CINCA Syndrome With New NLRP3 Mutation and Unreported Complication of Thyroid Carcinoma

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ABSTRACT

BACKGROUND: Chronic infantile neurologic cutaneous and articular syndrome (CINCA) is the most severe phenotype of cryopyrin-associated periodic syndromes (CAPS) and is caused by a missense mutation in *NLRP3* gene.

CASE PRESENTATION: We are reporting a 15-year-old male patient with complaints of chronic arthritis and mental involvement. Further investigations showed a heterozygous c.785G>A missense mutation in Exon 3 of *NLRP3* gene and coexisting medullary thyroid carcinoma 2 years later.

CONCLUSIONS: This case showed a recently identified gene variant of *NLRP3* in a CINCA patient, as a heterozygous c.785G>A missense mutation in Exon 3 of *NLRP3* gene and coexisted medullary thyroid carcinoma as an unreported complication of CINCA.

KEYWORDS: CINCA Syndrome,NLRP3 MUTATION,THYROID CARCINOMA

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Background

Cryopyrin-associated periodic syndromes (CAPS) and neonatal-onset multisystem inflammatory disease (NOMID) as one of its subgroups are inflammasome related auto-inflammatory conditions with chronic systemic inflammation associated mostly with myeloid cell class-related innate immunity. It is estimated that CAPS have a prevalence of 1 or 2 cases in 1 million.[1] CAPS are monogenic disorders caused by a missense mutation that can occur in different parts of *NLRP3* gene.[2] According to the infevers database, to date, approximately 210 *NLRP3* variants have been described.[3–7] *NLRP3* gene encodes a protein named cryopyrin, which is a member of intracellular nucleotide-binding oligomerization domain (NOD)—like receptors (NLRs) family, and it's a key component of the inflammasome. Inflammasome induces secretion of several cytokines including interleukin 1 beta (IL-1β).[8] The mutations causing CAPS result in a gain of function that increases *NLRP3* activation.[1] CAPS are a group of 3 overlapping diseases: familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and chronic infantile neurologic cutaneous articular (CINCA) or NOMID.[9] The most severe phenotype of CAPS is CINCA syndrome. In most cases, CINCA syndrome presents in early life with nonpruritic urticarial rashes and persistent low-grade fever. Other clinical presentations include a typical facies (frontal bossing), conjunctivitis, persistent papilledema, sensorineural loss of hearing, arthropathy of large joints like knee, renal failure caused by AA amyloidosis, and permanent central nervous system (CNS) damages resulting in intellectual abnormalities.[1,9,10] Thyroid involvement has not been reported as an associated feature of CINCA in the literature. We report a case of CINCA syndrome in a young boy with a new *NLRP3* mutation and medullary thyroid carcinoma, as an unreported neoplastic complication.

Case Report

A 15-year-old male patient with chief complaint of pain and swelling of left knee and right ankle was admitted at hospital. Apparent articular symptoms began 1 year before the admission and they were progressive, causing limited mobility for the patient. Fatigue, persistent fever, and morning stiffness were the other chronic significant complaints of the patient. He suffered from obvious symptoms and signs of mental involvement caused by a delayed mental development. He had delayed neurological development. In physical examination, weight for age and height for age were under third percentile. Mild microcephaly, high arch palate, fish mouth, cervical lymphadenopathy, lack of sexual maturation, hypotonia, increased patellar deep tendon reflex (DTR), deformity of lower limbs (thick and floppy), and decreased range of motion of both knees were found. In his past medical history, patient had chronic intermittent fever since his infancy. Magnetic resonance imaging without contrast revealed a severe articular effusion. Ophtalmologic examination showed corneal nerve enlargement and evidences of old iritis and uveitis. Main laboratory findings were increased ESR (erythrocyte sedimentation rate;

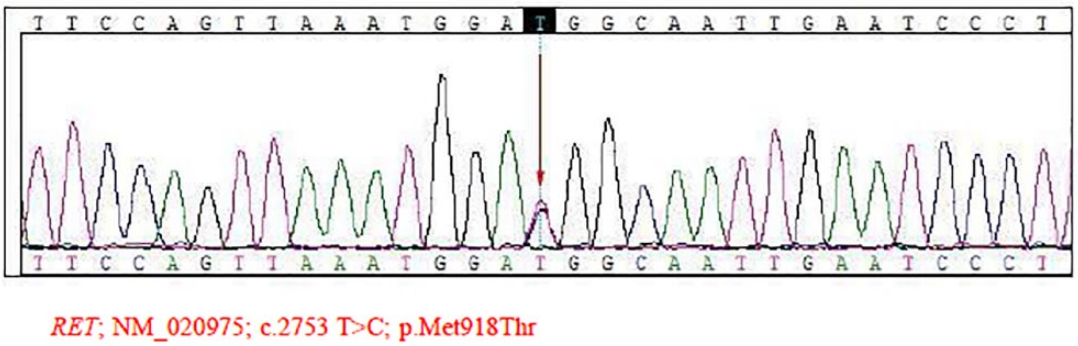

Figure 1. Validation of the variant found by Next Generation Sequencing in Exon 16 of *RET* gene.

