Case Report

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Detection of Cerebrovascular Disease in a Child with Hutchinson-Gilford Progeria Syndrome Using MR Angiography: A Case Report

Hutchison-Gilford 조로증 증후군 환아에서의 뇌 자기공명 혈관조영술 소견: 증례 보고

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Hutchinson-Gilford progeria syndrome (HGPS) is a rare, progressive, premature aging syndrome with early morbidity due to cardiovascular and cerebrovascular diseases. Clinical symptoms are very diverse, including non-specific symptoms such as growth retardation, scleroderma, alopecia, and osteoporosis, as well as hypertension and cardiovascular diseases that occur in childhood and adolescence due to accelerated vascular aging. In patients with HGPS, MR angiography is recommended for early diagnosis of asymptomatic stroke or vascular changes and to assess increased risk of cerebrovascular disease. We report the second domestic case of HGPS confirmed by genetic analysis in a 5-year-old child with typical clinical features, and the first English case report in Korea to present brain MR angiography findings.

Index terms Progeria; Hutchinson-Gilford progeria syndrome; Cerebrovascular Disorders; Atherosclerosis; Magnetic Resonance Angiography

INTRODUCTION

Hutchinson-Gilford progeria syndrome (HGPS) is a rare autosomal dominant segmental

premature aging disease that begins in early childhood and is uniformly fatal (1). The prevalence of HGPS is 1 in 4–8 million with male predominance (male:female ratio of 1.5:1) and a substantial racial susceptibility for Caucasians, representing over 97% of patients (2). HGPS is caused by a *de novo* mutation of *LMNA*, which encodes the inner nuclear membrane protein lamin A, also called progerin (3). Accumulation of progerin disrupts nuclear membrane integrity and results in aging (4). Individuals with HGPS experience early failure to thrive, scleroderma, easy bruising, alopecia, stunted growth, craniofacial disproportion, osteopenia, acroosteolysis, and joint contracture (1, 3, 5, 6). Children with HGPS experience cardiovascular and cerebrovascular events, which lead to serious morbidity and mortality, with a median survival of 13 years (3). Episodes of angina, myocardial infarction, transient ischemic attacks, and stroke occur in late childhood and the teenage years in patients with HGPS (1, 3, 6). A range of early- to late-stage plaques and complex calcified lesions have been identified within coronary arteries in postmortem studies (1), and carotid sonography has found atherosclerotic plaques in the cervical arteries (7, 8). To the best of our knowledge, only one case of HGPS has been confirmed by genetic analysis in Korea (9), and the patient showed a hypertrophied internal layer at the internal carotid artery (ICA) on carotid Doppler sonography, suggesting atherosclerosis.

Here, we report the second case of a child genetically confirmed with HGPS in South Korea, with classic physical features and cerebrovascular abnormalities on MRI and MR angiography (MRA).

CASE REPORT

A 5-year-old boy diagnosed with HGPS due to a mutation in *LMNA* (c.1824C>T) was referred to our pediatric outpatient department. Initially, he presented with abdominal bloating and coarsening of the skin, which had progressed diffusely to other parts of his body, and was diagnosed with sclerema neonatorum on skin biopsy. Since 1 year of age, he also presented with loss of scalp hair, slow growth of fingernails and toenails, easy bruising, and visible veins over the scalp and forehead. He was born full-term by emergency cesarean section due to cephalopelvic disproportion and premature rupture of the membrane. The patient had normal intelligence. No family history of similar symptoms was observed.

General examination revealed the child to be of short stature (94.9 cm) and underweight (11.85 kg), and was less than the 1st percentile of the Korean Child Growth Standards. On physical examination, he had difficulty flexing both his shoulder and left knee joints, and his back was slightly flexed at rest. He showed contracture in the second metacarpophalangeal joints of both hands and the third proximal interphalangeal joint of his left foot. Skull lateral radiograph and panoramic radiograph revealed mandibular condylar hypoplasia and micrognathia, indicative of underdevelopment of the jawbone, and consequent crowding of teeth (Fig. 1A, B). On duel-energy X-ray densitometer study, the Z-scores of the bone marrow densities of the total body, total body less head, and lumbar spine were low as -4.5, -4.1, and -1.9 accordingly. Blood laboratory results showed elevated total and low-density lipoprotein cholesterol levels.

