

## Case Report

# A Case of Hereditary Sensory and Autonomic Neuropathy Type II with Retinitis Pigmentosa

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A 20-year-old female had noted a mild truncal instability during her childhood. At 12 years of age, she became aware of decreased visual acuity. She was made a diagnosis of retinitis pigmentosa at that time. On admission, deep tendon reflexes were absent in all limbs. The patient's deep sensations were impaired throughout her entire body, except for her face and neck. Superficial sensations were impaired on her legs. Sensory nerve action potentials were not elicited, but motor nerve conduction velocities were all within normal ranges. A biopsy of the sural nerve showed a marked reduction in the myelinated fibers, but not in the unmyelinated fibers. The neurological findings were consistent with the hereditary sensory and autonomic neuropathy type II disease. The relationship between these two diseases remains unsolved.

ACTA MEDICA NAGASAKIENSIS 50: 119 - 121, 2005

**Keywords:** Hereditary sensory and autonomic neuropathy; HSAN type II; Retinitis pigmentosa

## Introduction

Hereditary sensory and autonomic neuropathy type II (HSAN type II) is an autosomal recessive disorder with an onset in early childhood, and involves mainly the impairment of distal function, impairment of pain, and formation of ulcers in the hand and foot. Autonomic function is usually normal except for abnormal sweating.<sup>1</sup>

We herein report a case of HSAN type II with retinitis pigmentosa which is a rare complication.

## Case report

A 20-year-old female was hospitalized for an evaluation of a numbness on her legs. The course of pregnancy was uncomplicated and she was born at full-term. She began to walk at the age of 2 years. She could run during childhood, but she tended to stumble, particularly in the dark. At the age of 12 years she was diagnosed to have a retinitis pigmentosa for a decrease in visual acuity. Even though she noted a mild numbness on her legs in her elementary school days, she never had a medical examination for it until the age of 20 years.

She had an elder brother who also had a retinitis pigmentosa, but

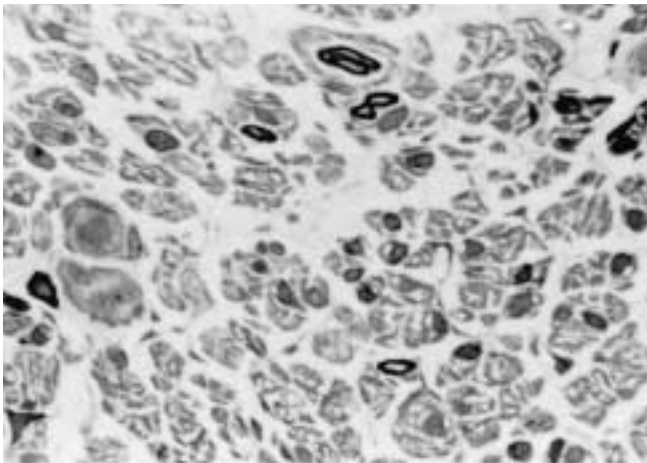
not of neurological disease. Her parents were cousins.

A general examination on admission showed no abnormal findings. Neurological examinations disclosed a decreased visual acuity (0.1 and 0.3 on the right and left eyes, respectively), concentric narrowing of the visual fields (less than 10 degrees), and retinitis pigmentosa. The optic discs were normal. The patient's IQ was 53. The deep tendon reflexes were absent in all limbs, and no pathologic reflexes were elicited. There was neither muscle atrophy nor weakness. The sensation to pain, temperature and touch was decreased on the legs, while the vibratory and position sense was impaired over the trunk and in all extremities, especially the lowers. No ataxia was observed in the upper extremities, but the heel to knee test was clumsy and Romberg test was positive. Her gait was somewhat wide-based and the tandem gait was difficult.

