Hutchinson-Gilford Progeria Syndrome

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Abstract

Hutchinson-Gilford progeria syndrome is an extremely rare condition of premature aging. It is characterized by growth retardation and accelerated degenerative changes of cutaneous, musculoskeletal and cardiovascular systems. The pathogenesis of the disease is unknown. The patients usually appear normal at birth. Typical manifestations develop gradually and are evident by the first or second year of life. They have a remarkably similar physical appearance consisting of short stature, alopecia, craniofacial disproportion, micrognathia, hypoplastic mandible, beak-like nose, decreased subcutaneous fat, atrophic skin, sclerodermoid lesion, mottling hyperpigmentation, prominent scalp veins, prominent eyes, protruding ears with absence of earlobes, faint midfacial cyanosis, delayed closure of fontanelles and sutures, delayed dentition, horse-riding stance, thin limbs with prominent stiff joints, coxa valga, skeletal hypoplasia and dysplasia, dystrophic nails and high-pitched voice. Laboratory investigations are unremarkable. Metabolic, endocrine, serum lipid and immunologic studies show no uniform abnormalities. Typical radiographs demonstrate evidence of resorption of the distal ends of clavicles, attenuation of the terminal phalanges, diffuse osteopenia, and fishmouth vertebral bodies. In this report, a 3-year-old Thai girl with typical characteristics of Hutchinson-Gilford progeria syndrome is described.

Key word : Hutchinson-Gilford Progeria Syndrome - Case Report

Hutchinson-Gilford progeria syndrome is an extremely rare disorder characterized by the unique appearance of premature aging. It was first described by Sir Jonathan Hutchinson in 1886[1]. One year later Hastings Gilford reported the second case and proposed the term progeria derived from the Greek word geras meaning old age[2]. The incidence of progeria has been estimated at about 1 in 4 to 8 million live births[3]. Although it is a rare syndrome, it has been reported widely from all over the world in medical literature probably because of its fascinating clinical features. To our

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knowledge, the patient in this report is the first published case of Hutchinson-Gilford progeria syndrome in Thailand.

CASE REPORT

The patient was a 3-year-old Thai girl from Bangkok. She was the product of a full-term uncomplicated second pregnancy and was delivered by cesarean section. There was no consanguinity between the parents, and the family history was negative. Her mother was 29 years old and her father was 33 years old. The infant's birth weight was 2,850 grams and height was 50 centimeters. After having her hair and eyebrows shaved at age 1 month, the eyebrows did not regrow. By age 4 months, the patient began to lose her hair starting at the occiput. Her physical growth was retarded since she was 5 months; however, her psychoneuromotor development was normal. When the patient was 9 months, her mother noticed thin shiny skin on her scalp and legs. There were brown spots on the skin. The abdomen and eyes were large. The patient was referred to the Department of Pediatrics, Siriraj Hospital for evaluation of the hair and skin problems. Examination at age 3 years revealed a small, well co-ordinated girl. Her physical measurements were 13 kilograms in weight (50 percentile), 89 centimeters in height (10 percentile) and 47.5 centimeters in head circumference (25 percentile). She had a relatively large head compared to her body with frontal bossing and micrognathia. The scalp had marked alopecia except for the vertex where coarse long hairs were present. There were no eyebrows and eyelashes. The skin on the scalp and both legs appeared thin, atrophic and shiny, and subcutaneous fat was diminished giving prominent scalp veins (Fig. 1). The skin over the trunk, neck, axillae and upper arms was dry and markedly mottled and hyperpigmented. The nose was thin and rather beaked causing a bird-like face (Fig. 2). The ears protruded with short straight wide diameter of the external canals. The eyes were prominent and the ophthalmological examination was normal. The temporary dentition was complete with crowding, disrotation and malocclusion of the teeth. The voice was thin and high-pitched. The chest was narrow with small and hypoplastic nipples. The abdomen was enlarged with the liver palpating 1 centimeter below the right costal margin. The external genitalia appeared normal. The limbs were thin and the knee joints were prominent without limitation of range of motion. Other physical examinations were unremarkable.

