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Hutchinson–Gilford Progeria Syndrome with G608G LMNA Mutation

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Hutchinson–Gilford progeria syndrome (HGPS) is a rare condition originally described by Hutchinson in 1886. Death result from cardiac complications in the majority of cases and usually occurs at average age of thirteen years. A 4-yr old boy had typical clinical findings such as short stature, craniofacial disproportion, alopecia, prominent scalp veins and sclerodermatous skin. This abnormal appearance began at age of 1 yr. On serological and hormonal evaluation, all values are within normal range. He was neurologically intact with motor and mental development. An echocardiogram showed calcification of aortic and mitral valves. Hypertrophy of internal layer at internal carotid artery suggesting atherosclerosis was found by carotid doppler sonography. He is on low dose aspirin to prevent thromboembolic episodes and on regular follow up. Gene study showed typical *G608G* (GGC- > GGT) point mutation at exon 11 in LMNA gene. This is a rare case of Hutchinson-Gilford progeria syndrome confirmed by genetic analysis in Korea.

Key Words: Hutchinson Gilford Progeria Syndrome; LMNA; Progeria

INTRODUCTION

Progeria is a genetic disorder rarely encountered and is characterized by features of premature aging. It is also known as "Hutchinson-Gilford Progeria syndrome" (1). Although signs and symptoms vary in age of onset and severity, they are remarkably consistent overall. Children with HGPS usually appear normal at birth. Profound failure to thrive occurs during the first year (2). Characteristic facies, with receding mandible, narrow nasal bridge and pointed nasal tip develop. Motor and mental development is normal. Death occurs as a result of complications of severe atherosclerosis, either cardiac disease (myocardial infarction) or cerebrovascular disease (stroke), generally between ages 6 and 20 yr. Average life span is approximately 13 yr (2).

We report here a 4-yr-old boy with an apparently typical Hutchinson–Gilford progeria syndrome with *G608G* LMNA mutation.

CASE DESCRIPTION

A 4-yr-old boy was referred to the department of pediatrics with short stature and sclerodermatous skin on 2 September 2010. He was the first child born to non-consanguinous parents with no significant family history. He was born at full term with birth weight of 3.35 kg by spontaneous virginal delivery. His abnormal appearance was not found at birth. At age of 1 yr, growth retardation, hair loss, and alteration of skin color on the abdominal region began.

On physical examination, his length was 88 cm and weight 11.5 kg, both less than 3rd percentile and head circumference was 52 cm (ca. 77th percentile) (Fig. 1). He had generalized indurated and shiny skin associated with decreased subcutaneous fat, especially on the abdomen. His hair was fine and sparse and his scalp veins were easily visible (Fig. 1). His anterior fontanelle was still patent (horizontal diameter 1.7 cm, vertical diameter 1.4 cm). He had craniofacial disproportion for his age due to micrognatia, prominent eyes, scant eyelashes and small nose. His bone age was 3 yr. He was neurologically intact with motor and mental development. On serological and hormonal evaluation, all values are within normal range. An echocardiogram did not show concentric left ventricular hypertrophy nor increased left ventricular pressure but showed calcification of aortic and mitral valves (Fig. 2). Hypertrophy of internal layer at internal carotid artery suggesting atherosclerosis was found by carotid doppler sonography (Fig. 2). He is on low dose aspirin to prevent thromboembolic episodes and on regular follow up.

We obtained his DNA from white blood cell in peripheral blood and sequencing was performed by such method as belows; Samples were extracted using a MG™ Tissue Kit. We designed polymerase chain reaction (PCR) primers using the Primer 3 program. The primers Tms ranged between 59°C and 62°C as far as possible. The PCR reaction was performed with 20 ng of genom-

