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Original Article - Case Report

NGF Mutation Associated with Hereditary Sensory and Autonomic Type V and Orthopedic Aspects

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ABSTRACT

Hereditary sensory and autonomic neuropathy type V is a very rare autosomal recessive disorder, manifested by the loss of temperature and pain sensation. This condition can cause painless fractures, bone necrosis, osteochondritis, and neuropathic joint destruction, subsequent to repetitive trauma. We report the case of a 7-year-old girl with ankle arthropathy that began 6 months after a minor trauma. The clinical condition was initially thought to be infectious or oncologic in nature. We later determined that the pathology was associated with the nerve growth factor gene mutation and proposed the pathogenicity of variant c.361C>T p.(Arg121Trp) based on clinical findings and genetic testing for the patient and her parents.

Abbreviations

Hereditary sensory and autonomic neuropathies (HSAN); Autosomal Recessive (AR); Nerve growth factor (NGF); Copy number variations (CNVs); American College of Medical Genetics and Genomics (ACMG).

Keywords

Pediatric Charcot Joint; Hereditary Sensory and Autonomic Neuropathy Type V; HSAN V; Mutation.

INTRODUCTION

Hereditary sensory and autonomic neuropathies (HSAN) are a clinically and genetically heterogeneous group of disorders characterized by the loss of pain sensation, in combination with other sensory and autonomic abnormalities. They are classified into five types by Dyck and other authors, based on genetic mutations, inheritance patterns, and predominant clinical features[1]. The classification later was expanded and included eight types and subtypes[2]. HSAN-V, which is part of the original classification, is an autosomal recessive disorder characterized by selective loss of pain sensation, thermal perception and neuropathic joints[3]. The responsible genetic mutation in HSAN V is the nerve growth factor (NGF) gene. We report the case of a girl who developed swelling and destruction of the left ankle joint over a 6-months period. Osteomyelitis or malignancy was considered as a possible diagnosis. Neurological examination, radiographs, and laboratory tests revealed abnormal characteristics for (HSAN V). The importance of this article is to present the atypical presentation of HSAN V, given the difficulty of diagnosing this patient.

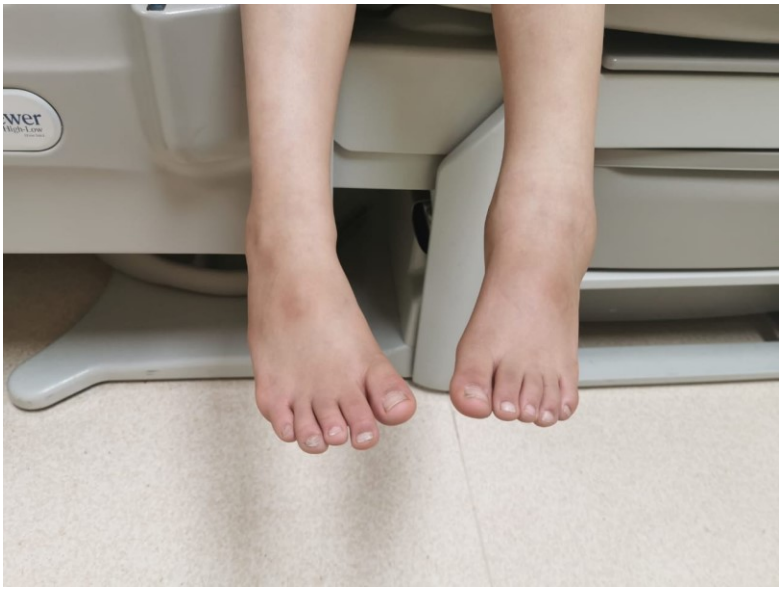

Figure 1: Showed swelling in left ankle.

