Journal of Clinical and Nursing Research, 2026, Volume 10, Issue 1
http://ojs.bbwpublisher.com/index.php/JCNR
Online ISSN: 2208-3693
Print ISSN: 2208-3685

A Case Report of Familial Episodic Pain Syndrome Type 3 in a 5-Year-Old Boy

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Abstract: Medical history summary: The child has suffered from episodic joint pain in the lower extremities since childhood, with occurrences ranging from 1 to 3 times daily, predominantly during rainy, cold, and humid weather, as well as in the afternoons and evenings. Symptoms and signs: The primary manifestation is episodic pain in the distal extremities, predominantly in the lower limbs, knees, and ankles. Occasionally, the pain may ascend to the elbows, wrists, and palms, and may occasionally affect the proximal extremities and waist. Diagnostic methods: Nerve biopsy and related pathological examinations, along with whole exome sequencing, are helpful for diagnosis, particularly the detection of variants in the SCN11A gene. Treatment approaches: (1) Pharmacotherapy: Sodium channel blockers and nonsteroidal anti-inflammatory drugs such as ibuprofen and naproxen can alleviate pain. (2) Neuromodulation techniques: Techniques such as transcranial magnetic stimulation (TMS) and spinal cord stimulation (SCS) can be employed to improve symptoms. (3) Psychotherapy: Cognitive-behavioral therapy (CBT), relaxation training, or psychological counseling can enhance the patient's coping abilities. Clinical outcome: Pain relief can be achieved with analgesic medication in children, and pain symptoms generally persist until adulthood, gradually diminishing or even disappearing. Patients can reduce the frequency of episodes by staying warm and avoiding cold and damp conditions.

Keywords: SCN11A; Paroxysmal pain; Autosomal dominant inheritance

Online publication: Feb 9, 2026

1. Introduction

Familial episodic pain syndrome (FEPS) is a rare autosomal dominant genetic disorder characterized primarily by severe, episodic, and relatively localized paroxysmal pain. This pain typically occurs in the distal lower extremities and joints. Patients usually develop symptoms in early childhood, but due to their young age and inability to articulate their discomfort, the condition is often overlooked by parents. Symptoms tend to gradually alleviate or even disappear upon reaching adulthood. Familial episodic pain syndrome can be classified into three types based on different gene mutations, with this case being classified as FEPS type 3. Given the rarity of this condition,

clinical awareness is relatively low, and it is prone to being missed or misdiagnosed. This study aims to contribute to the establishment of more comprehensive diagnostic methods and treatment strategies.

2. Clinical data

2.1. General information

(1) Chief complaint

A 5-year-old male child presented to our outpatient clinic on December 2, 2024, with a history of "joint pain since birth".

(2) Symptoms

The child has exhibited paroxysmal crying without obvious precipitating factors since infancy, predominantly occurring in the afternoons, nights, and during rainy or cold weather, with a frequency of 1 to 3 episodes per day, each lasting for tens of minutes. During these crying episodes, the child kicks their lower limbs and experiences excessive sweating. After being able to speak at the age of one and a half, the child self-reported intermittent and periodic pain in the lower limb joints. During pain episodes, there is no limitation in joint movement, no rash, redness, bruising, or other color changes, and no skin breakdown. Since the onset of the condition, the child's growth and development have been generally normal, with no limb numbness, satisfactory appetite, and no dysfunction in urination or defecation.

(3) Past medical history

The child has been generally healthy, with no history of infectious diseases such as hepatitis, tuberculosis, or typhoid fever, nor close contact with such cases. There is no history of significant psychological trauma, traumatic surgery, or blood transfusion. The child has received all scheduled vaccinations on time and has no history of exposure to special medications or toxins.

(4) Personal history

G1P1 (first pregnancy, first delivery), full-term spontaneous vaginal delivery, with unremarkable conditions at birth. The child was fed with a combination of breast milk and formula after birth and was weaned at one year old. Growth and development have been comparable to peers, with a regular daily routine.