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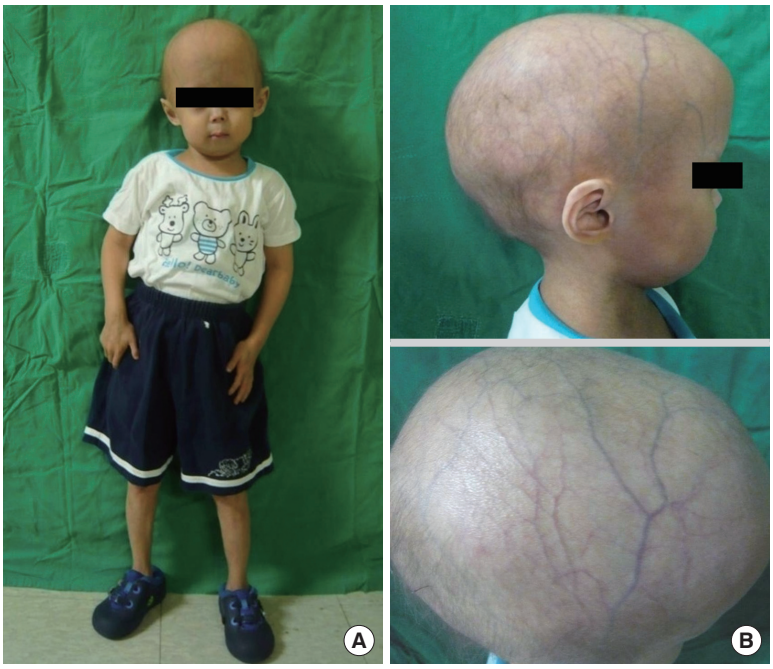

Fig. 1. (**A**) General appearance of the patient with characteristic prematurely aged appearance, retarded growth. (**B**) Lateral and top view of the head showing macrocephaly, alopecia, prominent scalp veins.