CASE REPORT

7 years old healthy girl whose history began 6 months ago with a trauma resulting from falling from around a half meter that caused her to complain of left ankle swelling. They proceeded to a local hospital, where she was diagnosed with an ankle sprain as the X-Ray initially showed no fracture, according to the family. Five months later, she was referred to our hospital as a case of left ankle osseus abnormality and deformity for further investigations after she started to have a painless swelling in the left ankle (Figure 1). On examination, she was conscious, alert, cooperative, and motivated with no dysmorphic features. She was afebrile, with all vital signs in the normal range, and was walking normally with no limping. Power, sensation, and reflexes were all normal. The levels of white blood cells, C-reactive protein, and erythrocyte sedimentation rate were all within normal limits. An X-ray revealed destruction in the left ankle joint with medial malleolus displaced fracture and sclerotic changes in subtalar, talonavicular, and calcaneocuboid joints (Figure 2) and left knee medial tibial plateau depression and destruction, which was not symptomatic and was not correlated to a noticeable history of trauma as per the parents' declarations (Figure 3). Magnetic resonance imaging revealed displaced medial malleolus fracture with significant joint effusion and enhanced bone marrow and thick enhancement synovial picture which are suggestive of prior fracture with underlying neuropathic arthropathy. The infection process could not be excluded. Three phases bone scan showed increased osteoblastic activity limited to distal left tibia in the background of dislocated fracture, likely suggestive of neuropathic arthropathy. Computed tomography (CT) guided biopsy taken from left ankle showed no bacterial growth. Genetic analysis revealed a mutation in nerve growth factor variant c.361C>T p.(Arg121Trp). Supportive management was considered for the patient with a brief non-weight bearing immobilization followed by weight bearing cam-walker.

METHODS

A blood sample in EDTA was obtained from the patient after informed written consent was given to the patient's parents. The sample was sent to Centogene in Rostock, Germany for whole exome sequencing. Double-stranded DNA capture baits against ~36.5 Mb of the human coding exome (targeting >98% of the coding RefSeq from the human genome build GRCh37/hg19) are used to enrich target regions from fragmented genomic DNA with the Twist Human Core Exome Plus kit. The depth of coverage of the identified variants ranged from 20 to 84, and the quality score was optimal. The interpretation of the NGF variant

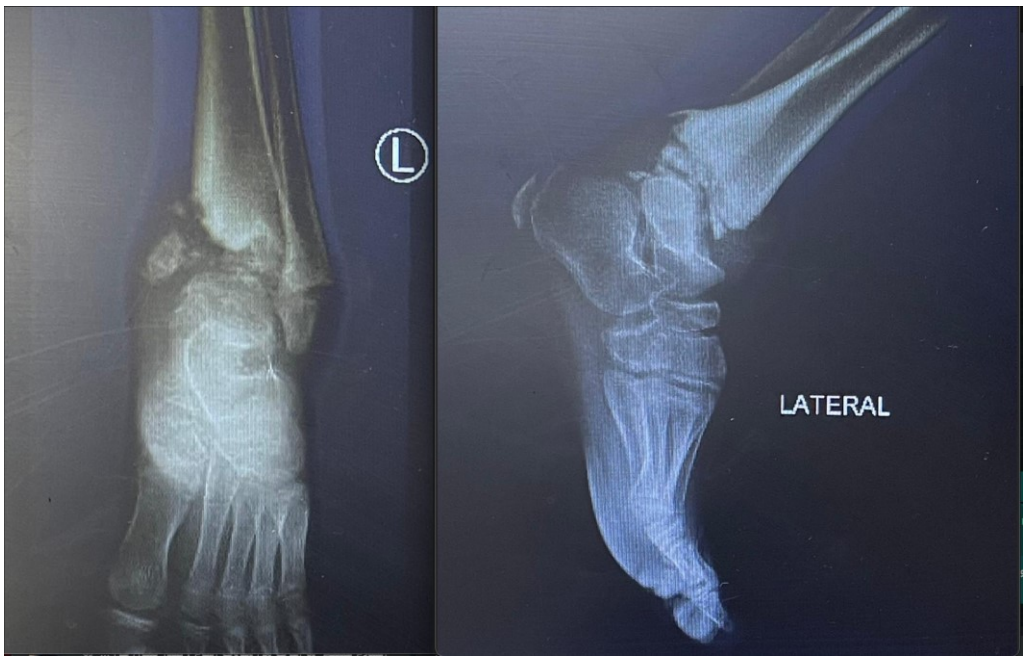

Figure 2. Anteroposterior and lateral x-ray views showed destruction in ankle joint with medial malleolus displaced fracture and sclerotic changes in subtalar, talonavicular and calcaneocuboid joints.

