CASE REPORT

A Case of Klippel-Trenaunay Syndrome Associated with Huntington’s Disease

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Abstract. We report here on a patient with Klippel-Trenaunay syndrome who was later diagnosed with Huntington’s disease. Consistent with the later diagnosis, a (CAG)n repeat longer than the normal range was observed on chromosome 4p. The presence of these two diseases in the same individual may represent coincidence or a true correlation which must be confirmed by other evidence. To our knowledge, this is the first published report of the concurrent presence of these diseases in the same individual. (Keio J Med 46 (3): 138-141, September 1997)

Key words: Klippel-Trenaunay syndrome, Huntington’s disease

Introduction

The three clinical findings of a cutaneous nevus, varicose veins and hypertrophy of bone and soft tissue affecting one or more limbs were first defined as a single disease entity by Klippel and Trenaunay in 1900.¹ Klippel-Trenaunay syndrome (KTS) is considered a primary mesodermal phakomatosis that appears to involve hypertrophy, hyperplasia, and dysplasia of multiple tissues originating from both ectodermal and mesodermal germ layers. Since the early reports, this syndrome has been associated with neurological symptoms and signs such as mental retardation, paralysis, seizures and myelopathy. However, this is the first case report (to our knowledge) linking this diagnosis with Huntington’s disease (HD).

Case Report

The patient is a 52-year-old Japanese male. Extensive varicose veins and hypertrophy of the left lower extremity have been present since birth. His mother’s pregnancy and delivery were uncomplicated. The patient is of average intelligence. He graduated from high school and worked as a painter for 30 years. He consulted our hospital because of a worsening motor disturbance; since adolescence his movements have been jerky and difficult to control. The affected left leg was 3 cm longer than the right; the thigh and calf circumferences were 5 and 8 cm larger, respectively (Fig 1). His left leg was abnormally large with macrodactyly and elongated toes. There were no anomalies of fingers and toes such as syndactyly, polydactyly, clinodactyly, camptodactyly, trigger finger or metatarsus varus. The soft tissue of the left chest was slightly hypertrophied. No port-wine nevus was apparent. The skin of the buttock was also normal. This patient had no history of rectal bleeding or hematuria.

The patient suffered from an apparent gait disturbance. His walk resembled what is colloquially referred to as “drunken sailor’s gait”, an ataxia in which stance is wide and balance is unsteady. Tandem gait was markedly unstable; he could not stand on one leg. He also had difficulty sitting erect. Choreaathetotic movements of the fingers and toes were noticeable. His speech was dysarthric. He also complained of urinary incontinence. Nystagmus horizontalis was noticed on bilateral lateral gaze. Finger-nose-finger test and heel-shin test were abnormal. Dysdiadochokinesis was present bilaterally. His irregular handwriting bore evidence of his difficulty in controlling and stabilizing his hand movements. There were no cranial disturbances. Deep tendon reflexes were normal. Babinski’s and Chaddock’s signs were negative. There were no other neu-
rologic symptoms such as seizures or headaches.

Routine hematological and biochemical investigations were normal. Phlebography (Fig 2) was done in the supine position with the tourniquet around the ankle. Contrast medium was injected into the dorsal vein. This revealed prominent varicose veins in the calf and lateral marginal vein, which probably communicated with the long saphenous vein. Deep veins were present and patent. Digital subtraction angiography visualized no apparent arteriovenous fistulas in the lower extremity. No significant findings were detected by cranial CT and MRI, except mild atrophy of the cortex and slight enlargement of the anterior horn of the lateral ventricles (Fig 3). The size of the skull was almost normal. The shape of the skull was symmetrical.

Fig 1 Extensive varicose veins and hypertrophy of the left lower extremity. The affected left leg was 3 cm longer than the right; the thigh and calf circumferences were 5 and 8 cm larger, respectively.

Fig 2 Phlebography revealed prominent varicose veins in the calf and lateral marginal vein (arrow heads). The latter probably communicates with the long saphenous vein. Deep veins (arrows) were present and patent.

Fig 3 Cranial MRI. Mild atrophy of the cortex and slight enlargement of the anterior horn of the lateral ventricles were detected by cranial MRI.

Fig 4 Patient's pedigree. No family members of this patient except his father were affected with HD according to the patient.
There were not malformations of the circle of Willis, no brain stem angiomas. Spinal MRI revealed no arterio-venous fistulas.