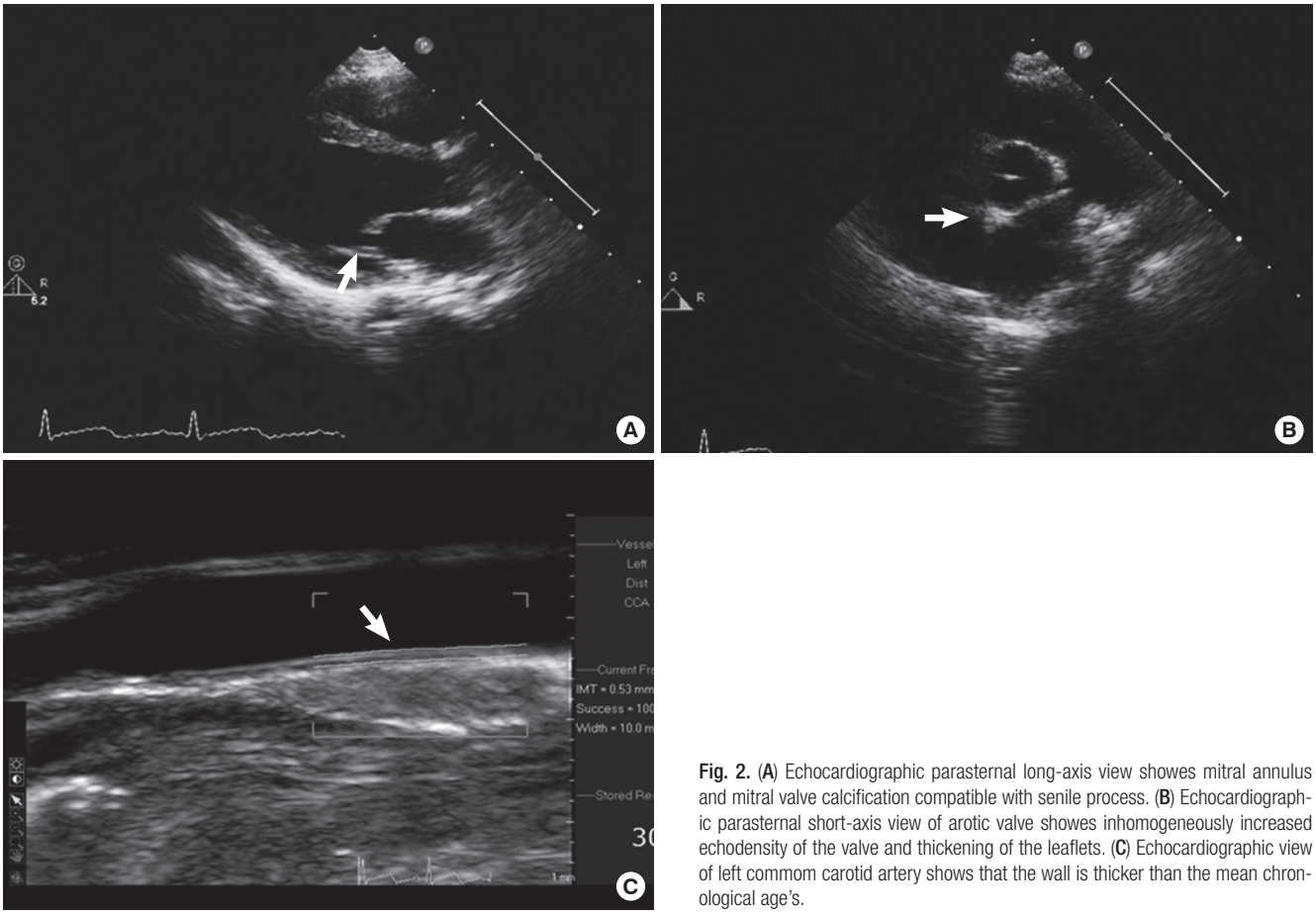

Fig. 2. (**A**) Echocardiographic parasternal long-axis view showes mitral annulus and mitral valve calcification compatible with senile process. (**B**) Echocardiographic parasternal short-axis view of arotic valve showes inhomogeneously increased echodensity of the valve and thickening of the leaflets. (**C**) Echocardiographic view of left commom carotid artery shows that the wall is thicker than the mean chronological age's.

ic DNA as the template in a 30 μL reaction mixture by using a EF-Taq (SolGent, Korea) as follows: activation of Taq polymerase at 95°C for 2 min, 35 cycles of 95°C for 1 min, 55°C-63°C, and 72°C for 1 min each were performed, finishing with a 10 min step at 72°C. The amplification products were purified with a multiscreen filter plate (Millipore Corp., Bedford, MA, USA). Sequenc-

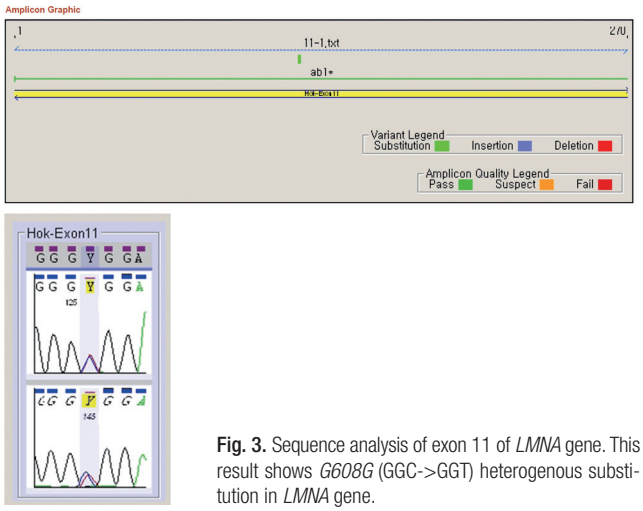

Fig. 3. Sequence analysis of exon 11 of *LMNA* gene. This result shows *G608G* (GGC->GGT) heterogenous substitution in *LMNA* gene.

ing reaction was performed using a PRISM BigDye Terminator v3.1 Cycle sequencing Kit. The DNA samples containing the extension products were added to Hi-Di formamide (Applied Biosystems, Foster City, CA). The mixture was incubated at 95°C for 5 min, followed by 5 min on ice and then analyzed by ABI Prism 3730XL DNA analyzer (Applied Biosystems, Foster City, CA, USA). The results were analyzed using the software DNAstar (http://www.dnastar.com).

Gene study showed typical *G608G* (GGC- > GGT) point mutation at exon 11 in LMNA gene (Fig. 3). He had a younger sister with normal appearance. we planned to carry out gene study for her and his family but couldn't for their refusal. After the diagnosis, he regularly visits our clinic for routine lab., echocardiogram and carotid doppler sonography. In addition, with our help, he was enrolled in The Progeria Research Foundation (PRF) in USA and is waiting for farnesyltransferase inhibitors (FTIs) for clinical trials.

DISCUSSION

Progeria was described for the first time in 1886, by Hutchinson, and ratified by Gilford, in 1904. It occurs sporadically, with an incidence of 1 in 8 million live births and there are approximately 150 cases described in the medical literature. It predominates in males with a ratio of 1.5:1 and greater susceptibility of Caucasians can be seen in 97% of cases (3). In Korea, 5 cases were reported in the medical literature (4-9). This is the first case diagnosed as Hutchinson-Gilford Progeria syndrome by gene study in Korea.

