Hereditary and Sensory Autonomic Neuropathies

Mojdeh Khaledi1, MD, and Nima Rezaei1,2, MD, PhD

1. Research Center for Immunodeficiencies, Pediatrics Center of Excellence, Children’s Medical Center, Tehran University of Medical Sciences, Tehran, Iran
2. Department of Immunology, Molecular Immunology Research Center, Tehran University of Medical Sciences, Tehran, Iran

Received: Jul 19, 2012; Accepted: Oct 31, 2012

Dear Editor;

We read with interest two recent papers on Congenital insensitivity to pain with anhidrosis, entitled “Congenital insensitivity to pain and anhidrosis (CIPA) syndrome; a report of 4 cases” by Daneshjou et al1 and “Congenital insensitivity to pain with anhidrosis (HSAN type IV), extremely rare syndrome that can be easily missed by bone and joint surgeons: a case report” by Ali et al2. Although the clinical phenotypes of the cases are compatible with diagnosis of congenital insensitivity to pain with anhidrosis (CIPA), different presentations of the disease and lack of simple diagnostic tests makes CIPA a tricky diagnosis3. Thus making definite diagnosis should rest on genetic studies.

Hereditary and Sensory Autonomic Neuropathies (HSAN) could be classified into five known subgroups; HSAN1A (OMIM #162400), inherited as an autosomal dominant trait, due to a mutation in the SPTLC1 gene (OMIM*605712), on chromosome 9q22.1-22, has an onset in the 2nd to 4th decade of life with slow and progressive distal sensory loss due to the dorsal ganglia degeneration and motor loss, leading to weakness and muscle wasting. The patient may complain of paresthesia, numbness, distal motor loss, and heel ulcers4. HSAN2A (OMIM #201300), inherited as an autosomal recessive trait, due to a mutation in the WNK1 gene (OMIM* 605232), on chromosome 12p13.33, has an onset in infancy and early years of life. No pain, thermal, touch, and pressure sensation is reported. Sensory loss has a pattern of glove and stocking, and the deep tendon reflex (DTR) is depressed in some patients. Skin biopsy shows involvement of large and small nerve fibers5,6. HSAN3 (OMIM#223900), also known as familial dysautonomia, or Riley Day syndrome, is inherited as an autosomal recessive trait, due to a mutation in the IKBKAP gene (OMIM*603722), on chromosome 9q31, and has an onset in infancy and early years of life. This syndrome presents with little or no sensation to pain and temperature, but normal touch sensation. Other features include recurrent gastrointestinal upsets, little lacrimation, anhidrosis, no sensation of tongue, depressed or no DTR, temperature fluctuations, recurrent fractures, osteomyelitis, gait difficulties, Charcot joints, ligamentous laxity, scoliosis, obvious lack of tong fungiform papillae, and no axon flare6,7. HSAN5 (OMIM#608654) is inherited as an autosomal recessive trait, due to a mutation in the NGFBI gene (OMIM*162030), on chromosome 1p13.

HSAN IV, also known as CIPA (OMIM #256800), is inherited as an autosomal recessive trait, due to mutations in the Neurotrophic Tyrosine Kinase Receptor type 1 (NTRK1) gene (OMIM*191315), which is also known as TRKA, on chromosome 1q21-228. This gene encodes a receptor protein made of 790-796 amino acids, and is divided into extracellular and intracellular domains by a single membrane domain9. The NTRK1 gene via exons 1-8 encodes Nerve Growth Factor (NGF) that is essential for the neural differentiation of the small sensory and sympathetic neurons from the embryonic state10. Loss of function mutations of the gene result in loss of mentioned nerves, and this is the key point in understanding the pathophysiology of CIPA. Although there is complete loss of the unmyelinated nerve fibers, reduced small myelinated fibers, and normal distribution of the

* Corresponding Author: Address: Children’s Medical Center, No 62, Dr Gharib St, Koshavarz Blvd, Tehran, Iran
E-mail: rezaei_nima@yahoo.com

Published by: Tehran University of Medical Sciences (http://ijp.tums.ac.ir)
large nerve fibers is also seen[9]. Skin biopsy could be suggested as a second line confirmatory exam for CIPA.

It should be noted that rule out of the common disorders by the strongest possible evidences should be considered as the first step in diagnosis. Although the clinical manifestations of the presented cases are compatible with CIPA, having a confirmatory paraclinic data is also needed, especially because of lack of suggestive family history and rare prevalence of this syndrome. For definite diagnosis of CIPA, genetic analysis of the NTRK gene, as the most powerful confirmatory laboratory test, could be recommended in suspicious cases.

References


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