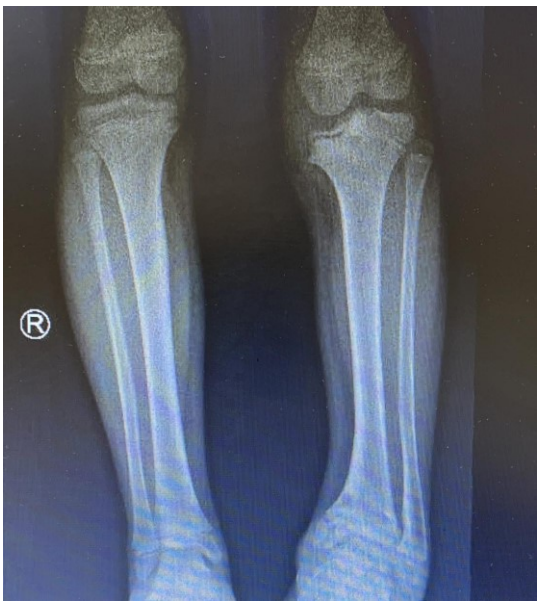

Figure 3. Anteroposterior x-ray view of bilateral lower limb showed left knee medial tibial plateau depression and destruction in addition to left ankle medial malleolus fracture.

was c.361C>T p.(Arg121Trp), which causes an amino acid change from Arg to Trp at position 121. According to the Human Gene Mutation Database Professional 2019.4, this variant has previously been described as disease-causing for autism spectrum disorder[14]. Functional analysis of the variant, found in one patient, by Shaikh et al., 2018[15] is supportive of its pathogenic effect.

All potential modes of inheritance patterns are taken into consideration. Moreover, available family

Table 1. Identified NGF gene mutation variant annotation based on OTFA (using VEP v94)
* AlignGVD: C0: least likely to interfere with function, C65: most likely to interfere with function; splicing pre-dictions: Ada and RF scores. ** Genome Aggregation Database (gnomAD), Exome Sequencing Project (ESP), 1000Genome project (1000G) and CentoMD® (latest database available). *** based on ACMG recommendations.

CNV DESCRIPTION	AMINO ACID Change	ZYGOSITY	IN SILICO PARAMETERS*	ALLELE FREQUENCIES*
NM_002506.2:c.361C>T	p.(Arg121Trp	Homozygous	PolyPhen: Probably damaging Align-GVGD: C65 SIFT: Deleterious MutationTaster:Disease causing Conservation_nt: moderate Conservation_aa: high	gnomAD: 0.0000040 ESP: - 1000 G: 0.00010 CentoMD: 0.000087

history and clinical data are employed to investigate identified variants concerning their pathogenicity and causality. Variants are categorized into five classes (pathogenic; likely pathogenic, variant of uncertain significance, likely benign; benign). All variants related to the phenotype of the patient are reported. Centogene has established validation and quality criteria that are very stringent for the detection of variants by NGS. Orthogonal methods are employed to confirm variants with low quality and/or unclear zygosity. Consequently, a specificity of >99.9% for all reported variants is warranted.

DISCUSSION

Hereditary sensory and autonomic neuropathy type V (HSAN-V) is manifested by the loss of pain and temperature sensations, leading to painless fractures, bone necrosis, osteochondritis, and neuropathic joints destructions, with preserved muscle strength and retained tendon reflexes[4-9]. The severity of anhidrosis and the absence of mental retardation distinguish it clinically from HSAN IV[10-11]. Our patient has arthropathy of the left knee and ankle joints, with no skin manifestations or autonomic disorders, and no mental retardation.

