청소년기에 보행장애로 발현된 일차성 뇌석회화 1례

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A Case of Primary Brain Calcification Presenting with Gait Disturbance in an Adolescent

Primary brain calcification (PBC) is a neurodegenerative disorder characterized by idiopathic calcification of the basal ganglia that is rare in children and adolescents. This report describes a 16-year-old boy who complained of progressive walking difficulty and gait disturbance for 3 years. Physical examination showed positive reaction to ankle clonus and increased deep tendon reflex on both legs. There was no family history of metabolic disorder or neurologic diseases. Brain computed tomography (CT) and brain magnetic resonance imaging (MRI) revealed extensive calcifications in the bilateral cerebral white matter, basal ganglia, thalamus and dentate nucleus of the cerebellum. Laboratory and genetic studies showed nothing of note. This case report describes an unusual case of sporadic primary brain calcification, diagnosed in adolescence by the presence of gait difficulty and mild mental retardation and its review.

Key Words: Idiopathic basal ganglia calcification, Primary familial brain calcification, childhood onset, Gait disorders, Adolescence, Intellectual disability

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Introduction

Primary brain calcification (PBC, also known as idiopathic basal ganglia calcification or Fahr's disease) is characterized by idiopathic bilateral calcification in the basal ganglia and other parts of the brain^{1,2}. It is usually diagnosed in adulthood and old age and associated with an autosomal dominant pattern of inheritance, but it can also demonstrate genetic heterogeneity^{3,4}. Clinical symptoms of this condition can include Parkinsonism, extrapyramidal symptoms, cerebellar impairment, convulsive seizures, psychiatric features, dementia and speech problems^{1,5}. The most common manifestations of PBC are movement dysfunction and cognitive impairment, followed by cerebellar impairment and speech disorders¹.

PBC has been associated with several genes, including *solute carrier family 20 member 2 (SLC20A2)*⁶ and *platelet-derived growth factor receptor β (PDGFRB)*⁷. Nevertheless, these genes do not account for all cases of PBC. This report describes an adolescent patient with PBC, without any of these associated genes, who presented with progressive gait difficulty and mild mental retardation.

Case Report

A 16-year-old boy presented with progressive walking difficulty for 3 years. Initially, he had slightly unnatural walking appearance and then difficulty in sitting down, and standing or climbing up. In addition, he experienced sudden pain in both calves while moving. He was born via a normal vaginal delivery at 40 weeks of gestation with a birth weight 3.4 kg, but required treatment for 4 days in a neonatal intensive care unit for non-specific pneumonia. He first walked by himself at 17 months of age. According to his parents' statement, he had delayed development in language and mathematic skills, but had no difficulty walking and climbing until three years before presentation. His family history was not contributory. He had a circumduction gait, positive ankle clonus and increased deep tendon reflex in both extremities. He did not have definite muscle weakness, but had spasticity on both lower extremities. There were no abnormal findings on cranial nerve examination and cerebellum function test including balance. He did not have a psychiatric disorder. Electromyography, nerve conduction velocity and eye examination were normal, as were renal parameters; liver function tests; and serum concentrations of calcium, magnesium, phosphorus, vitamin D, parathyroid hormonal (PTH), calcitonin, rheumatic factor, antinuclear antibody, lead, alkaline phosphatase, Tandem mass spectrometry, lactic acid, ammonia and toxoplasma serology. Chromosomal analysis showed he was 46, XY. Brain computed tomography (CT) revealed areas of calcified densities in the bilateral cerebral white matter, basal ganglia and dentate nucleus of the cerebellum (Fig. 1). Brain magnetic resonance imaging (MRI) showed multiple signal changes in the bilateral cerebral white matter, basal ganglia, thalamus, and dentate nucleus of the cerebellum (Fig. 2). His Deoxyribonucleic acid (DNA) was

subjected to a panel sequencing test (Trusight One sequencing panel, Illumina, USA) which covers 12 Mb of the human genome,

Fig. 2. Brain magnetic resonance imaging of the patient. T1- and T2-weighted images showed multiple signal change (A) in the dentate nucleus of the cerebellum (B), bilateral cerebral white matter (C, D), basal ganglia and thalamus (E, F).

Fig. 1. Brain computed tomography (CT) of the patient. Non-contrast axial CT-scans showed extensive calcifications in the bilateral cerebral white matter (A), basal ganglia, thalamus (B) and dentate nucleus of the cerebellum (C).

including 4,813 genes associated with a clinical phenotype. Although this panel covered *SLC20A2* and *PDGFRB*, neither was associated with his disorder, and there was no evidence of an underlying inherited disorder.

