The longest surviving child with Hoyeraal-Hreidarsson syndrome

We describe the case of a 12-year old boy with Hoyeraal-Hreidarsson syndrome (HHS). This syndrome includes intrauterine growth retardation, microcephaly, mental retardation, cerebellar malformation, and pancytopenia. HHS is a severe multisystem disorder associated with premature mortality, due to bone marrow failure. The pathogenesis and genetic basis presently is unknown. Onset of HHS has only been described in boys and reporters speculated that HHS may be a severe form of X-linked dyskeratosis congenita (DKC). In this paper, we reported an autosomal recessive form of HHS in a family. Almost all cases have died before 4 years (except one at 7 years) our patient is alive at his 12th year at all, probably because of autosomal recessive gene transmission.

Dyskeratosis congenita (DKC) is a rare genodermatosis characterized by cutaneous reticulated hyperpigmentation, nail dystrophy, premalignant leukoplakia and ulcerations affecting oral and gastrointestinal mucosa, and progressive pancytopenia.[1,2] Bone marrow failure is the principal cause of early mortality with an additional predisposition to malignancy and fatal pulmonary complications. X-linked recessive, autosomal dominant and autosomal recessive forms of the disease are recognized. Death usually occurs as a result of pancytopenia or malignant transformation of mucocutaneous lesions.[1,3] DKC1, located at Xq28, is the responsible gene. This gene encodes dyskerin, a highly conserved protein with putative nucleolar functions.[4] Hoyeraal-Hreidarsson syndrome (HHS) was firstly described in two siblings by Hoyeraal then similar genetic defect and some clinical symptoms accompanied by DKC were reported in this syndrome.[4-11]

HHS includes intrauterine growth retardation, microcephaly, mental retardation, cerebellar hypoplasia, progressive bone marrow failure, and mucocutaneous lesions.[12] But the clinical symptoms and clinical course are still not clear because HHS is a rare syndrome and almost all cases died before 4 years of age.[13] In this paper, we report the case of a 12-year old boy with HHS who represents the longest surviving case of HHS, and we describe an autosomal recessive pattern in a family, seems likely.

Case Report

A 12-year-old boy was referred for evaluation of pancytopenia and failure to thrive and delayed psychomotor development. The patient was born as the third child of the family after an uneventful pregnancy at 39 weeks of gestation, with slightly intrauterine growth retardation (weight 2400 gram, length 44 cm and head circumference 32 cm). However, no serological and clinical evidence of intrauterine infection was found. His parents were cousins and they had three sons. Elder brother of our patient admitted with the symptoms of growth failure, mental retardation, microcephaly and seizures. He had been followed in pediatric neurology department for his mental retardation and seizures but his electroencephalogram (EEG) was normal. Also he had had partial alopesia and nail dystrophy. In follow up time, his blood counts altered and pancytopenia was detected in the hemogram (leukocyte count 3400/μL, hemoglobin 6.6 g/dL and platelet count 7 000/mm^3) The examination of bone marrow aspiration showed hypocellularity and absence of megakaryocytes. He had died at 11-years-old due to intracranial hemorrhage. The second child of family is healthy and alive.

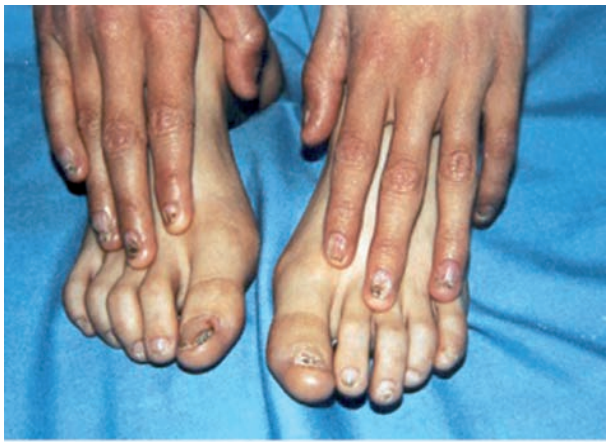

Figure 1. Nail dystrophy with complete loss of nail plate.