NGF is a gene that codes for a protein that stimulates nerve growth and belongs to the NGF-beta family. The protein is involved in the regulation of sympathetic and certain sensory neuron growth and differentiation. NGF is originally found in a 7S, 130-kDa complex composed of three proteins – alpha-NGF, beta-NGF, and gamma-NGF (2:1:2 ratio). The nerve growth factor-beta gene (NGFB) is found on chromosome 1p13.2 [12]. This gene is part of the NGF-beta family and encodes a secreted protein that homodimerizes and is incorporated into a larger complex, that is involved in the development and maintenance of the sympathetic and sensory nervous systems[9]. Mutations in this gene have been linked to hereditary sensory and autonomic neuropathy, type 5 (HSANV)[13]. The proband was homozygous for the c.361C>T p.(Arg121Trp) and causes an amino acid change from Arg to Trp at position 121 (Table 1). According to the Human Gene Mutation Database Professional 2019.4, this variant has been previously described as a disease-causing for autism spectrum disorder[14] and neuropathy, as well as hereditary sensory and autonomic type V[15]. Functional analysis of this variant found in one patient by Shaikh is supportive of its pathogenic effect[15]. Only one other patient has been found in the house to have this variant. The phenotypic overlap of these patients is inconsistent, until more is known about this variant, it is classified as a variant of uncertain significance (class 3) according to the recommendations of Centogene and ACMG.

So far, pathogenic variants in NGF have been associated with neuropathy, hereditary sensory and autonomic, type V (HSAN 5). Dyck et al.[16] reported a girl with congenital insensitivity to pain. She was tactile responsive, retained tendon reflexes, and exhibited normal motor and sensory nerve conductions. She self-mutilated her lips, tongue, and fingers and displayed mild autonomic dysfunction, including blotching of the skin, decreased sweating, and episodic elevations in body temperature. Nerve

conduction velocities were normal, but there were no somatosensory evoked responses to stimulation of the tibial nerve over the spine. Nerve biopsy revealed a selective, nearly complete absence of small myelinated afferent fibers and a relatively small, reduced number of unmyelinated fibers. Carvalho et al.[9] reported that five members of a consanguineous Emirati Bedouin family, aged two to twelve, were found to have HSAN V, and mild mental retardation was evident by the age of four. The first symptom was painless lip, tongue, and digit biting. They were all anhidrosis patients and could not distinguish hot from cold or detect hot spicy food. In addition, all developed a premature age-related change, including malar hypoplasia, sunken eyes, and tooth loss. All had multiple, painless injuries of variable intensity and demonstrated poor wound healing. Their parents were asymptomatic and their clinical phenotype was normal, but their molecular genetic tests showed the NGF variant c.361C>T p.(Arg121Trp) causing an amino acid change from Arg to Trp at position 121. The targeted variant of the NGF gene was identified in a heterozygous state. The carrier status of the NGF variant is confirmed. Pathogenic variants in this gene are related to autosomal recessive neuropathy, hereditary sensory and autonomic, type V. Parental testing confirms homozygosity of the identified variant in the index patient. Thus, depending on the clinical picture of the index case and based on a genetic test for her and the parental carrier testing, we are proposing the pathogenicity of this variant and its upgrade from a variant of uncertain significance to a pathogenic variant.

Nerve biopsy and neurophysiological studies have not been performed because they would not benefit the patient and would not change her diagnosis or management. However, Jan Minde et al. reported a normal velocity study except for increased temperature thresholds, and a Sural nerve biopsy with morphometric analysis revealed a moderate loss of thin myelinated fibers and a severe reduction in unmyelinated fibers[6]. We treated our patient conservatively, and we carefully educated the patient and family to help slow the progression of joint destruction. Deformity and instability are the main issues due to the disease's progressive nature. Arthrodesis, corrective osteotomy, and limb lengthening may be considered in the future[17].

CONCLUSION

HSAN-V can present with neuropathic joints in a young child without other clinical features of HSAN. They can be misdiagnosed as osteomyelitis. A HSAN workup should be considered in children with neuropathic joints to avoid further delay in diagnosis or the use of unnecessary interventions. We suggest upgrading c.361C>T p.(Arg121Trp) as a likely pathogenic variant.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgements

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