(5) Family history

The child's mother reports experiencing paroxysmal pain in the lower limb joints since childhood, with the intensity of pain increasing with each episode. She was previously misdiagnosed with growing pains in children and was treated with oral traditional Chinese medicine preparations, which were ineffective. The symptoms could be alleviated by immediately taking pain relievers such as paracetamol tablets after an episode. However, if medication was delayed, the effect was poor, and the paroxysmal pain would recur. Paying attention to keeping warm and avoiding cold and dampness can reduce the frequency of attacks. The symptoms of the child's mother gradually alleviated with age until the pain almost disappeared in adulthood. In the family, a total of 12 family members across four consecutive generations, including the child's mother, exhibited similar symptoms, all of whom experienced gradual relief or even complete disappearance of symptoms after reaching adulthood.

3. Examination

(1) Physical examination

The patient's body temperature was 36.5 ℃, pulse rate was 68 beats/min, respiratory rate was 16 breaths/min, and blood pressure was 115/70 mmHg. The patient was conscious, in good spirits, with normal respiration, strong heart sounds, regular rhythm, and a normal heart border upon percussion. No murmurs were heard in any valve area. Breath sounds in both lungs were clear, superficial lymph nodes were of normal size, and there were no petechiae or ecchymoses on the skin. No significant muscle atrophy was observed in the limbs.

(2) Auxiliary examination

Blood routine examination showed no significant abnormalities in white blood cells, neutrophils, eosinophils, or C-reactive protein ("0.10 mg/L", reference range: 0–10 mg/L). Trace elements, vitamin D, rheumatoid factor ("8.3 IU/mL", reference range: 0.0–20.0 IU/mL), antistreptolysin O ("8 IU/mL", reference range: 0–200 IU/mL), immunoglobulin M ("1.29 g/L", reference range: 0.43–1.93 g/L), immunoglobulin G ("5.60 mg/L", reference range: 5.4–13.4 mg/L), immunoglobulin A ("0.88 g/L", reference range: 0.3–1.88 g/L), and complement C3 ("0.98 g/L", reference range: 0.78–2.1 g/L) showed no significant abnormalities, while C4 ("0.10 g/L") was slightly lower than the normal range (reference range: 0.17–0.48 g/L). Folic acid, at "13.80 ng/mL" (reference range: 5.21–24 ng/mL), is normal, while vitamin B12, at "1188 pg/mL", is higher than the normal range (reference range: 180–916 pg/mL).

(3) Genetic testing

Next-generation sequencing revealed a heterozygous mutation c.665G > A in the SCN11A gene, and family verification indicated that the child's mother also carries this mutation. This variant is a single nucleotide variation located on chromosome 5 at chr3:38966953, resulting in the substitution of arginine (Arg) with histidine (His) at position 3P22 in the protein. This locus (p.R222H) has been reported in the literature as familial episodic pain syndrome type 3. The inheritance pattern of familial episodic pain syndrome type 3 associated with this gene is autosomal dominant. Other related diseases of this gene include hereditary sensory and autonomic neuropathy type 7, which also follows an autosomal dominant inheritance pattern (**Figure 1**).

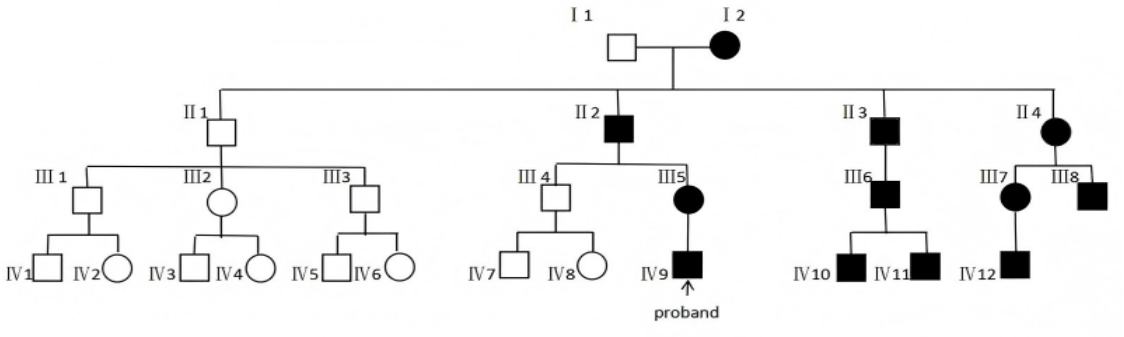

Figure 1. Patient's pedigree chart.

