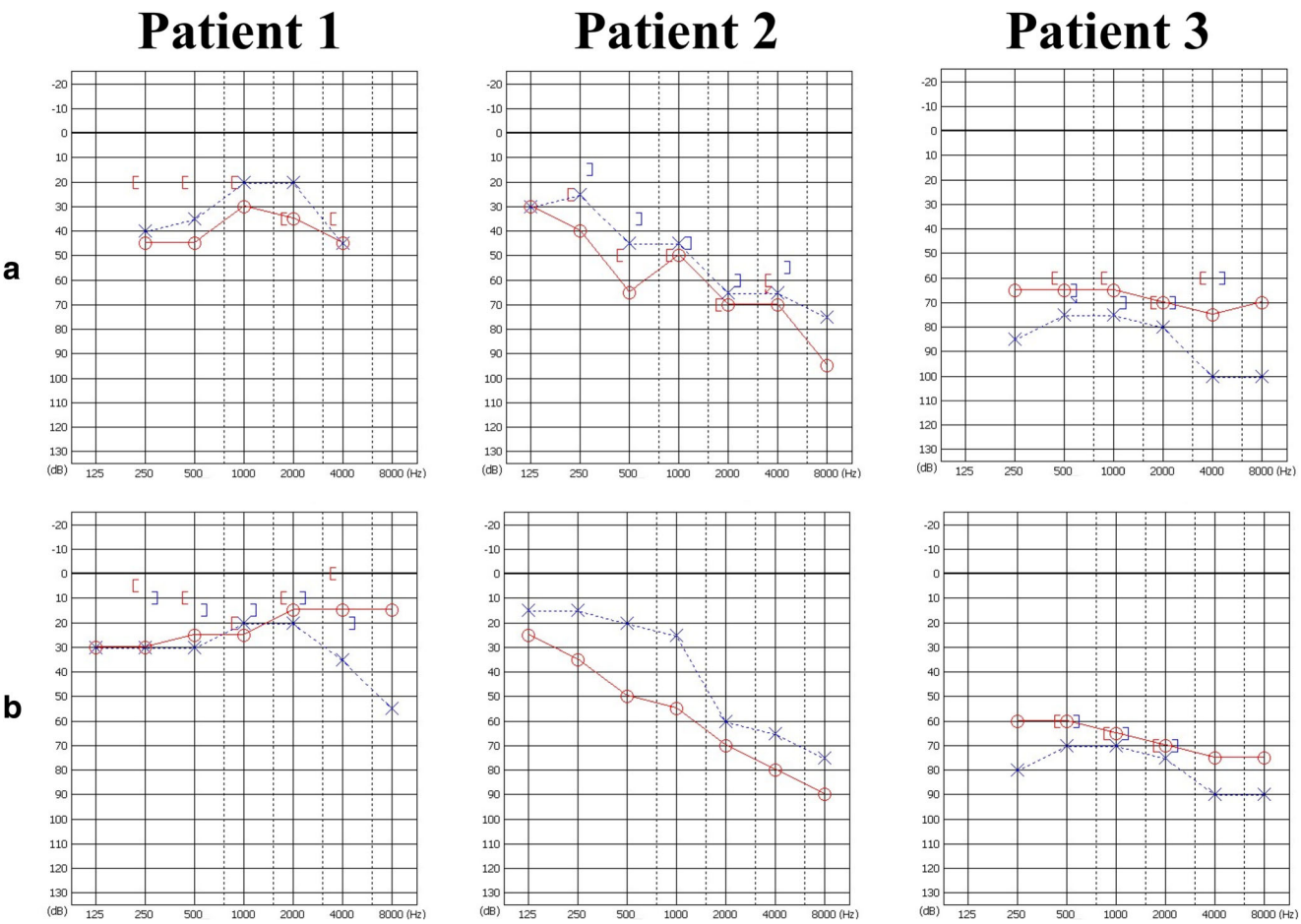

Fig. 3 Audibility test before **a** and after **b** the start of treatment. The proband (patient 1) shows improvement of hearing, but not his mother (patient 2) and his grandmother (patient 3). ○: right ear (air hearing), ×: left ear (air hearing), ⊏: right ear (bone conduction hearing), ⊐: left ear (bone conduction hearing)

loss, short stature or secondary amyloidosis, especially renal amyloidosis. In this proband, the chief complaint was short stature. CAPS patients have abnormality in endochondral ossification at growth plate cartilage, and it is thought to be one of the reasons that CAPS patients present short stature. In addition to that, inflammatory cytokine may have relations to short stature. Not IL-1β but IL-6 was reported to lead growth impairment through a decrease in insulin-like growth factor I (IGF-I) in mice model [12], and over production of other cytokines such as IL-1β might lead short stature.