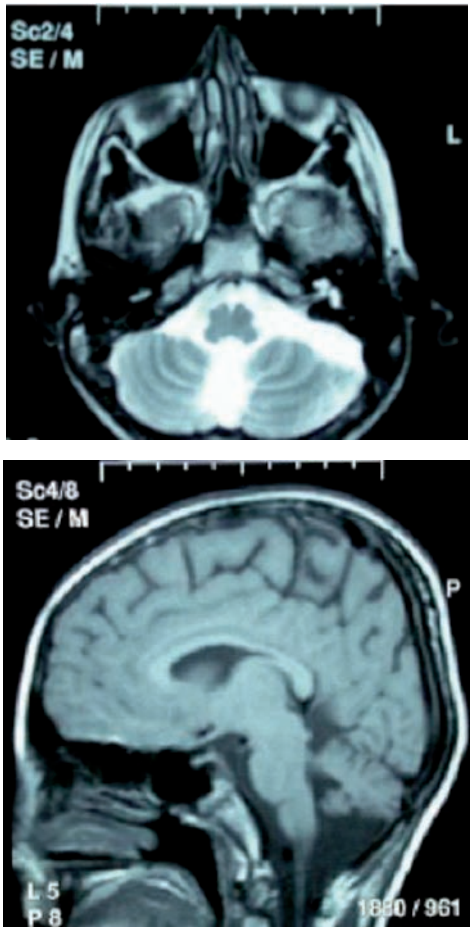

Figure 2. Magnetic resonance image of the patient's brain at the age of 11 years, demonstrating cerebellum (a). Cerebellar vermis hypoplasia (b).

At the time of admission when he was 19-month-old, he showed microcephaly, growth failure and slow psychomotor development. His cranial tomography and EEG

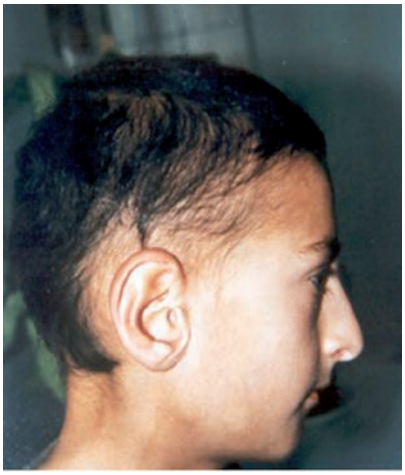

Figure 3. Alopesia in the hair of the patient.

were normal. He was able to sit alone at 24 months of age, walk at 4 years of age and speak a few meaningful words at 5 years of age.

At 8 years of age, he admitted to our hospital to evaluation of epistaxis and cerebellar ataxia. In his physical examination microsephaly, thin face with micrognathia, and retrognathia, high palate and low-set ears, general musculer atrophy and pes cavus has been found. Significant nail dystrophy was noted (Figure 1). The neurological examination revealed cerebellar ataxi, nystagmus, dysmetria, dysdiadochokinesia and positive Romberg maneuver. Magnetic resonance imaging of the brain was performed because of developmental delay and revealed hypoplasia of the cerebellum and cerebellar vermis (Figure 2). He had thrombocytopenia (platelet count 67 000/mm^3) but pancytopenia and hypogamaglobulinemia were not detected.

At 12 years of age, he admitted to our hospital because of fever, cough and aphthous lesions of the oral mucosa. Physical examination revealed a weight of 23 kg (below 3 percentile) and a height of 141 cm (about the 10-25th percentile). The head circumference was 47 cm (below 3 percentile). Thin and sparse scalp hair and partial alopesia were noted (Figure 3). Oral ulcers on the tongue and buccal mucosa, gingival hypertrophy, ksantoma on the ear lop, and flashing were present.