4. Diagnosis and differential diagnosis

(1) Differentiating from growing pains

Growing pains typically present without other accompanying symptoms, whereas familial episodic pain syndrome type 3 may be accompanied by other neurological symptoms. Genetic testing can aid in differentiation.

(2) Differentiating from rheumatism

Rheumatism often manifests as migratory soreness and pain in joints and muscles, with significantly elevated erythrocyte sedimentation rate and antistreptolysin O levels. In contrast, familial episodic pain syndrome type 3 is a hereditary neuralgia characterized by paroxysmal pain without the joint and muscle symptoms and laboratory abnormalities associated with rheumatism.

(3) Differential diagnosis of orthopedic diseases

Osteoarthritis, gouty arthritis, and other orthopedic diseases often present with symptoms such as joint pain, stiffness, and deformation, and joint lesions can be observed on X-ray or CT scans. In contrast, the pain in familial episodic pain syndrome type 3 is unrelated to joint lesions, and no abnormalities are detected on imaging examinations.

(4) Differential diagnosis of FEPS1 and FEPS2

The pain symptoms of FEPS1 primarily occur in the upper body, such as the arms, shoulders, and chest. The pain symptoms of FEPS2 mainly occur in the feet. In contrast, the pain in familial episodic pain syndrome type 3 primarily occurs in the distal joints of the limbs.

In summary, the child was diagnosed with familial episodic pain syndrome type 3.

5. Treatment

The child did not receive oral medications or other treatments at our hospital. The child's mother had previously self-administered pain relievers such as paracetamol tablets and traditional Chinese medicine preparations.

6. Treatment outcomes, follow-up, and prognosis

The child still experiences episodic pain in the distal extremities of both lower limbs several times a day, but keeping warm and avoiding damp and cold conditions can reduce the frequency of episodes.

7. Discussion

Familial episodic pain syndrome (FEPS) is a rare autosomal dominant genetic disorder characterized by severe episodic pain that manifests in early childhood, primarily affecting the distal extremities. The symptoms of FEPS gradually alleviate and may even completely disappear as the patient ages [1]. The underlying mechanism may be related to the gradual decline in the physiological expression levels of voltage-gated sodium channels (VGSCs) with age. Due to the relatively limited clinical awareness of FEPS, misdiagnosis or missed diagnosis frequently occurs. Therefore, when encountering patients with similar symptoms, after excluding secondary limb pain disorders such as rheumatism, hematological diseases, and orthopedic conditions, it is advisable to consider the possibility of FEPS. Genetic screening of patients and their family members can facilitate a definitive diagnosis, thereby preventing secondary harm caused by the misuse or abuse of medications. Some patients may develop

psychological abnormalities; in this case, the patient's family members attributed the symptoms to superstitious beliefs due to the presence of similar symptoms in multiple family members. Early diagnosis can significantly alleviate the psychological and financial burdens on the patient's family.

The clinical features of FEPS primarily manifest as episodic limb pain and numbness, with the pain predominantly concentrated in the lower extremities, knees, and ankles. Occasionally, the pain may ascend to the elbows, wrists, and palms, and may even affect the proximal extremities and waist. The pain is intense and paroxysmal, often occurring in the afternoon or evening, and exhibits a periodic pattern. The precipitating factors include weather changes, cold, and stressful events, among others, while heat application or the use of nonsteroidal anti-inflammatory drugs (NSAIDs) can partially alleviate the pain. FEPS can be classified into three types based on different gene mutations: FEPS1, FEPS2, and FEPS3 [2].

(1) FEPS1

It is caused by heterozygous variations in the transient receptor potential ankyrin 1 gene (TRPA1) located on chromosome 8q21. The pain primarily occurs in the upper body, such as the arms, shoulders, and chest, and is often triggered by factors such as eating, fatigue, and cold. A warm environment can alleviate the pain, while NSAIDs have no significant effect [3].