65 mm Hg/h; normal = 0-22), positive CRP (c-reactive protein; 35 mg/L; normal: 0-3), semiclear urine, without proteinuria. Serum luteinizing hormone (LH), follicle stimulating hormone (FSH), and testosterone levels were lower than normal range, but serum growth hormone level was in normal range. Antinuclear antibody (ANA) and anticyclic citrullinated peptide (anti-CCP) were all negative. Finally, genetic studies based on Sanger-based PCR-sequencing of the entire coding region (including splicing sites) showed a heterozygous variant NM_001243133: c.785G>A (NP_001230062: p.Arg262Gln) in Exon 3 of *NLRP3* gene, which confirmed the diagnosis of CAPS. The noted variant has not been reported yet, and it has been registered as a new *NLRP3* gene mutation in the database of International Society for Systemic Auto Inflammatory Diseases (as c.779G>A; p.R260Q).[3–7] The detected variant has not been previously reported for its pathogenicity. However, multiple lines of in silico computational analysis (Mutation Taster, CADD, etc) support the deleterious effect of the variant on the gene or gene product(s). The variant is absent in population databases (ExAC, 1000G, etc).

Two years later, swelling and nodularity of thyroid was detected during an outpatient visit. Further investigations revealed an elevated serum level of calcitonin (86/7 pg/mL) and T_4 (228 nmol/L) in spite of low thyroid stimulating hormone (TSH; 0/07 mIU/mL). Thyroid scan showed multinodular goiter with 2 cold nodules in right lobe and increased uptake in the remainder of thyroid gland. Biopsies taken showed medullary carcinoma of thyroid.

Sequence of 2 genes related with thyroid cancer (*RET* and *NTRK1*) was enriched and sequenced by high-throughput platform. All exons and flanking 10 bp were detected and analyzed. Detected variations include the following: single-point mutation and small Indel (within 20 bp). Large duplication and deletion, balanced translocation, inversions, ploidy changes, uniparental disomy, and methylation alterations cannot be detected by this test. One heterozygous variant in Exon 16 of *RET* gene (NM_020975: c.2753T>C; NP_066124: p. Met918Thr) that has been previously reported for its pathogenicity were found. Two homozygous variants (c.337+9G>A and c.2071G>A; p. Gly691Ser) that have been reported as benign variants (polymorphism) were determined, as well. The presence of the mutation c.2753T>C has been confirmed using Sanger-based PCR-sequencing (Figure 1).

Discussion

CAPS are a rare syndrome with an autosomal dominant heredity pattern that occurs sporadically, mainly in white population.[9] Certain missense mutations of *NLRP3* gene resulting in inflammasome over activation, causes CAPS. CINCA syndrome is the most severe phenotype of the disease with probable complication of amyloidosis.[10]

Although urticarial rashes are seen in more than 85% of CAPS patients,[11] it was not a dominant clinical symptom in our patient. A recent study suggests that CAPS may be presented without urticarial-like rash in late onset forms of the disease occasionally.[12] Hydrocephaly, ventriculomegaly, and frontal bossing are usual in CINCA patients,[1] but in spite of mild microcephaly, his brain magnetic resonance imaging (MRI) showed ventriculomegaly.

Approximately 60% of CINCA patients have arthropathy. Joint involvement is most commonly asymmetrical and mainly involves the knee; however, the condition can be symmetrical. Involvement of other joints is less usual.[13] This patient had developed an asymmetrical oligo-arthritis, involving left knee and right ankle, although during his course, both knees were involved.

Some studies mentioned short stature as a symptom of CINCA syndrome.[13] Our patient had a short stature despite normal serum growth hormone (GH) level.

If untreated, CINCA patients develop permanent CNS damage. Neurological symptoms typical of CINCA syndrome include irritability, headache, vomiting and intellectual disability and seizure, although it is a rare complication. Chronic aseptic meningitis may cause increased intracranial pressure resulting in hydrocephalus, brain atrophy and chronic papilledema. If untreated, chronic papilledema can cause optic nerve atrophy. Other clinical features of eye involvement include conjunctivitis, anterior uveitis, strabismus, nystagmus, and photophobia.[14] Sensorineural hearing loss is seen in less than half of CAPS patients resulted from

chronic cochlear inflammation.[11] The patient had a symmetrical dilation of lateral ventricles and a slight change of periventricular white matter signal in MRI, which should be due to chronic recurrent aseptic meningitis.

To date, approximately 210 *NLRP3* variants have been registered in infevers database.[3–7] 164 variants are related to Exon 3, and our patient had a heterozygous missense mutation in Exon 3 of *NLRP3* gene that was not reported previously. Beside, the mutations affecting the same amino acid residue has been described in other literature, which shows that this site may be an important site in the genetical basis of the disease.[15]

More ever this patient later 2 years found thyroid nodularities that finally diagnosed as medullary thyroid carcinoma. In our knowledge, it is an unreported complication or coexisted disease of CINCA syndrome. Some unique features and this coexisted complication of patient may be related to the new described genotype variant of the disease.

Author Contributions

FS and MB managed diagnosis and treatment of the patient. SH provided genetic analysis, and ES wrote the manuscript. All authors read and approved the final manuscript.

Availability of Data and Materials

Author can be contacted for data requests.

Consent for Publication

Written informed consent was obtained from the patient for publication of this case report.

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