Children with HGPS look so similar that they could all be mistaken for siblings. There is variability in onset and rate of progression of disease among children, although the final phenotype in these patients is remarkably similar, underscoring the identical common mutation that leads downstream to similar pathobiology (10). In this syndrome, the rate of aging is accelerated up to seven times that of normal. The average life span is 13 yr (range 7-27 yr), but occasionally can survive till the age of 45 yr. The death is mainly due to cardiovascular complications like myocardial infarction or congestive heart failure. The evidence supports the de novo point mutations in lamin A (LMNA) gene as the causative factor has been increasing (11).

The most common HGPS-associated mutation, *Gly608Gly*, causes 150 nucleotides encoded in exon 11 to be spliced out of the final mRNA and results in a protein that lacks 50 amino acids. This protein, progerin, retains its C-terminal CAAX motif but lacks sequences that are required for complete processing and is, therefore, stably farnesylated (12). Lamin A is a protein meshwork lining the nucleoplasmic face of the inner nuclear membrane and represents an important determinant of interphase nuclear architecture (13). Progerin apparently acts in a dominant-negative manner on the nuclear function of cell types that express Lamin A (14). The increased progerin causes nuclear blebbing and altered shape of the nucleus.

The clinical manifestations are divided into major criteria and signs usually presents itself as follows: the major criteria are a bird-like face (which occurs around 6 months to one year of age), alopecia, prominent veins on the scalp, big eyes, micrognathia, abnormal and slow dentition, pear-shaped chest, short clavicles, bow legs (coxa valga), short upper limbs and prominent articulations, low stature and weight with normal bone age, incomplete sexual maturation, reduction of the adipose tissue and adequate psycho-motor development with normal intelligence. Diagnosis is essentially clinical with major criteria appearing during the first and second years of life (15). Cutaneous manifestations are earlier to appear followed by skeletal and cardiovascular systems. In our case, cardiovascular systems showed calcification of aortic and mitral valves and hypertrophy of internal layer at internal carotid artery suggesting atherosclerosis. Skeletal abnormalities include osteolysis, osteoporosis, dystrophic clavicles, coxa valga, "horse riding" stance, thinning of cranial bones, delayed closure of cranial sutures and anterior fontanelle.

Prognosis is detrimental to the health of the patient and life expectancy is around 13 yr. The main mortality factors are cardiovascular diseases (75%) like acute myocardial infarction. Despite the advances in cardiovascular surgery, the low survival rate remains due to the high capacity of the disease to reproduce the erythematous plaques. Low-dose aspirin is recommended as prophylaxis to prevent atherosclerotic changes (15).

A vigorous research effort in the pharmaceutical industry has identified and developed a number of small-molecule compounds that potently and selectively inhibit farnesyltransferase (FTase). In vitro studies in mice suggest a possible role for the use of farnesyltransferase inhibitors (FTIs) in progeria (15). Farnesylation, a posttranslational modification involving the addition of a 15-carbon isoprene moiety, was implicated as a potential

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anticancer target when it was discovered that the oncoprotein Ras, which has been estimated to be involved in up to 30% of all human cancers, required farnesylation for its function. Two of these drugs (lonafarnib_SCH66336 from Schering-Plough, Kenilworth, NJ, and tipifarnib_R115777 from Johnson & Johnson, New Brunswick, NJ) have entered phase III trials and have been well tolerated, including in trials involving children (16). Lonafarnib competes with protein substrates for binding to the FTase enzyme (17). Similar to Ras, the Lamin A precursor is also farnesylated, with farnesylation serving as a required step to insert prelamin A into the nuclear membrane as well as to allow for the two downstream cleavage steps which complete the processing of Lamin A (18). For this patient, we are waiting for FTIs for clinical trials.

With the knowledge that the single C-to-T base change seen in nearly all cases of HGPS created a cryptic splice site and, thus, deleted the normal second endoproteolytic cleavage site in the Lamin A processing pathway, it was hypothesized that progerin was forced to retain its farnesyl group and, therefore, could not dissociate itself from the nuclear membrane. With other members of the nuclear lamina also potentially becoming trapped in complexes with the mislocalized progerin, a mechanistic connection between this permanently farnesylated state and the striking nuclear blebbing and disrupted nuclear architecture seen in HGPS cells was proposed, and the possibility of preventing or reversing this phenotype through FTIs was raised. Detailed study of HGPS and LMNA mutations may also advance our understanding of the process of aging. Why do LMNA mutant cells enter senescence earlier than normal cells? (19).

In summary, we found a new patient with typical Hutchinson-Gilford Progeria syndrome with mutation of the *G608G* in the LMNA gene. This is the first case diagnosed as Hutchinson-Gilford Progeria syndrome by gene study in Korea.

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