Results of urinalysis, complete blood cell count, and blood chemistry values (including urea nitrogen, uric acid, electrolytes, protein, creatine kinase, lactate dehydrogenase, and serum glutamic oxalase and pyruvate transferase) were all within normal limits. The motor conduction velocities were normal in all extremities, while the sensory nerves were not elicited in the extremities at all. The active sweating densities were 256/cm<sup>2</sup> (normal lower limit is 165/cm<sup>2</sup>). A sural nerve biopsy showed a marked decrease in myelinated fibers

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Received April 18, 2005; Accepted June 21, 2005



**Figure 1.** Sural nerve biopsy. Marked loss of the myelinated fibers are observed. The onion-bulb formations are not seen. Epon-embedded thick section and toluidine blue staining.



**Figure 2.** The unmyelinated fibers are well preserved. Uranyl acetate and lead citrate stained section. Bar=2  $\mu$ m.

(437/mm<sup>2</sup>). However, unmyelinated fibers were preserved (50,048/mm<sup>2</sup>) (Figures 1 and 2). The onion-bulb formations were not observed. Mutations in peripheral myelin protein 22kD (PMP22) gene, duplication on chromosome 17, were not demonstrated.

## Discussion

In 1973, Ohta et al.<sup>2</sup> proposed a descriptive classification of the hereditary sensory neuropathies (HSN) and divided it into four types. Thereafter, it was proposed to use the term of hereditary sensory and autonomic neuropathies (HSAN) for autonomic dysfunctions in patients suffering from hereditary sensory neuropathy.<sup>1,3</sup>

The HSAN type I is an autosomal dominant disease, usually affects young adults and results in distal loss of pain and temperature sensation, and sudomotor autonomic reflexes. The HSAN type II, known as Morvan disease, is an autosomal recessive disorder with onset in early childhood and affects both large and small sensory fibers. The disorder involves mainly the impairment of distal function, impairment of pain, and formation of ulcers in the hand and foot. Autonomic function is usually normal, with the exception of abnormal sweating. In the HSAN type II, two distinct subgroups, a congenital (or non-progressive) form and a late onset (or progressive) form have been reported.<sup>4</sup> The non-progressive form has its onset of sensory impairment at birth. The sensory loss may involve all modalities or may show only partial involvement. The disorder may be confined to the limbs alone or show diffuse involvement over the entire body. In contrast to the non-progressive form, the progressive form begins during childhood, and regions of sensory impairment may vary in the body. The HSAN type III, known as familial dysautonomia or Riley-Day syndrome, appears at birth and progresses to severe autonomic crises with postural hypotension, hypothermia or fever, fainting, reduced tearing, and vomiting. On nerve biopsy, there is loss of unmyelinated axons, usually with sparing

of large myelinated axons. The HSAN type IV is characterized by congenital insensitivity to pain and anhidrosis. The HSAN type V is an extremely rare disorder characterized by congenital insensitivity to pain with partial anhidrosis.

The onset of our patient was supposed to be at the early childhood and the course of the disease seemed to be non-progressive. The distribution of sensory impairment was spread to whole body except for the face and neck. We diagnosed her to have a HSAN type II and a non-progressive form because (1) only sensory nerves were involved; (2) the myelinated fibers were lost markedly, while unmyelinated fibers were not lost; and (3) the patient was supposed to be sporadic or of autosomal recessive inheritance.

Since Morvan first described in 1883 a patient who had a form of peripheral sensory neuropathy, there have been many reports on this disease. However, classification of each case was not clear. There have been many reports since Kuroiwa et al.<sup>5</sup> first described a case of HSN in Japan. However, differentiation of HSAN type I from type II was not distinct. As far as we know, 11 cases of HSAN type II have been reported in Japan.<sup>6-12</sup> As the complication of the HSAN type II, the mental retardation, tonic pupils, hearing disturbance and retinitis pigmentosa have been reported. Landwirth<sup>13</sup> first described a case of HSAN type II associated with the retinitis pigmentosa in 1964 and thereafter two other papers have been reported.<sup>12,14</sup> The retinitis pigmentosa is frequently seen in association with many diseases such as degenerative neurological diseases, muscle diseases, metabolic disorders or in renal diseases. Its inheritance is an autosomal dominant or recessive, or X-linked recessive. Since Dryja et al.<sup>15</sup> described in 1990 a point mutation of the rhodopsin gene in one form of retinitis pigmentosa, many kinds of the gene mutations have been reported.<sup>16</sup>

Lafreniere et al.<sup>17</sup> found in HSAN type II a gene termed "HSN2," which consists of a single exon located within intron 8 of the PRKWNK1 gene. This HSN2 protein may play a role in the development and/or maintenance of peripheral sensory neurons. There

is, however, no evidence at present that both the HSAN type II and retinitis pigmentosa occurred because of their correlation. Further progress concerning the embryogenetic biochemical mediators and gene mutations is needed to understand HSANs better.