(2) FEPS2

It is caused by variations in the sodium voltage-gated channel alpha subunit 10 gene (SCN10A) located on chromosome 3p22. The pain mainly occurs in the feet and is unrelated to cold or other triggering factors, although warmth can sometimes alleviate the pain. Skin biopsies reveal partial or complete loss of intraepidermal nerve fiber density [4].

(3) FEPS3

Caused by variations in the sodium voltage-gated channel alpha subunit 11 gene (SCN11A) located on chromosome 3p22. The pain primarily occurs in the distal joints of the limbs, particularly the knees and ankles. Some patients show a certain therapeutic response to NSAIDs, and the frequency of pain episodes decreases with age [5].

This case is classified as FEPS3.

Familial episodic pain syndrome type 3 (FEPS3) is an autosomal dominant genetic disorder. The phenotypic details of this disease are as follows: During pain episodes, patients experience hyperhidrosis, abnormal physiological functions of the autonomic nervous system, and pain, while other sensory modalities may remain normal or diminished. The onset of the disease occurs in early childhood, with patients perceiving pain as cold. Episodes are triggered by fatigue, illness, or strenuous exercise [6]. Nonsteroidal anti-inflammatory drugs (NSAIDs) can alleviate pain, which often occurs later in the day. There is a tendency for episodes to decrease with age, and some patients may develop adult-onset small fiber neuropathy [7].

Neuroelectrophysiological tests and nerve biopsies lack specificity in diagnosing FEPS during the onset period. However, as clinical symptoms resolve, some patients may develop lesions in unmyelinated nerve fibers. These lesions aid clinicians in differentiating FEPS from other types of peripheral neuropathies. Exome sequencing has revealed that FEPS patients carry SCN11A gene variants, including known mutations and newly discovered heterozygous mutations.

Currently, the treatment strategy for FEPS primarily relies on symptom relief, such as using hot compresses and NSAIDs like ibuprofen and naproxen to alleviate mild to moderate pain. However, long-term use of NSAIDs requires attention to potential side effects. For patients who do not respond well to pharmacological treatment,

neuromodulation techniques, such as transcranial magnetic stimulation (TMS) and spinal cord stimulation (SCS), may be effective treatment options. Additionally, psychotherapy, such as cognitive-behavioral therapy (CBT), can help improve patients' coping abilities and reduce psychological stress caused by pain.

As a rare autosomal dominant inherited neuropathic pain syndrome, the treatment of FEPS may focus on the following aspects in the future.

(1) Pharmacotherapy

Develop novel drugs targeting specific ion channels or receptors to more precisely regulate pain signal transduction. For instance, drugs targeting sodium ion channels such as Nav1.7, Nav1.8, and Nav1.9, or drugs targeting transient receptor potential (TRP) channels, may become new treatment options for FEPS in the future.

(2) Physical therapy and neuromodulation

Explore more effective physical therapy methods, such as electrical stimulation and magnetic stimulation, as well as neuromodulation techniques, such as spinal cord stimulation and deep brain stimulation, to alleviate or eliminate pain symptoms.

(3) Gene therapy

With the continuous advancement of gene editing technologies, such as CRISPR-Cas9, it may be possible in the future to precisely repair or replace the disease-causing genes of FEPS, thereby fundamentally addressing the pain issue.

At present, due to the genetic heterogeneity and diverse clinical manifestations of FEPS, establishing unified treatment standards still poses challenges. Additionally, for FEPS patients with negative genetic tests or unknown pathogenic mechanisms, diagnosis and treatment become even more complex.

8. Conclusion

Pediatric limb pain is a symptom that encompasses a wide range of diseases. When encountering such cases, clinicians need to carefully differentiate and diagnose them, rather than simply categorizing them as growing pains or arthritis. It is also necessary to consider the possibility of some uncommon or rare diseases. Additionally, genetic screening can be performed on children when necessary to clarify the cause of the disease and avoid unnecessary secondary harm caused by the misuse of medications.

Disclosure statement

The authors declare no conflict of interest.

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