Hyperkalemic Periodic Paralysis in Twenty-Two Family Members Over Four Generations: A Rare Case Report

Dear Sir,

Acute, generalized, muscle paralysis in a young and healthy individual causes much distress.[1] Periodic paralysis is a rare disorder affecting muscle ion channels. It may be genetic or acquired. Chiefly these are classified into four types: hypokalemic, hyperkalemic, thyrotoxic periodic paralysis, and Anderson Tawil syndrome.[2] Potassium plays a vital role in the normal physiology of different tissues and membranes in the body like the cardiac, skeletal muscles, and neurons.[3] Hyperkalemic periodic paralysis is characterized by attacks of flaccid limb muscle weakness, which may be associated with weakness of trunk, extraocular muscles, throat, and respiration. Serum potassium tends to be higher than normal blood levels during the episode.[4] We are reporting a case of hyperkalemic periodic paralysis with positive family history in 21 other family members, four of whom revealed the same mutation.

A 24 years old male born out of non-consanguineous marriage came to our hospital with complaints of episodic pure motor weakness in all four limbs since childhood. The frequency of attacks was multiple in a month. The duration of a single attack ranged from minutes to hours in different episodes. The triggers of the events were cold exposure, physical exertion, and anxiety episodes. There was no associated tingling or numbness in limbs, breathlessness, dysphagia, or dysphonia. There was no history of any associated comorbidities. His birth, developmental, and vaccination history were normal. The history of exposure to addictive substances or any medications was negative. Family history revealed similar complaints

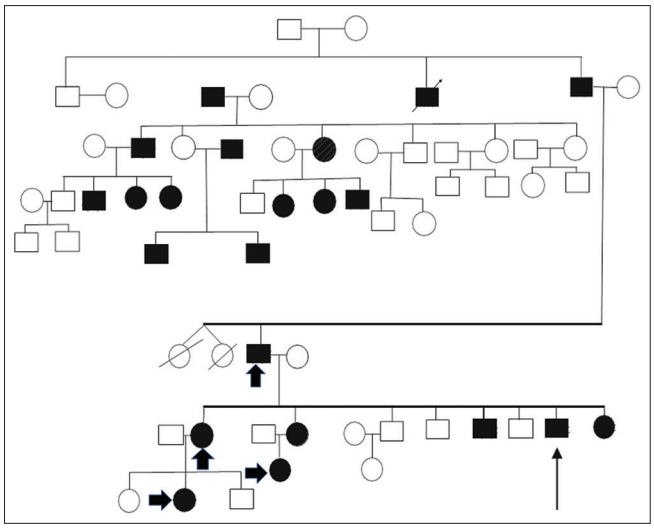

Figure 1: Pedigree chart showing the family tree of the patient (arrow) having similar symptoms of episodic flaccid muscle weakness in 22 family members. Four other members (bold arrows) revealed SCN 4A (p.Thr704Met c.2111C>T) mutation

of recurrent episodes of quadriparesis without dysphagia or dyspnea in 21 other family members [Figure 1]. The common triggers were cold exposure and physical exertion.

On examination, his vitals were stable. Neurological examination revealed bilateral, symmetrical, weakness of all groups of muscles at all joints (MRC grade 4/5). The rest of the general and systemic examination findings were unremarkable.

On laboratory testing, serum potassium was 5.8 mEq/L (4.5-5.5), calcium 10.2 mg/dl (8.5-10.2), phosphorus 2.4 mg/dl (2.8-4.5), and thyroid stimulating hormone was 4.24 (0.5-5 Miu/L). His serum creatine kinase was 711.4 IU/L (24-195) and lactate dehydrogenase was 334.8 IU/L (140-280). Electrocardiogram was within normal limit. Motor and sensory nerve conduction study of all four limbs revealed the normal study. Electromyography revealed myopathic motor unit action potential without any spontaneous activity in upper and lower limbs muscles. Genetic testing was done which was SCN 4A positive (p.Thr704Met c. 2111C>T). Genetic testing was also done on four other family members who revealed similar mutation [Figure 1]. Hence a diagnosis of hyperkalemic periodic paralysis was made. The patient was started on acetazolamide 250 mg three times a day with lifestyle and dietary modification. For the past 6 months, the patient did not have any new episode.