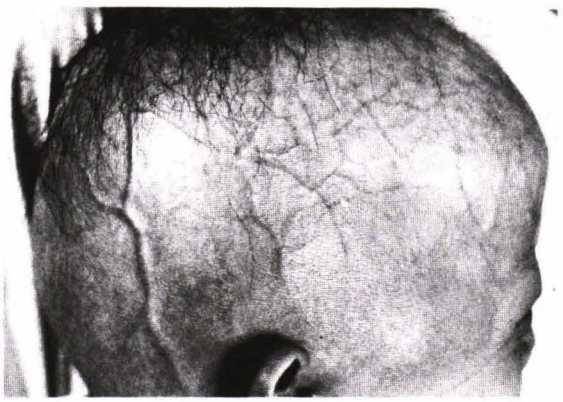

Fig 1. Prominent veins on the scalp.

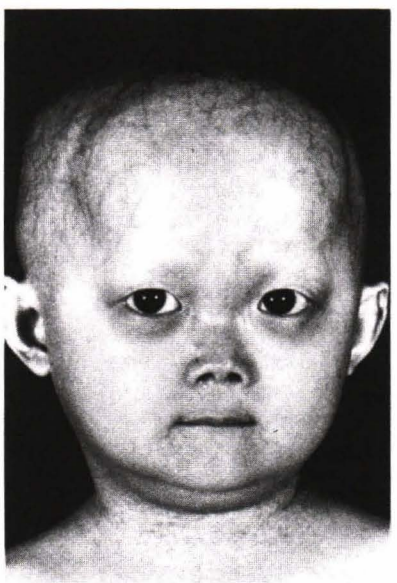

Fig 2. Characteristic face of Hutchinson-Gilford progeria syndrome.

Laboratory studies showed normal complete blood count, urinalysis, liver function test, BUN, creatinine, fasting blood sugar, triglyceride, thyroid function tests including T_3, T_4, free T_4 and TSH, plasma insulin-like growth factor 1 (IGF_1), insulin-like growth factor binding protein 3 ($IGFBP_3$), urine for hyaluronic acid, electrocar-

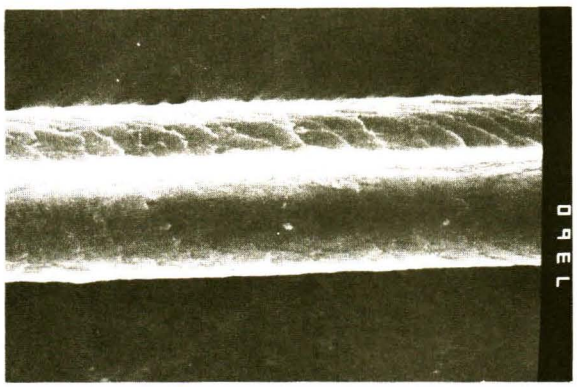

Fig 3. Longitudinal groove of the hair shaft on scanning electron microscope.

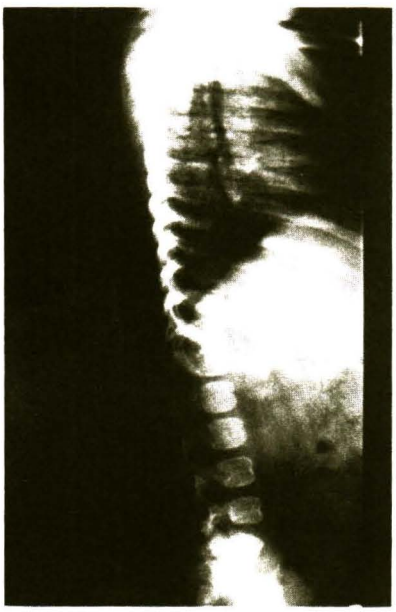

Fig 4. Fishmouth appearance of vertebral bodies.