The patient's father also had involuntary movements and had been hospitalized in a mental asylum for about one year before he died (Fig 4). No relatives of our patient had limb hypertrophy or port-wine nevus and varices. However, we could not obtain detailed medical history of the patient's family because he was divorced and had no contact with other family members. Chromosomes of cultured peripheral blood lymphocytes revealed no rearrangements, however, a (CAG)n repeat longer than the normal range was observed on chromosome 4p (Fig 5).

Discussion

The association of varicose veins, soft tissue and bony hypertrophy and cutaneous hemangioma of the "port-wine" variety confined to one extremity was first reported by Klippel and Trenaunay. In 1918 Parkes-Weber described a similar entity. Subsequently there has been much confusion between KTS and Parkes-Weber syndrome. Parkes-Weber suggested that unless the arteriovenous fistula is present, the condition should be considered KTS. However, most agree that KTS and Parkes-Weber syndrome are variants of the same condition. Another group of patients with two of the three characteristics are classified as forme fruste. Since our patient does not have the port-wine nevus, but does have the other two characteristics, we would classify him as forme fruste.

These syndromes are thought to be caused by abnormal development in the fetus. Because of the wide variety of clinical manifestations that have been associated with them, including neurological involvement, they can be classified as a phakomatosis. Other diseases in this category are von Hippel-Lindau, Bourneville-Pringle, and von Recklinghausen diseases. There are also a few cases reported in which patients have a combination of Sturge-Weber and KTS.

Among the phakomatosis, von Hippel-Lindau disease is known to be a heritable tumor syndrome. It is caused by the loss of the function of a tumor suppressor gene on the short arm of chromosome 3. However, very little is known about the genetic defects responsible for KTS.

KTS is generally thought to occur sporadically. A recent extensive evaluation of relatives of KTS patients documented that two out of 86 families had two clearly affected individuals. No relatives of our patient had limb hypertrophy or port-wine nevus and varices.

Whelan et al reported on a case of KTS associated with a reciprocal translocation [46, XX, t(5; 11) (q13.3; p15.1)]. These authors suggested that KTS may be due to a single gene(s), perhaps 5q or 11p. Our case revealed no chromosome rearrangements.

There are some case reports of KTS associated with neurological disorders such as microcephaly, macrocephaly, hemimegalocephaly, cerebral and spinal arteriovenous malformations or brain stem angiomas. In this patient, no significant findings were detected by cranial CT and MRI except mild atrophy of the cortex.

Huntington's disease can be diagnosed without difficulty in an adult when the triad of chorea, dementia and positive family history is present. Chorea interferes with co-ordination but cerebellar ataxia is rare in affected adults. We previously reported on this case as

Fig 5 Electrophoresis of PCR products. Chromosomes taken from the patient's cultured peripheral blood lymphocytes were investigated with improved PCR conditions for the stretch of (CAG)n repeats causing HD. PCR products have been separated through a 2% agarose gel (120V, 120min). Lane 1 indicates the size marker; Lane 2 represents this patient; and Lane 3 represents the genetic HD patient's pattern.
an example of KTS associated with cerebellar dysfunction. We based that report on the fact that the patient had nearly average intelligence, and that we could not obtain detailed medical history of the patient's family. The prevalence of HD in Europe and North America is generally considered to be between 30 and 70 affected individuals per million, whereas the disease appears to be particularly uncommon in Japan. The patient's father also had involuntary movements and had been hospitalized in a mental asylum for about one year before he died. While we cannot make a precise diagnosis, we strongly suspect that the father had HD. HD is transmitted from parent to offspring in autosomal dominant fashion with full penetrance. Hence 50% of the children of those affected are also affected, although the disease may not become apparent until middle age. This patient has five siblings and three children of his own (Fig 4). No other family members are affected by HD according to the patient.

In 1993 the gene IT15 was identified on chromosome 4p and was demonstrated to contain an unstable (CAG)n trinucleotide repeat that is elongated in patients with HD. We investigated chromosomes of cultured peripheral blood lymphocytes and used the improved polymerase chain reaction conditions for the stretch of (CAG)n repeats causing HD. As shown in Fig 5, this patient's chromosome findings are compatible with HD. Perhaps this case represents merely a coincidental pairing of two genetically unrelated conditions, KTS and HD. Their appearance in the same individual has never been reported in the world literature before. We hope our report will alert others to the possibility of this link so as to clarify the relationship, if there is one, between these two conditions. Since KTS is a relatively rare syndrome, little consensus exists as to the best approach to treatment. Identifying the gene responsible for KTS should advance our understanding of this syndrome and our ability to advise and treat patients.

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References