After consultation with a physiatrist and an orthopedist, the patient was fitted with a short leg cast for one month and an ankle foot orthosis for three months and was prescribed Levodopa. However, his gait disturbance was not improved and more deteriorated at the age of 18 year.

Discussion

PBC is a rare, degenerative neurological condition, characterized by the idiopathic calcification of the basal ganglia, especially the globus pallidus, and occasional involvement of the internal capsule, thalamus, and cerebral white matter. It is most commonly transmitted as an autosomal dominant trait; but it may also be passed on as an autosomal recessive trait or may occur sporadically^{1,5)}. Average ages at symptom onset of 37²⁾ and 47¹⁾ years have been reported. The most common manifestation of PBC is movement dysfunction (55%), with Parkinsonian features accounting for over half of all movement disorders and hyperkinetic movement disorders accounting for the rest. The second most common manifestation is cognitive impairment, followed by cerebellar impairment and speech disorder^{1,5)}. Less frequent neurologic manifestations include pyramidal signs, psychiatric features, gait disorders, sensory changes and pain. Our patient presented with mild mental retardation during childhood and progressive decline of motor function in both legs during adolescence.

Brain calcinosis syndrome (BCS) is a broader condition than PBC and is usually defined as bilateral calcium accumulation in the brain parenchyma, primarily in the basal ganglia²⁾. Among the causes of BCS are abnormalities in calcium, phosphorous and PTH metabolism; physiological aging; genetic disorders, including deficiencies in biotinidase and carbonic anhydrase IIc; and metabolic disorders, including dihydropteridine reductase deficiency, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes syndrome (MELAS syndrome). Other causes may include connective tissue disorders, such as systemic lupus erythematosus; infectious disorders, including acquired immune deficiency syndrome, chronic active Epstein-Barr virus infection, mumps encephalitis, and syphilis; and lead poisoning. In the absence of a specific cause, the condition is diagnosed as primary BCS, also called PBC^{1,2)}. Etiologically, abnormalities of calcium, phosphorus, and PTH metabolism are the most common causes of calcification of the bilateral subcortical nuclei and white matter. As no specific cause could be identified in our

patient, he was diagnosed with PBC.

Genetic loci associated with PBC have been mapped to chromosomes 14q11.2-21.3, 2q37 and 9p21.1-q11.1^{4,8,9)}. Genetic causes include mutations in *SLC20A2*⁶⁾ and *PDGFRB*⁷⁾, with calcification being more severe in patients with *SLC20A2* than *PDGFRB* mutations¹⁰⁾. Moreover, the mean severity of calcification was greater in symptomatic than in asymptomatic individuals and correlated positively with age¹⁰⁾. However, we couldn't find *SLC20A2* and *PDGFRB* gene mutations in our patient.

The course of PBC is progressive, as calcium deposition generally begins during the third decade of life, with neurological deterioration two decades later¹¹⁾. Individuals are generally asymptomatic in childhood and early adulthood, with only a few case reports of onset at an early age. One report described an 18-year-old woman with cognitive impairment and progressively uncontrolled behavior¹²⁾, and a third report described a 17-year-old boy with autistic disorder and PBC who showed catatonia presenting with prominent dystonic features caused by mood disturbances¹³⁾. Our patient also had mild cognitive impairment, but no mood disturbances.

Although calcification can involve other structures, the globus pallidus is by far the most common site. The exact pathological processes initiating these calcifications have not been determined, but may reflect slowly progressive metabolic and/or inflammatory processes in the brain, resulting in subsequent calcification and probably responsible for neurologic deficits¹⁴⁾. The reason the basal ganglia are targeted for calcium deposition has not been determined, but these ganglia are also targeted by many other deposits, including bilirubin, which causes kernicterus in newborns; 1-methyl-4-phenyl, 1, 2, 3, 6-tetrahydropyridine (MPTP); and carbon monoxide poisoning leading to Parkinsonism.

As this case or the other PBC children, patients with movement disorders, behavioral changes and developmental disabilities should need to consider brain imaging. To our knowledge, no specific treatments can limit the progression of calcification in the basal ganglia in patients with PBC. The prognosis of PBC is variable and hard to predict, although progressive neurological disorders may result in chronic disability. Further research is needed to determine the pathophysiological mechanisms leading to localized calcium deposition and to find effective treatments.