diography and echocardiography. Serum cholesterol was increased with the level of 224 mg/dl. Serum immunoglobulin, CD_4 : CD_8 T-lymphocyte ratio and NK cell number were normal. The karyotype showed normal 46XX. The audiometric examination was normal. The Standford-Binet IQ testing showed bright normal intelligence (113). The skin biopsy obtained from the left leg revealed superficial lymphocytic perivascular infiltration and non-specific changes. Scalp hair samples were grossly normal by light microscope and refractive light microscope. Individual hair shafts had longitudinal grooves on scanning electron microscope without cuticular defect (Fig. 3). Roentgenographic studies showed hypoplasia of facial bones with slightly decreased craniofacial ratio and small mandible. There were multiple wormian bones, thin diploic space and delayed closure of anterior fontanelle. There was normal thoracic cage with slender clavicles which tapered to the distal ends. The anterior vascular channels of the lower thoracic and upper lumbar vertebrae were persistent giving the fish-mouth appearance vertebral bodies (Fig. 4). Bilateral coxa valga deformities were present and the femoral necks showed no angulation. The phalanges of the hands were suspected of acro-osteolytic change. The realtime ultrasonography of the abdomen showed mild diffuse hepatomegaly without space occupying lesion.

DISCUSSION

Hutchinson-Gilford progeria syndrome is the most classic and earliest described premature aging syndrome. It is more common in males than females with 1.5-2 : 1 ratio. Most reported cases are Caucasian[3]. Children with this syndrome demonstrate many features of old age suggesting a possible accelerated aging phenomenon. Recent research studies have evaluated the role of fibroblast life span, gamma ray DNA-repair capacity, immune function, endocrine function, thermolabile enzyme, atherosclerosis, hyaluronic acid excretion, protein metabolism and utilization but the basic defect remains unknown[4-10]. The pathogenesis of premature atherosclerosis is unknown but it may be related to abnormalities in the antioxidant, other enzyme systems, basic defect in DNA metabolism or structural changes in the vascular wall as a consequence of mesenchymal dysplasia. Hyperlipidemia has been documented but it is not a uniform finding[11]. Increased hyaluronic acid excretion has been reported in progeria and Werner's syndrome. Progeria may be an example of the effect of increased hyaluronic acid and concomittant reduced vascularity leading to sclerodermatous changes in skin, a high incidence of cardiovascular abnormalities, and a decreased density of vascularity. Analyses of the degree of genetic complexity underlying longevity have suggested that aging appears to have a strong genetic component. No recognized chromosomal

abnormality has been detected and patients have not been known to reproduce. The precise mode of inheritance is difficult to determine. Germinal mosaicism, a de novo sporadic autosomal dominant, autosomal recessive modes of inheritance have been proposed[12-17]. An alternative explanation is that Hutchinson-Gilford progeria syndrome is etiologically heterogenous.

