Case Report

Systemic juvenile idiopathic arthritis complicated with PSTPIP1 gene variant: A case report

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Abstract

Objective: Systemic Juvenile Idiopathic Arthritis (SJIA) is a subtype of childhood rheumatoid arthritis, with the main clinical manifestations of high fever, recurrent rash, and arthritis. At present, it is generally believed that it is caused by the interaction of gene and environmental factors and has complex genetic characteristics. We report a case of a 1-year and 4-month SJIA patient with heterozygous mutation in PSTPIP1, and we studied the literature on this gene and related autoinflammatory diseases.

Methods: We searched the WanFang database and PubMed using the following search terms: SJIA, juvenile idiopathic arthritis systemic type, PSTPIP1 Gene.

Results: The literature reported SJIA pathogenesis and HLA (A kind of leukocyte antigen) gene and PTPN22 (casein protein amino acid phosphatase of 22) receptor gene, STAT4 (T cell signal transduction and transcriptional activation of A 4) gene, TNF-α (tumor necrosis factor α), IL (interleukins), and other related diction were included. This case existed PSTPIP1 variant, with other different clinical phenotypes PSTPIP1 mutation, however, PSTPIP1 gene variant may participate in SJIA the happening of the disease of disease development.

Conclusion: The autoinflammatory single gene and the pathogenesis of SJIA may have the same immune pathway, and further studies are needed to find genetic abnormalities that have not been found between these interrelated diseases.

Systemic Juvenile Idiopathic Arthritis (SJIA) is a subtype of childhood rheumatoid arthritis. Its clinical manifestations include relaxation and high fever, intermittent rash, and arthritis [1]. In addition to local joint manifestations, it is often accompanied by fatigue, enlargement of liver and spleen lymph nodes, serositis, and involvement of heart, liver, lung, kidney, and other organs [2]. PSTPIP1 gene (proline. Serine. Threonine. The variant of phosphatase binding protein 1 can cause PAPA syndrome, which has been previously reported in A230T, E250Q [3,4], and E250K [5] and involves mutation pathogenesis. The clinical manifestations of this disease are suppurrative arthritis, pyoderma gangrenae, and acne [6]. Here, we present a 1-year and 4-month SJIA case of SJIA associated with the PSTPIP1 variant.

Basic information

The patient is a 1-year and 4-month girl, admitted to our hospital because of the “repeatedly fever for 10 days, high fever with the hot peak of 40.2 , the thermal model is unknown, fever 1-2 times a day, the local hospital to” mezlocillin, oseltamivir treatment for 4 days, such as temperature control, and still had a fever again, accompanied by diarrhea, heat rash, there were no symptoms such as cough, conjunctival congestion, chapping of the lips, and rigid edema of hand and foot. After reexamination, leukocytes and CRP were significantly increased, and the patients were treated with infusion of “ceftriaxone ×5 days, azithromycin ×3 days” and propyl ball. The symptoms did not improve, and they were transferred to our hospital for treatment. On admission, physical examination showed scattered miliary rash in the trunk, discoloration under pressure, enlarged lymph nodes in the neck, rhythm of heart, no murmur in the anterior heart area, no special auscultation of both lungs, no enlargement of liver and spleen, and no redness of joints. Auxiliary inspection: WBC, neutral ratio, CRP, ESR,
and SF were significantly increased in peripheral blood routine. WBC 23.61×10⁹/L, N%62.8%, CRP34.7mg/L, ESR 95mm/h, ferric 1299ng/mL were indicated by peripheral blood test. T-spot, PPD, EBV/CMV-DNA, ANA, head MR, chest CT, heart color ultrasound, abdominal color ultrasound, cerebrospinal fluid cytology, bone marrow cytology, and other examinations showed no obvious abnormalities, and no joint swelling and pain, suppurative skin changes. SJIA was diagnosed after several examinations, excluding the possibilities of infections, tumors, and other febrile illnesses.

After approval by the medical ethics committee of Anhui Provincial Children's Hospital, detailed communication with the parents, and informed consent, EDTA anticoagulant peripheral venous blood was collected from the child and their parents for complete exon testing. The test is mainly divided into three steps: (1) Whole exon sequencing. The xGen Exome Research Panel V 1.0 full exon capture chip was used to complete the sequencing by Illumina NovaSeq 6000 series sequencer, and the coverage of the target sequence was not less than 99%. (2) Genetic data analysis. Diagnostic system platform analysis screening for genetic testing company, combined with pathogenic mutation database, normal human genome database, 4000 kinds of known genetic disease clinical feature database and the data analysis algorithm and so on, to the classification of genetic variation, variation graded by the American Institute of Medical Genetics (ACMG) gene variants classification system [7]. (3) Verification of suspected pathogenic mutation. After PCR, the target sequences were verified by Sanger sequencing using the ABI3730 sequencer, and the results were verified by the sequence analysis software.

