ATYPICAL PRESENTATION OF HETEROTROPIC OSSIFICATIONS IN A PATIENT WITH CONGENITAL INSENSITIVITY TO PAIN WITH ANHIDROSIS (CIPA)

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Introduction

Congenital insensitivity to pain with anhidrosis

also known as hereditary sensory and autonomic neuropathy type IV is a rare **autosomal recessive disorder** with an estimated prevalence (in Japan) of 1 in 600,000 - 950,000.

Early diagnosis is possible in children with generalized loss of pain and thermal sensation, anhidrosis, predisposing to recurrent febrile episodes self-mutilating behavior, bone fractures, many of which fail to heal properly, developmental delay, and intellectual disability of variable degree.

Biallelic mutations of the gene for the **neurotrophic tyrosine kinase-1 receptor** account for **all cases of properly classified CIPA**. **Neurotrophic tyrosine kinase-1 receptor**, also known as tropomyosin-related kinase A is a **high-affinity receptor for nerve growth factor** contributing to nerve development and differentiation.

➤ Here we report on a woman with CIPA, manifesting with progressive joint destruction with massive osteophytosis developed in adolescence.

Material and Methods

Microarray-based chromosome analysis

• Microarray-based chromosome analysis was performed using an Affymetrix CytoScan® HD array (Affymetrix, Santa Clara, CA, USA).

Data were analyzed:Chromosome Analysis Suite software version 3.1.1.27 (Affymetrix) at ≤50 kb resolution & Databases: DECIPHER, Database of Genomic Variants, Online Mendelian Inheritance in Man, UCSC, the International Standards for Cytogenomic Arrays, Ensembl database

❑**Next Generation Sequencing (NGS) analysis** – 2762 genes (patient and her parents).

•Lymphocyte DNA was sequenced on a NextSeq500 system (Illumina, San Diego, CA, USA).

➤All detected variants were checked against **publicly available reference** datasets (dbSNP150, 1000 Genomes Project, Exome Variant Server, gnomAD population database, VarSome database, OMIM, HGMD, ClinVar) and other sources in a **self-implemented user interface**

➤Sequence variants **were interpreted according to the 2015 guidelines** of the ACMG/AMP

➤**Segregation analysis** was performed by **Sanger sequencing** on a **Beckman Coulter CEQ 8800 Genetic Analysis System**

❑**Sweat gland function was assessed using pilocarpine iontophoresis producing only negligible amounts of sweat**

Clinical report

❑ A 23-year-old female from Northern Macedonia presented with a tumorous swelling of multiple joints and a deformed thumb.

❑ **Past history: 2 years** – spontaneous wound on the sole of her left foot, healed only after several months of treatment; **7 years** – soft tissue calcifications at the right elbow; **10years** – fracture of her left hip requiring surgery with a surgical wound that took 5 years to heal; **16 years** - right knee swelling without a known trauma; **17 years** – IQ score 60, suspected intellectual disability

Physical examination:

- alert female patient with a retracted alveolar region, prominent chin, overcrowded teeth with severe caries and thin irregularly lined lips.
- tumor-like, firm swellings (right elbow, knee ,ankle); dislocation of distal phalanx of the left thumb), shortened distal phalanges (some fingers); short, subluxated halluces were present
- Skeletal survey: severe right elbow and knee anomalies, subluxated joints, destroyed articular surfaces and a mixture of sclerosis, massive osteophytosis and bone fragmentation
- Hand films: multiple osteolytic lesions of the end phalanges of some fingers and dislocation of the left thumb

Figure 1. Swelling of the right hindfoot, clawing of the toes.

Results and Discussion

- Alkaline phosphatase was slightly elevated at 216 U/L (normal range 38–126 U/L). All other studied laboratory tests were normal
- NGS analysis of the patient's DNA: a novel variant in the NTRK1 gene, confirmed by Sanger-sequencing.**
- To our knowledge, **this is the first NTRK1 mutation reported from Macedonia and Southeast Europe.**
- Bioinformatic pathogenicity prediction tools indicated **pathological effects.**
- ACMG/AMP classification predicted a Class 5 variant.** The mother and father of the girl were found to be heterozygous for this novel variant.
- ❖A few hundred CIPA patients have been reported. The disorder is often diagnosed late, as in this patient
- ❖To date, a total of 108 different NTRK1 mutations have been reported including missense, nonsense, and splice-site mutations, small insertions or deletions, and gross deletions. Other authors reported further gene alterations.
- ❖Based on the non-consanguinity of the parents of this patient and a previous report of CIPA from Macedonia, Greece , this novel mutation represents a local founder mutation in Macedonia or SEE. In the Turkish population, a founder splice-site mutation in the NTRK1 gene has already been reported. NTRK1 mutations are rare in Europe. Mutations have been reported from Italy, Spain, Poland, and Austria.
- ✓Family education remains necessary. Temperature control is important as malignant hyperthermia or hypothermia can be lethal. The major complications of CIPA are largely orthopaedic.
- ✓Therapeutic approaches are primarily conservative: closed reduction, cast immobilization or surgical fracture repair to achieve an early functional recovery, and possibly bisphosphonates.

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Conclusion

➤This novel sequence variant in the NTRK1 gene **was not reported previously with CIPA** and could possibly represent a **founder mutation in Macedonia or Southeast Europe.**