This condition is usually the product of an uncomplicated pregnancy and delivery. All children with the syndrome look remarkedly similar. Individuals appear normal at birth although some patients may show sclerodermatous skin changes at birth or in early infancy[18,19]. The onset usually takes place between 6 to 12 months of age when the characteristic facial and cutaneous features develop gradually. The head appears relatively large compared to the small face but the head circumference is normal with a tendency toward frontal and parietal bossing. The cranial fontanelles and sutures close either relatively late or persist throughout life. Facial manifestations include facial bone hypoplasia, poor midface development, mandibular hypoplasia and micrognathia. Because of hypoplastic jaws, the teeth show crowding, malposition and malocclusion[20]. The dental development is markedly delayed. Varying degrees of oligodontia, anodontia, hypoplasia and discoloration of permanent teeth are manifested[21]. The mouth opening is small and the glottic opening is narrow leading to the typical thin high-pitched voice[22]. The nose is small, thin and beaked with a glyphic or scultured appearance, with the nasal cartilage contours visible under the skin giving a pluck-bird-like appearance. The eyes are large, prominent but normal without findings usually associated with aging. The ears are low set and tend to protrude with frequently absent earlobes. The external auditory canals are wide, short and straight resulting in the observation of tympanic membrane without special light. Approximately 35 per cent of patients with Hutchinson-Gilford progeria syndrome initially seek medical care because of the dermatologic manifestations. The abnormal skin can be the first clinical symptom[3]. The skin is thin, atrophic, taut and shiny with prominenc of superficial veins. Scalp hairs, eyebrows and eyelashes are lost. Subcutaneous fat over most of the body decreases resulting in an inelastic waxy of sclerodermoid appearance. Generalized alopecia and sparse subcutaneous fat on the scalp results in prominent scalp veins, eyes and ears. Ecrine sweating is often diminished and older children exhibit mottle hyperpigmentation. This irregular pigmentary changes particularly on sun-exposed areas and becomes progressively more prominent over several years[23]. Several patients bruise and sunburn easily. Other nonspecific cutaneous changes include scleroderma-like lesions, keloids and hyperplastic scars which were found to be subcutaneous nodules[24,25]. Wounds seem to heal much faster than in other children but laceration and bruises tend to form heavy scars[26]. Hypoplastic nipples may also be present. The trunk is pear shaped because of shortened clavicles. Skeletal changes are quite uniform. The limbs are thin and the joints especially the knee, elbow and finger joints are relatively enlarged, prominent and become progressively stiffer with age. Marked coxa valga is evident by 2 or 3 years of age which along with joint stiffness, contributes to the wide-based shuffling gait and horse-riding stance. Progressive osteolysis is a common feature of the Hutchinson-Gilford progeria syndrome. Progressive disappearance of the clavicles, thinning of the ribs, acro-osteolysis and the dissolution of the distal phalanges are well documented. Fracture healing is impaired with unknown cause so non-union is often encountered[27,28]. Cardiovascular findings are especially important because of the associated high incidence of mortality. Atherosclerotic cardiovascular diseases, angina pectoris, cardiac valvular disease, arteriosclerosis obliterans, hypertension, and congestive heart failure are commonly seen in this syndrome. Severe occlusive atherosclerotic disease is by far the most frequent finding. Carotid aneurysm, cerebral infarction and cardiomyopathy have also been reported[29,30]. Electrocardiography showed sinus rhythm, bundle branch block, ventricular hypertrophy and myocardial change. Echocardiography revealed calcifications of aortic and mitral valve, concentric cardiac hypertrophy, aortic valvular stenoregurgitation and mitral and tricuspid regurgitation[31]. Hutchinson-Gilford progeria mimics the aging process in many regards. However, it cannot be considered as a phenocopy of normal aging. Children with the syndrome demonstrate many of the aspects of old age, except for senile cataracts, presbycusis, presbyopia, arcus senilis, osteoarthritis and senile personalities[3]. Typical patients have normal motor and cognitive development. Intelligence is always in the normal to above average range[9].

Laboratory investigations for the most part are unremarkable. Metabolic, endocrine, serum lipid and immunologic studies have shown no uniform abnormalities. The greatest significance is the finding of an increased urinary excretion of hyaluronic acid[9]. Electroencephalogram patterns during sleep are consistent with the patients's chronological age and do not reflect the aging phenomenon[32]. Histopathologic studies from skin biopsy specimen on patients with progeria demonstrate nonspecific findings. The hairs show longitudinal depression, minor cuticular defects and loose scales on scanning electron microscope[33]. Audiometric examination occasionally indicates a mild sensorineural hearing loss[26]. Roentgenographic findings usually manifest within the first or second year of life and most commonly are the skull, thorax, long bones and phalanges[9]. The vertebral bodies are ovoid with a steplike indentation anteriorly giving the fish mouthed appearance of vertebral bodies[34].