Although he had no cerebrovascular or cardiovascular events, baseline brain MRI was per-

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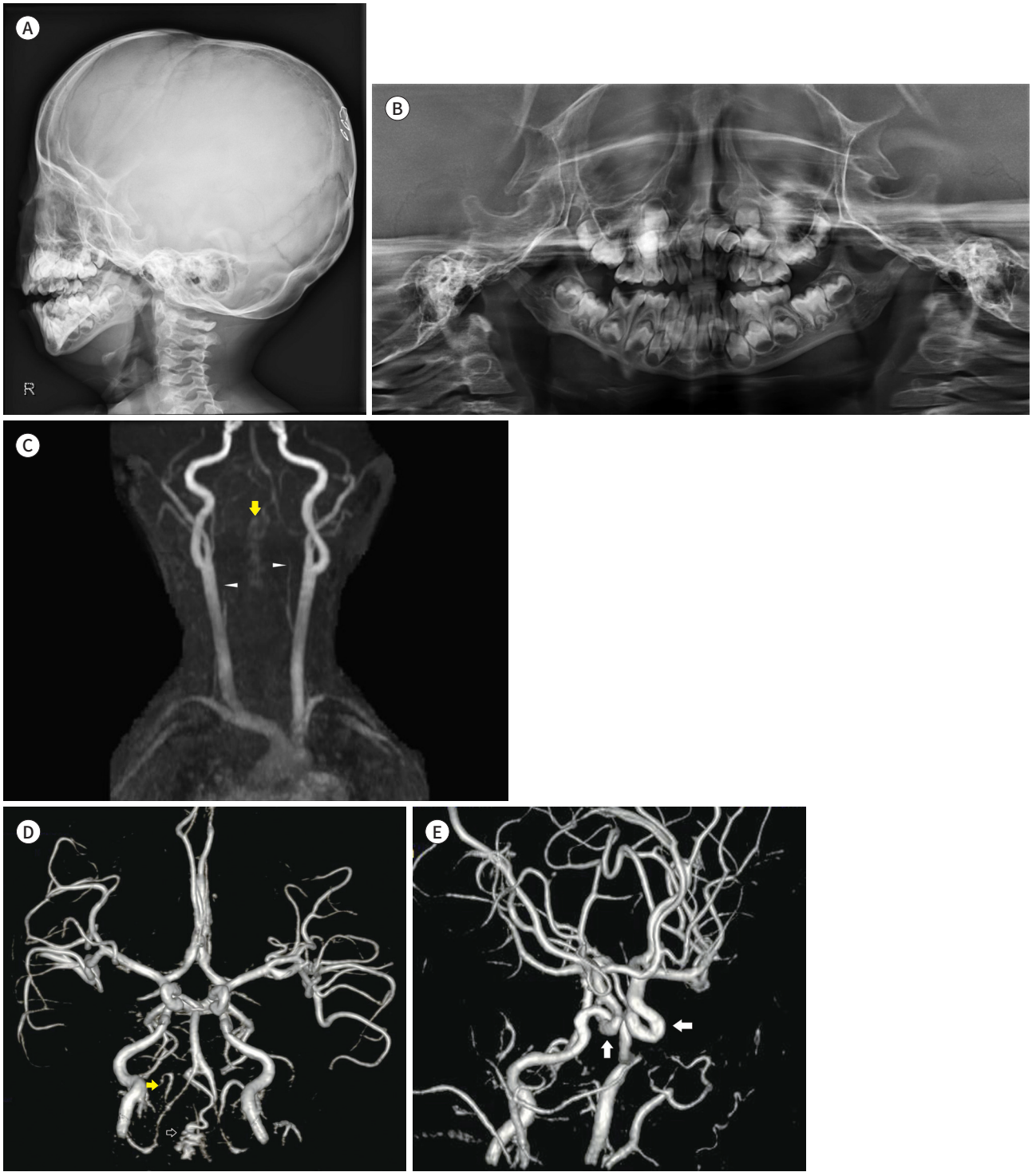
Fig. 1. A 5-year-old boy genetically confirmed with Hutchinson-Gilford progeria syndrome.
A, B. Right lateral radiograph of the skull (A) and panoramic radiograph (B) show mandibular condylar hypoplasia and micrognathia, and consequent crowding of teeth.
C-E. Neck and brain MR angiography reveals segmental severe stenosis in the V2-V3 segments of bilateral vertebral arteries (arrowheads), with collaterals from an enlarged anterior spinal artery and the external carotid artery (yellow arrows). Bilateral internal carotid arteries are tortuous for his age (white arrows).