The above case presented with multiple attacks of episodic weakness of all four limbs precipitated by various triggers since childhood. Family history revealed similar illnesses in multiple family members. Serum potassium and creatine kinase level was higher. SCN 4A (p.Thr704Met c. 2111C>T) mutation was present on genetic testing in the patient as well as in his four family members.

Periodic paralysis encompasses a group of inherited disorders. Episodic muscle weakness and paralysis are the common clinical features among them. Hyperkalemic periodic paralysis, a rare sodium channelopathy, is inherited in an autosomal dominant fashion with complete penetrance. It manifests in early childhood and can last until middle age or even late adulthood.[5] The mutation typically involves pore-forming segments S5-S6 and the voltage sensor segments S4 of Nav1.4. Apart from the above sites, a few cases are also reported with mutations in domains II and IV of segment S1.[6]

Recurrent attacks may lead to progression to chronic progressive myopathy which results in permanent muscle weakness.[7] Hyperkalemic periodic paralysis may manifest with or without myotonia or with paramyotonia congenita (PMC).[8] In the present case, apart from grade 4/5 weakness, there were no other manifestations like myotonia or paramyotonia. On electromyography, the presence of myopathic motor unit action potential confirms the development of myopathy owing to the chronicity of illness.

Both acute attack management and prevention should be part of the therapeutic strategy of hyperkalemic periodic paralysis. Treatment options include carbonic anhydrase inhibitors, diuretics, behavioral treatments aimed at avoiding triggers, and dietary changes to alter potassium levels. Attacks can be managed by engaging in light exercise, eating foods high in carbohydrates, inhaling salbutamol, or administering calcium gluconate intravenously.[9]

Since over 50 years, acetazolamide and dichlorphenamide, two carbonic anhydrase inhibitors, have been utilized as an initial treatment for hyperkalemic periodic paralysis. Uncertainty surrounds the mechanism of action in periodic paralysis. By increasing urine bicarbonate excretion, carbonic anhydrase inhibitors cause kaliuresis and a nonanion gap acidosis.[10] The systemic acidosis may reduce the susceptibility to periodic paralysis. Enhancing the opening of calcium-activated K channels is an alternative hypothesis.[11] In order to prevent attacks, people should abstain from fasting, physical activity, and exposure to the cold.

Sushan Luo *et al.*[12] reported a case of hypokalemic periodic paralysis with a similar history in four members of the family. Genetic analysis revealed p.R1451L mutation. Our case is the first-ever case of hyperkalemic periodic paralysis with positive family history in 22 members.

Today, genomic data holds significant promise for enhancing healthcare strategy in a variety of ways, including illness prevention, improved diagnosis, and improved therapy. The lack of genotype-phenotype correlations for Indians at both the populational and individual levels is one of the major challenges faced by the country's medical and research communities.[13]

Numerous genetic databases, including Index-DB, TMC-SNPdB, SAGE, IGDD, IGVdB, GWAS Central, Indian SNP Data, Genotype/Phenotype DB, and Indigen Project, are available for the Indian population. A total of 15015608 germline variations were discovered, according to TMC-SNPdB data.[14] Sanger sequencing is a single-gene sequencing technique in which small segments of DNA are sequenced to look for particular mutations. When confirming mutations among family members of a proband

who has been identified with the same genetic mutation, this test has been shown to be cost-effective. At present, next generation sequencing (NGS) proved to be much quicker and cost-effective than other genetic analysis methods.[15] However, in the Indian subcontinent, apart from ignorance of these advanced techniques, the major hurdles are financial constraints and fear of social outcast after being diagnosed with genetic diseases.

To conclude, a detailed family history and pedigree charting aid in diagnostic evaluation and determination of the mode of inheritance in cases with episodic muscle weakness. Large-scale genetic studies in Indian patients are needed to study disease-causing mutations and to establish individualized treatment methods. A proper genetic counseling session for the affected ones will help in alleviating apprehension, understanding the inheritance, prevention, and therapeutic measures.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

Ankur Vivek and Pratishtha Sengar contributed equally and shared first authorship. Rest there are no conflicts of ineterst.

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Submitted: 14-May-2023 **Revised:** 03-Jul-2023 **Accepted:** 04-Jul-2023
Published: 11-Sep-2023

DOI: 10.4103/aian.aian_425_23