요약

일차성 뇌 석회화는 특별한 원인 없이 뇌에 석회화가 진행되는 퇴행성 신경질환으로 상염색체 우성으로 유전되는 경우도 있으나 특별한 가족력 없이 발병하기도 하는 질환이다. 증상은 다양하지만 주로

운동장애, 인지장애가 나타나는 경우가 많으며 기분 장애, 언어 장애, 감각이상 등이 동반되기도 한다. 본 증례의 16세 남아는 특별한 주산기 병력 및 가족력이 없이 3년전부터 점차 악화되는 양상의 보행장애를 호소하여 내원하였다. 뇌 전산화단층촬영 및 자기공명영상에서 대뇌, 기저핵, 시상, 소뇌의 치상핵 부위에 석회화가 확인되었으나 원인 질환에 대한 검사에서는 특이소견을 보이지 않아 본 저자들은 일차성 뇌 석회화를 진단하게 되었으며 동반되는 가장 흔한 유전자의 이상으로 *SLC20A2* 혹은 *PDGFRB* 가 알려져 있어 이에 대한 검사를 시행하였으나 유전자 변이를 발견하지는 못하였다. 환자는 현재 정형외과적 보조기 치료, 재활치료, L-도파 투약 등의 시도에도 증상은 악화되는 양상을 보이는 중으로 소아 및 청소년기에서는 거의 보고되지 않은 일차성 뇌 석회화를 진단하여 그에 대한 고찰과 함께 보고하는 바이다.

References

- 1) Manyam BV. What is and what is not 'Fahr's disease'. *Parkinsonism Relat Disord* 2005;11:73-80.
- 2) Baba Y, Broderick DF, Uitti RJ, Hutton ML, Wszolek ZK. Heredo-familial brain calcinosis syndrome. *Mayo Clinic Proc* 2005;80: 641-51.
- 3) Oliveira JR, Spiteri E, Sobrido MJ, Hopfer S, Klepper J, Voit T, et al. Genetic heterogeneity in familial idiopathic basal ganglia calcification (Fahr disease). *Neurology* 2004;63:2165-7.
- 4) Geschwind DH, Loginov M, Stern JM. Identification of a locus on chromosome 14q for idiopathic basal ganglia calcification (Fahr disease). *Am J Hum Genet* 1999;65:764-72.
- 5) Manyam BV, Walters AS, Narla KR. Bilateral striopallidodentate calcinosis: clinical characteristics of patients seen in a registry. *Mov Disord* 2001;16:258-64.
- 6) Wang C, Li Y, Shi L, Ren J, Patti M, Wang T, et al. Mutations in *SLC20A2* link familial idiopathic basal ganglia calcification with phosphate homeostasis. *Nat Genet* 2012;44:254-6.
- 7) Nicolas G, Pottier C, Maltete D, Coutant S, Rovelet-Lecrux A, Legallic S, et al. Mutation of the *PDGFRB* gene as a cause of idiopathic basal ganglia calcification. *Neurology* 2013;80:181-7.
- 8) Volpato CB, De Grandi A, Buffone E, Facheris M, Gebert U, Schif-ferle G, et al. 2q37 as a susceptibility locus for idiopathic basal ganglia calcification (IBGC) in a large South Tyrolean family. *J Mol Neurosci* 2009;39:346-53.
- 9) Dai X, Gao Y, Xu Z, Cui X, Liu J, Li Y, et al. Identification of a novel genetic locus on chromosome 8p21.1-q11.23 for idiopathic basal ganglia calcification. *Am J Med Genet B Neuropsychiatr Genet* 2010;153B:1305-10.
- 10) Nicolas G, Pottier C, Charbonnier C, Guyant-Maréchal L, Le Ber I, Pariente J, et al. Phenotypic spectrum of probable and genetically-confirmed idiopathic basal ganglia calcification. *Brain* 2013; 136:3395-407.
- 11) Manyam BV, Bhatt MH, Moore WD, Devleschoward AB, Anderson DR, Caline DB. Bilateral striopallidodentate calcinosis: cerebrospinal fluid, imaging and electrophysiological studies. *Ann Neurol* 1992;31:379-84.
- 12) Goyal D, Khan M, Qureshi B, Mier C, Lippmann S. Would you recognize Fahr's Disease if you saw it? *Innov Clin Neurosci* 2014; 11:26-8.
- 13) Ishitobi M, Kawatani M, Asano M, Kosaka H, Goto T, Hiratani M, et al. Quetiapine responsive catatonia in an autistic patient with comorbid bipolar disorder and idiopathic basal ganglia calcification. *Brain Dev* 2014;36:823-5.
- 14) Avrahami E, Cohn DF, Feibel M, Tadmor R. MRI demonstration and CT correlation of the brain in patients with idiopathic intra-cerebral calcification. *J Neurol* 1994;241:381-4.