formed to detect the presence of silent strokes or vascular changes and to assess increases in risk over time. MRA revealed segmental severe stenosis in the V2-V3 segments of the bilateral vertebral arteries (VAs) with collaterals from an enlarged anterior spinal artery and external carotid artery (ECA) (Fig. 1C, D). Tortuosity in the cavernous segments of both ICAs was also observed without significant stenosis (Fig. 1E). There were no demonstrable brain parenchymal abnormalities.

He was administered clopidogrel (37.5 mg) every other day and atorvastatin (2.5 mg) to reduce the risk of stroke. Stem cell therapy was planned as HGPS treatment. On outpatient follow-up, he complained of intermittent left tinnitus, and a subsequent physical examination revealed intact ear drums and external auditory canals. He recently experienced occasional muscle cramps in the soles of his feet during the night and laboratory results showed low parathyroid hormone (6.0 pg/mL, normal range: 8.00–76.00 pg/mL), high phosphorus (5.0 mg/dL, normal range: 2.5–4.5 mg/mL), and normal calcium levels.

This study was approved by the Institutional Review Board of Inha University Hospital (IRB No. 2022-03-024), and the requirement for informed consent was waived.

DISCUSSION

HGPS is caused by a sporadic single-base mutation of *LMNA*, which results in an abnormal form of the inner membrane protein lamin A, also known as progerin (1-7). Progerin is expressed in cell types that are fundamental to vascular function and structure, such as vascular smooth muscle cells, endothelial cells, and adventitial fibroblasts, and progerin levels are known to increase throughout the life of normal individuals during the regular aging process (1). Thus, children with HGPS suffer from early onset of cardiovascular disease, coronary artery atherosclerosis, myocardial infarction, and stroke, which are usually observed in a normally aging population (3, 6). We have presented the second case of genetically diagnosed HGPS in Korea and the first Korean case to show cerebrovascular disease on brain MRA.

Approximately 90% of patients with HGPS succumb to atherosclerosis in the form of myocardial infarction, stroke, or other vascular or cardiac complications (2). Olive et al. (1) reported global atherosclerosis and pathological features in patients with HGPS that significantly resembled classic atherosclerosis associated with aging. A variety of early- to late-stage plaques and calcifications, inflammation, and evidence of plaque erosion or rupture are noted in arterial lesions of HGPS samples (1). In the study by Olive et al. (1), the extracellular matrix of HGPS lesions was similar to that seen in adult cardiovascular disease, suggesting progressive development of atherosclerotic lesions and an *in situ* inflammatory process. Vascular smooth muscle cells are involved in HGPS vascular pathology, which has a potentially limited capacity for cell renewal (1). They also noted markedly thickened adventitia in the large, medium, and small arteries and veins in comparison with classic adult cardiovascular disease. Such extensive fibrosis leads to reduced vascular compliance, increased vessel stiffness, and potential predilection for the formation of intimal plaque (1). In HGPS, progerin build-up may be a key factor in the development of these premature vascular lesions (1).