## References

1. Dyck PJ. Neuronal atrophy and degeneration predominantly affecting peripheral sensory and autonomic neurons. In *Peripheral Neuropathy* (Dyck PJ, Thomas PK, Griffin JW, Low PA eds.; WB Saunders, Philadelphia) pp. 1065-1093, 1993
2. Ohta M, Ellefson RD, Lambert EH, Dyck PJ. Hereditary sensory neuropathy, type II. *Arch Neurol* 29: 23-37, 1973
3. Donaghy M, Hakin RN, Bamford JM et al. Hereditary sensory neuropathy with neurotrophic keratitis. *Brain* 110: 563-583, 1987
4. Ferriere G, Guzzetta F, Kulakowski S, Evrard P. Nonprogressive type II hereditary sensory autonomic neuropathy: A homogeneous clinicopathologic entity. *J Child Neurol* 7: 364-370, 1992
5. Kuroiwa Y, Murai Y. Hereditary sensory radicular neuropathy with special reference to conduction velocity study. *Neurology* 14: 574-577, 1964
6. Kijima H, Tachikawa K, Sumida J et al. Hereditary sensory neuropathy; A study on 5 cases in 3 families. *Tohoku Seikei-Saigaijeka Kyo* 25: 29-34, 1982 (in Japanese)
7. Kon S, Matsuda M. Hereditary sensory neuropathy with foot perforation. *Hifuka Rinsho* 30: 1403-1409, 1988 (in Japanese)
8. Kim K, Takagi K, Ohta J, Kawatsu T. A case of hereditary sensory neuropathy type II. *Hifu* 31: 206-212, 1989 (in Japanese)
9. Asami A, Watanabe H, Ishii T. Two cases with hereditary sensory neuropathy. *Seikeigeka To Saigaijeka (Orthopedics & Traumatology)* 43: 335-339, 1994
10. Shimoya K, Ishimoto S, Ohnishi A, Yamamoto T. A case of hereditary sensory neuropathy type II with late onset. *Rinsho Shinkei (Clinical Neurology)* 39: 551-554, 1999 (in Japanese)
11. Yoshida M. A case of hereditary sensory neuropathy type II. *Hifuka Rinsho* 44: 697-699, 2002 (in Japanese)
12. Saito T, Kowa H, Torii J, Yokoi F, Tasaki Y. A sporadic case of hereditary sensory neuropathy with tonic pupil, ichthyosis vulgaris, deafness and atypical retinitis pigmentosa. *Rinsho Shinkei (Clinical Neurology)* 20: 201-208, 1980 (in Japanese)
13. Landworth J. Sensory radicular neuropathy and retinitis pigmentosa. *Pediatrics* 34: 519-524, 1964
14. Dyck PJ, Mellinger JF, Reagan TJ et al. Not 'Indifference to pain' but varieties of hereditary sensory and autonomic neuropathy. *Brain* 106: 373-390, 1983
15. Dryja TP, McGee TL, Reichel E et al. A point mutation of the rhodopsin gene in one form of retinitis pigmentosa. *Nature* 25: 364-366, 1990
16. Wada Y. Retinitis pigmentosa. *Atarashii Gannka* 18: 1297-1299, 2001 (in Japanese)
17. Lafreniere RG, MacDonald ML, Dube MP et al. Identification of a novel gene (HSN2) causing hereditary sensory and autonomic neuropathy type II through the study of Canadian Genetic Isolates. *Am J Hum Genet* 74: 1064-1073, 2004