**Laboratory results and treatments**

The results of complete exon testing showed that the heterozygous mutation of PSTPIP1 gene C.196T>C: P.V399A was paternal (Figure 1), but the clinical significance of AGMG variation rating was unclear.

This child was given a high dose of methylprednisolone (30mg/kg×4 days) and gamma globulin (1g/kg×4 days). The fever symptoms were not improved significantly, and the monitoring of erythrocyte rate, CRP, SF, cytokines, and other

| Name          | Gene    | dbSNP           | Variation description | Type     | Amino acid variation |
|---------------|---------|-----------------|-----------------------|----------|---------------------|
| Patient       | PSTPIP1 | rs1193580867    | 78 exon5:c.I196T>G    | Heterozygous | C:p.V399A           |
| Patient’s father | PSTPIP1 | rs1193580867    | 78 exon5:c.I196T>G    | Heterozygous | C:p.V399A           |
| Patient’s mother | PSTPIP1 | None            |                       |          |                     |

**Figure 1:** PSTPIP1NM_003978:exon5:c.I196T>G:C:p.V399A hybrid Mutation site map of patient.
inflammatory indicators were still significantly increased, indicating disease activity. The child was treated with additional immunosuppressant cyclosporine, methotrexate, and the biological agent Tocilizumab (160mg), and the progressive body temperature was stable, besides, the rash subsided, and the inflammatory indicators were normal. The parents of the child did not provide similar family history and denied any previous joint swelling and pain, morning stiffness, oral or nasal mucosal ulcers, facial redness, and Raynaud’s phenomenon. Denying a family history of other rheumatic diseases, including SLE, scleroderma, or rheumatoid arthritis.

The child was subsequently treated with low-dose methylprednisolone (8mg/d), cyclosporine (0.5ml/d), methylaminopteryrin (5mg/qw), and monthly infusion of tocilizumab. The body temperature was stable, routine blood leukocytes, CRP, ESR, SF, and cytokines were normal without joint involvement. There was no disease activity in the follow-up of 15 months.

Research method

We searched WanFang database and Pubmed using the following search terms: JIA, juvenile idiopathic arthritis systemic type, PSTPIP1 gene. The included year was set from 1990 to 2021.

Search results and discussion

SJIA is a systemic inflammatory disease, classified as a category of juvenile idiopathic arthritis nowadays. The systemic inflammation of SJIA has been proved to be related to the dysregulation of the innate immune system, suggesting that it may rather be part of the spectrum of autoinflammatory disorders. The pathogenesis of SJIA has been reported to be associated with multiple immunogenetics genes, such as HLA (human leukocyte antigen) gene, PTPN22 (protein tyrosine phosphatase non-receptor 22) gene, STAT4 (T lymphocyte signal transducer, and transcriptional activator 4) gene, TNF-α (tumor necrosis factor A) and IL (interleukin) genes.

In the present case, we reported a case of SJIA patient with PSTPIP1 gene mutation. Some studies indicated different clinical phenotypes from other PSTPIP1 mutation–induced diseases. According to Ellis JA, et al. JIA was confirmed to be related to SNP (single nucleic acid polymorphisms) of neighboring clororf30, c30rf1, PTPN22, STAT4, and TRAF1-CL5 based on independent replication data of JIA susceptibility loci and identification.

We also produced evidence supporting the replication of JIA with gene sites including AFF3, CD226, MBL2, PSTPIP1, and RANTES (CCL5). Day TG, et al. using MassArray genotyping, analyzed 950 white British patients with JIA and 728 healthy people of the same race. The results showed that MEFV was significantly correlated with 6 SNPs in JIA. Four loci, including NLRP3, NOD2, MEFV, and PSTPIP1, were found to be associated with 12 SNPs in the subgroup of patients with psoriasis JIA. The syndrome caused by these genes is collectively known as hereditary periodic fever syndrome (HPFS), which is an autoinflammatory single gene syndrome characterized by inflammation and seemingly unprovoked recurrent fever.

Arthritis and joint pain are common, and these clinical features overlap with the systemic form of juvenile idiopathic arthritis, but due to the small cohort sample size, further study is needed. PSTPIP1 mediates single–gene autoinflammatory diseases, the pathophysiological basis has not been fully defined. It can lead to IL-1 oversecretion in acute and chronic inflammatory diseases. This inflammatory factor is also involved in the pathogenesis of SJIA. We represented that clinical symptoms and laboratory indicators were significantly improved after the application of immunosuppressive agents and biological agents in this case. Therefore, there may be the same immune pathway between SJIA and autoinflammatory single–gene diseases.

Conclusion

Immunosuppressive therapy and biological agents were effective for patients with PSTPIP1 gene variant this time. Currently, there is a lack of cases and clinical studies confirming a clear correlation between the autoinflammatory single gene variant and the onset of SJIA. However, according to this case report, there may be a broader susceptibility gene spectrum of SJIA. Further research is needed to identify undiscovered genetic abnormalities associated with these related diseases.

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