In the literature, multi-staged infarctions and associated intracranial and neck steno-occlusive arterial lesions, basal cistern collateral vessels, and slow compensatory collateral convexi-

ty flow are the most common brain MR findings in patients with HGPS (3, 4, 10). In a case series of 25 patients, the distribution of arterial pathology in HGPS was different from other vasculopathies in childhood, such as moyamoya disease and cerebrovascular disease in aging adults (3). Unlike atherosclerosis in aging, arterial stenosis in the mid and lower neck is less dominant. The most typically involved sites in HGPS are a short segment of the precavernous or cavernous ICA and a distal segment of the cervical VA, along with the proximal anterior and middle cerebral arteries (ACA and MCA, respectively). MCA narrowing is less common than ACA stenosis, and stenosis of the V4 segment of the VA and basilar artery are not present, whereas the midbasilar artery, V4 segments of the VA, and posterior cerebral artery are mostly involved; MCA narrowing is more common than ACA stenosis in adult atherosclerosis. Proliferative collateral vessel formation within the perisplenial, subfrontal, and suprasellar regions; enlargement of the middle meningeal and internal maxillary arteries; and slow compensatory collateral convexity flow are frequently observed, similar to those found in moyamoya disease. Furthermore, the high incidence of distal V2 and proximal V3 segment VA stenosis accompanied by enlargement of the anterior spinal artery is noteworthy, as seen in our case. Enlargement of the anterior spinal artery is uncommon in the adult population and is considered an unusual collateral pathway in patients with severe atherosclerotic disease involving both the V4 segments of the VA (3). This may mirror a segmental vulnerability of the vascular tree to secondary causes such as hypertension, hypercholesterolemia, hyperinsulinemia, and insulin resistance (7, 8).

We report a rare case of genetically confirmed HGPS in South Korea with typical clinical features and cerebrovascular manifestations revealed by brain MRA. Baseline brain MRI and MRA revealed stenosis in V2-V3 segments of the bilateral VA, with collaterals from the anterior spinal artery and ECA. This case report highlights the importance and necessity of baseline MRI and MRA of the head and neck in HGPS patients for evaluating the presence of silent strokes and vascular changes, even without any relevant signs or symptoms. For HGPS patients, clinical awareness and appropriate imaging work-up can be helpful to prevent and manage cerebrovascular diseases.

Author Contributions

Conceptualization, L.H.Y., L.J.H.; investigation, L.H.Y., L.J.H.; methodology, L.H.Y., L.J.H.; writing—original draft, L.J.H.; and writing—review & editing, L.H.Y., L.M.K., K.Y.H.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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Hutchison-Gilford 조로증 증후군 환아에서의 뇌 자기공명 혈관조영술 소견: 증례 보고

이재호 · 이하영* · 임명관 · 강영혜

Hutchinson-Gilford progeria 증후군(syndrome) (이하 HGPS)은 심혈관 및 뇌혈관 질환의 조기 이환율을 갖는 드문 진행성 조기 노화 증후군이다. 임상증상은 매우 다양하여 성장 부진, 경피증, 탈모증, 골다공증과 같은 비특이적 증상 외에도 가속화된 혈관 노화에 의해 유년기 및 청소년기에 발생하는 고혈압과 심뇌혈관 질환을 포함한다. HGPS 환자에게 자기공명 혈관조영술은 무증상 뇌졸중 또는 혈관 변화를 조기에 진단하고 뇌혈관 질환의 위험성 증가를 평가하기 위해 권장된다. 이 증례 보고는 전형적인 임상 특징을 보인 5세 환아에서 유전자 분석으로 확진된 국내 두 번째 HGPS이며, 뇌 자기공명 혈관조영술 소견을 제시한 국내 최초 영문 증례 보고이다.

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