The diagnosis of Hutchinson-Gilford progeria syndrome is based on the clinical presentations and usually can be made by the end of the first or second year of life with little difficulty when characteristic features begin to appear[9,20]. The rarity of the condition and the delayed insidious onset make early diagnosis difficult. There is no diagnostic laboratory test. Radiographs can confirm the diagnosis. The case described in this report is diagnosed as this syndrome on the basis of characteristic physical findings such as failure to thrive, short stature, craniofacial disproportion, alopecia, diminished subcutaneous fat, prominent scalp veins, prominent eyes, protruding ears, beak nose, micrognathia, coxa valga and many typical radiographic findings. Hutchinson-Gilford progeria syndrome should be differentiated from other premature aging diseases such as Werner's syndrome, acrogeria, metageria, Cockayne's syndrome, Rothmund-Thomson syndrome, total lipodystrophy, ataxia telangiectasia, Wiedemann-Rautenstrauch syndrome, Hallermann-Streiff syndrome[35-40].

Treatment of Hutchinson-Gilford progeria is complicated because the pathogenesis of the disease is not clearly understood. To date, no effective therapy is available. Nutritional supplement with a high caloric diet does not increase linear growth rate in the older patients[12]. A polyunsaturated fat diet usually controls hyperlipidemia, however, atherosclerosis develops despite the dietary regimen[11]. Ischemic heart disease and congestive heart failure have been treated with medical care including digitalis, diuretics, vasodilators, and converting enzyme inhibitors. Appropriate medical care contributes to the prolongation of life. Coronary artery bypass surgery is reported as a successful treatment in controlling the pain of angina pectoris in the patient[41]. Hutchinson-Gilford progeria syndrome is a rare condition which uniformly has a grave prognosis. The average life expectancy is 13 years with a range between 7 and 27 years. Death usually occurs in the second decade from myocardial infarction, congestive heart failure, or cerebrovascular accident secondary to premature atherosclerosis[42]. Other causes of death include marasmus and inanition, convulsions and accidental head trauma[20]. Throughout the course of the disease, widespread skeletal deformities, disfiguring cutaneous changes and cardiovascular abnormalities hamper the quality of life[9].

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กลุ่มอาการฮัทชินสัน-กิลฟอร์ด โปรจีเรีย

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ฮัทชินสัน-กิลฟอร์ด โปรจีเรีย เป็นกลุ่มอาการที่ผู้ป่วยมีลักษณะแก่ก่อนวัย ความผิดปกติเกิดในระบบผิวหนัง กล้ามเนื้อ กระดูก หัวใจและหลอดเลือดโดยไม่ทราบสาเหตุแน่ชัด แรกเกิดผู้ป่วยเหมือนทารกปกติ ลักษณะเฉพาะของโรคจะค่อยๆปรากฏขึ้นและเห็นได้ชัดเจน เมื่อผู้ป่วยมีอายุ 1-2 ปี โดยผู้ป่วยเกือบทั้งหมดมีหน้าตาคล้ายคลึงกันคือ เจริญเติบโตช้า ตัวเตี้ย ผมและขนร่วง หน้าเล็ก คางและกรามเล็ก จมูกแหลม ตาใหญ่ หูกางและมักไม่มีติ่งหู ผิวหนังบาง ตกกระ ไขมันใต้ผิวหนังน้อยลงทำให้มองเห็นเส้นเลือดข้างใต้ชัดเจนขึ้น กระหม่อมและรอยแยกของกะโหลกปิดช้าหรือไม่ปิด ฟันขึ้นช้าและเรียงตัวซ้อนกันผิดปกติ กระดูกบางผิดรูป ต้นขากางทำให้ท่ายืนคล้ายกำลังขี่ม้า เสียงแหลม ในปัจจุบันยังไม่พบความผิดปกติในการตรวจทางห้องปฏิบัติการที่จะช่วยยืนยันการวินิจฉัยโรค ภาพรังสีกระดูกมักพบปลายกระดูกไหปลาร้าและกระดูกนิ้วบางเล็กลง รายงานนี้นำเสนอผู้ป่วยเด็กหญิงไทยอายุ 3 ปี ที่มีลักษณะเข้าได้กับกลุ่มอาการนี้

คำสำคัญ : กลุ่มอาการฮัทชินสัน-กิลฟอร์ด โปรจีเรีย – รายงานผู้ป่วย

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