The majority of Japanese patients with CAPS shows fever and skin rash as the first presentation [3]. The proband also suffered from urticaria-like rashes and joint pains, but had not received the diagnosis of CAPS or MWS until 5 years of age. The delayed diagnosis must be due to non-severe typical symptoms, especially periodic fever (Table 1). According to the reports of the phenotypic and genotypic correlation of CAPS [13], rare *NLRP3* variants were at risk of severe CAPS. On the other hand, the present family members tended to have the mild clinical expressions without periodic fever. The variants of R260W, T348M, D303N, A439V, E311K, V198M, and Q703K were recurrently reported in *NLRP3* gene [5, 13]. Three family members had a novel mutation of c.G983A. This is the novel gene mutation not been reported so far. The product, p.G328E was predicted to be deleterious with a score of 0.994 by the PolyPhen-2 program (http://genetics.bwh.harvard.edu/pph2/, benign: 0.00–0.20, possibly damaging: 0.20–0.85, probably damaging: 0.85–1.00). Lacked periodic fever, cold-triggered episodes, and chronic aseptic meningitis may be a characteristic phenotype of p.G328E (Table 1). If the mild expression makes it difficult to early diagnose, the novel genotype might not be overlooked as the variant of *NLRP3* in the population.

Progressive sensorineural hearing loss is one of serious symptoms in the MWS patients [14]. As shown in Fig. 3a and b, the proband's hearing was improved after start of canakinumab treatment, but not mother (patient 2) and grandmother (patient 3) even though they have the same mutation. The discrepancy can be explained by the different age at the start of biologic treatment between the proband and two others, as reported previously [14, 15]. Because of the different efficacy of canakinumab against sensorineural deafness in the family members with the same mutation, the effect of early canakinumab may depend on the treatment age of biologics rather than the genotype of CAPS. The proband showed the recovery of both hearing and growth due to administration of canakinumab, as shown in Fig. 3a and b. The early diagnosis and treatment of CAPS with IL-1β inhibitor may promote the growth and then prevent the complete deafness. To improve hearing ability, early canakinumab therapy intervention is very important.

In Japan, only canakinumab is allowed to use for CAPS patient at present, but other drugs such as anakinra and rilonacept are reported about effectiveness to CAPS [16, 17]. It was reported that anakinra might be superior to canakinumab for control of central nervous system inflammation [18]; however, comparison of these drugs is limited. Moreover, dapansutrile might be useful because of the oral administration [19].

Our data of cytokines showed no significant findings. IL-18 was elevated but no change was observed before and after the treatment. IL-1β was elevated after the treatment, but the change might be due to the prolonged half-life of IL-1β-canakinumab complex after the administration of canakinumab. The other cytokines were not elevated. From the results, the cytokine profiles may not be useful for diagnosis or assessment of treatment effect of CAPS. After all, clinical symptoms are

Table 1 Clinical characteristics of a family with MWS

	Case 1: proband	Case 2: mother	Case 3: grandmother
Age, sex	5 years, male	36 years, female	60 years, female
Clinical expressions			
Periodic fever	No	No	No
Rash	Yes	Yes	Yes
Hearing difficulty	Yes, mild	Yes, moderate	Yes, severe
Arthralgia	Yes	Yes	Yes
Congestion of bulbar conjunctiva	Yes	Yes	Yes
Gastrointestinal symptoms	No	No	No
Central nervous system symptoms	No	No	No
Short stature	Yes (−2.3 SD)	No (−1.9 SD)	No (−1.7 SD)
Treatment	Canakinumab (2 mg/kg/8 weeks)	Canakinumab (150 mg/8 weeks)	Canakinumab (150 mg/8 weeks)
Age at the start, and duration of treatment	5 years old, 4 years	36 years old, 3 years	60 years old, 2 years
Treatment response: Rash and arthralgia	Good	Good	Good
Hearing and growth	Improved	Unchanged	Unchanged
Mutation	Exon 3, p.G328E, c.G983A	Exon 3, p.G328E, c.G983A	Exon 3, p.G328E, c.G983A

important in doubting CAPS. Six typical CAPS manifestations included urticaria-like rash, cold-triggered episodes, sensorineural hearing loss, musculoskeletal symptoms, chronic aseptic meningitis, and skeletal abnormalities [20]. Not only these symptoms but also familial history must be useful in doubting CAPS. The clue of diagnosis was the investigation of short stature in our patient. Because the prevalence rate of CAPS is extremely low, we may not list CAPS as differential diagnosis of short stature. However, we had better list CAPS, if there is a characteristic history, familial history, or unexplainable inflammation reaction in blood examination.

In conclusion, there are three novelties in this study. 1) This is the novel *NLRP3* gene mutation report (p.G328E, c.G983A), and phenotypic features might include lack of periodic fever, cold-triggered episodes, and chronic aseptic meningitis. 2) Early canakinumab therapy must be necessary for improvement of hearing ability. 3) There might be CAPS patients in patients who come to hospital with short stature.

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Compliance with ethical standards

Disclosures None.

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