

Stroke in a child with type IV hereditary sensory autonomic neuropathy: A coincidence or complication?

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ABSTRACT

Hereditary sensory autonomic neuropathy Type IV is a rare autosomal recessive disorder characterized by congenital insensitivity to pain and generalized anhidrosis and resulting in recurrent hyperpyrexia, self-mutilation behavior. The clinical presentation of a child with this rare disease complicated with stroke is described.

KEY WORDS: Anhidrosis, Insensitivity to pain, Stroke, Hereditary neuropathy.

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INTRODUCTION

Sensory autonomic neuropathy Type IV (Congenital Insensitivity to Pain and Anhidrosis) is a rare syndrome inherited as an autosomal recessive trait. This type of hereditary neuropathy is characterized with episodes of hyperpyrexia, anhidrosis, insensitivity to pain and developmental delay. These patients often have self-amputated fingers and some kinds of self-mutility behaviours. The disease was thought to be caused by a mutation in the Trka gene, encoding for receptor of tyrosine kinase (Tyrosin kinase receptor A) for nerve growth factor, which is necessary for the survival of nociceptive sensory and autonomic neurons. Nerve conduction study shows motor and sensory nerve action potentials to be normal, but somatosensory reflex (SSR)

is absent. The histopathology of peripheral nerve biopsy reveals absent small unmyelinated fibers and mitochondria are abnormally enlarged.¹⁻⁴ The association between HSAN IV and other diseases is not well known.^{1,5,6} We describe a case of HSAN IV with ischemic stroke which to our knowledge, has never previously been reported. Our purpose is to introduce this rarely encountered association, and to present informations related to clinical features of this syndrome.

CASE REPORT

A six-year-old male child was admitted in paediatric neurology ward with complaint of generalized weakness since two weeks age. After admission, left limbs preference was noted. The baby was the first child of a non-consanguineous parents. The second child was a healthy four month baby. He was delivered full term by cesarean section with unremarkable antenatal maternal history and there were no postnatal complications. He had frequent previous admissions. The first one was because of febrile convulsion in four months. He had repeated episodes of convulsion since four months and was symptomatically treated with anticonvulsant drugs. In 5th month of age he was admitted with protracted fever, a full sepsis work-up showed no positive results and cause of the fever was not found. He had unexplained recurrent fevers constantly especially during summer months, he was unable to tolerate the sun exposure. After his teeth started to grow in,

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he began to chew his fingers and bit off the tip of his tongue. At that time, his parents noticed that he was insensitive to painful stimuli. At 2.5 years of age he admitted with painless ulceration of soles of both feet since two years of age. At this time his disease was preliminary diagnosed as HSAN type IV by considering his history of insensitivity to pain and anhidrosis.

In recent admission on physical examination the child had self-inflicted injuries to the lips and a mutilated tongue, the tips of toes and fingers were missing, there were multiple ulcers on both feet. His body temperature was 39.2 C, but his skin was dry and warm. Anthropometric measurements of weight and length were within normal limits (weight:15 kg, height:115 cm, head circumference: 49cm). On neurologic examination the patient was lethargic and could be temporarily awakened with verbal stimuli, there was no evidence of meningism and the optic fundi were normal, he had also severe weakness in right upper and lower limbs with power of grade 1/5 for right hand and foot with a hypoactive deep tendon reflex and an up-going plantar reflex on the right foot. There was a global delay in the developmental milestones and the child was mentally retarded. He was not able to walk.

RESULTS

Routine hematologic and chemistry measurements were normal. Negative or normal results were noted in uric acid, serum glucose, creatine kinase liver, renal, thyroid and parathyroid function tests and lumbar puncture. Nerve Conduction Study findings were normal but somatosensory reflex (SSR) were unobtainable compatible with a sensory-autonomic neuropathy. Intradermal injection of 0.05 mL 1:1000 histamine solution gave rise to the expected wheal without axon flare. Iodine-starch test revealed no sweating. The parents did not give consent to sural nerve biopsy. genetic analysis was not available. Brain CT scan showed a large hypodense lesion in bilateral frontal lobes and left temporoparietal lobe suggestive of severe ischemia.

Bilateral calcification was seen in lentiform nuclei. For the assessment of specific causes of stroke some investigations were done including rheumatoid factor, antinuclear factor, anti-Ds DNA, erythrocyte sedimentation rate, prothrombin time, partial thromboplastin time and lipid profile that all these findings were in normal levels. Heart color Doppler showed nothing abnormal and investigations were negative for sickle cell disease. In addition to supportive care, the patient received physiotherapy

during admission. After improvement of his consciousness, the patient responded well to touch sensation but pain and temperature sensations were absent. He was discharged after eight days with the diagnosis of stroke.

DISCUSSION

According to Dyck classification, hereditary neuropathies are classified as Hereditary Sensory Motor Neuropathy (HSMN) and Hereditary Sensory Autonomic Neuropathy (HSAN). HSAN is sub-classified into five groups on the basis of clinical, histopathologic and genetic characteristics. The clinical picture of HSAN IV patients consists of recurrent high fevers, absence of pain and temperature sense, impaired perspiration and self-mutilation behavior.^{1,7,8} As in our patient, most of them suffer from mild to moderate mental retardation and have delayed motor milestones. Due to the varying phenotypical expression, mental retardation can range from mild to severe. This rare disease has a non-specific radiographic and magnetic resonance imaging (MRI) appearance. Differential diagnosis includes other types of hereditary and acquired sensory neuropathies affecting small myelinated and unmyelinated nerve fibers.^{9,10}

We report this case with a distinctive feature of stroke imposed on a case of hereditary sensory autonomic neuropathy type IV. We found no previous report of the association of stroke with HSAN IV.

In a previous report, two cases of HSMN II (Charcot-Marie-Tooth disease) with stroke are described. One of those patients had ischemic and the other one had hemorrhagic stroke.¹¹

Iwanagaa et al, reported a 9-month-old girl with congenital sensory neuropathy with anhidrosis who had a brain MRI showing a bilateral symmetrical paracentral hypo-intensity of the white matter with occipital hypo-intensity. MRI findings were considered to represent the brain damage as a complications of the recurrent episodes of high fever with a loss of water from the cerebral parenchyma.¹²

In a report by Juri et al a 14-month-old girl presented with acute encephalopathy and because of a history suggestive of remittent fever and hypohydrosis biopsy of sural nerve was performed. This patient was diagnosed as having HSAN IV and the acute encephalopathy was known as a complication of the underlying neuropathy and as a result of heat stroke.¹³

Our 6-year-old patient is the first case, in the medicine-based literature, of the association of HSAN IV

with stroke. In a review of the literature, some important aspects of these patients are emphasized, especially in relation to the nociceptive dysfunction and impaired thermoregulation.

Systems other than the central nervous system may also be involved in this type of congenital neuropathy including bone fractures requiring protracted healing times, joint deformities, immune system disturbances and chronic inflammatory state leading to amyloidosis.¹⁴ Investigation did not yield any finding suggesting a multisystem involvement in our patient. Because of paucity of reports about the association of stroke and HSAN it is difficult to define whether the stroke occurred as a complication of the neuropathy or that was just a coincidence. After confirmation of stroke in any child by imaging, comprehensive investigations to determine the predisposing cause is recommended. HSAN IV should be considered as a rare underlying cause of childhood stroke.

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