Laboratory data revealed a leukocyte count of 2500/μL, with 29.2% neutrophils, 33.8% lymphocytes, 35.0% monocytes and 1.3% eosinophils; a red blood cell count of 2.39×10^6 /μL, hemoglobin of 9.2 g/dL, a platelet count of 44 000/mm^3 and mean corpuscular volume of 115.6. Serum levels of electrolyte, ferritin, folate, vitamin B12 and ?-fetoprotein were normal. Results of Coombs' test, coagulation studies, human immunodeficiency virus serology, hemoglobin protein electrophoresis and serum lipids levels were normal, as were findings on renal, abdominal ultrasonography and lung radiography. In the subsets of lymphocytes CD45, CD3, CD4, CD8, CD16 and CD19 were 98.6%, 85.3%, 22.8%, 48.2%, 4.9% and 9.9% respectively, which indicated a decrease in Thelper cells and an increase Tsupresor cells. Serum IgG, IgA, IgM and IgE levels were normal at 937 mg/dl, 169 mg/dL, 104 mg/dl and 5.46 IU/mL respectively. Serum IgG1 (726 mg/dl) level was low but serum IgG2, IgG3 and IgG4 levels were normal at 1230 mg/dl, 724 mg/dl and 76.7 mg/dl respectively. Serum compleman C4 level was normal but C3 level was found high. Examination of bone marrow aspiration showed hypocellularity with eritroid series and left-shifted myelopoiesis and an absence of megakaryocytes. Metabolic disorders analyses were made of amino acids both urine and serum, lactate and pyruvate in blood. All the results were normal. Serum T3, T4, TSH, tyroglobulin, cortizol, ACTH, insulin levels were normal but leptin level was found low. IQ scores of our case were found 66 for the Porteus and 70 for the Goodenough at 12 years old.

Based on these features of the patient, a diagnosis of HHS was made. The coding regions of the responsible for X-linked and autosomal dominant dyskeratosis congenita (DKC1 and hTERC respectively) have been screened for mutation by denaturing HPLC analysis. Also analysis of the DNA was screened in the patient's family. Chromosome karyotypes in peripheral blood were normal. The mother had a random X-chromosome inactivation pattern (XCIP) and DNA samples of our patient, his father and healthy brother were found to be normal. The fact that the parents were cousins suggests that the inheritance is autosomal recessive. However both affected children were boys making X-linked inheritance a possiblility if the mother is a genetic mosaic.

Discussion

The patient is unusual when compared with typical symptoms of DKC because of the findings, IUGR, mental-motor retardation, microcephaly and cerebellar malformation. Classical DKC is an inherited disease characterized by the triad of abnormal skin pigmentation, nail dystrophy and mucosal leucoplakia, and progressive pancytopenia. A variety of non cutaneous abnormalities such as gastrointestinal, neurological, ophthalmic, pulmonary and skeletal have also been reported.[3] Microcephaly and cerebellar malformation have rarely been seen in association with DKC, and mild to moderate developmental delay is seen in 18% of patients with X-linked DKC.[14,15] In this respect, HHS can be defined as the symptoms, IUGR, microcephaly and cerebellar malformation add to DKC findings. The recognition that HHS is a severe variant of DKC has further highlighted the considerable variability of the DKC phenotype. Some hypothesis suggested that this syndrome might be a severe form of X-linked DKC.[16] Mutations in the DKC1 gene on Xq28 have been identified in the X-linked form of DKC and in some HHS patients.[16-19] The absence of mutations of the DKC1 gene in patients with HHS emphasises the probable implication of one or more other loci.

Analysis of the DNA was screened in our patient's family. The mother had a random X-chromosome inactivation pattern (XCIP). This means she is unlikely to be a carrier for X-linked DKC. This in turn makes X-linked DKC (due to mutations in DKC1) unlikely in this family as she has had 2 boys with disease. DNA samples of his father and healthy brother were found to be normal. DNA sample of our patient has been screened for the hTR gene (mutated in autosomal dominant DKC) and this again was found to be normal. The conclusion from these studies is that our patient probably represents an autosomal recessive form of DKC for which the genetic basis presently is unknown. These result is also supported by the fact the parents are first cousins. According to our data, any case of the HHS that is still alive at 12-year-old was not reported yet.

The details of 12 cases of HHS, including ours, are summarized in Table 1. This syndrome also has been defined in females, which favors autosomal recessive transmission as a possible mode of inheritance in HHS.[13,20] The

Table 1. Clinical features of the previously reported cases of HHS and our patient.

Reported by	Hoyeraal		Hreidarsson	Bertbet	Ohga	Aalfs	Nespoli	Mahmood		Yaghmai	Akaboshi	Cossu	Our case
Case	1	2						1	2				
Reference number	5	5	6	7	8	9	10	20	20	16	13	18	
Sex	M	M	M	M	M	M	M	F	F	M	F	M	M
IUGR	+	+	+	+	+	+	+	+	+	+	+	+	+
Growth failure	+	+	+	+	+	+	+	+	+	+	+	+	+
Microcephaly	+	+	+	+	+	+	+	+	+	+	+	+	+
Mental retardasyon	+	+	+	+	+	+	+	+	+	+	+	+	+
Facial dysmorphism	+	+	-	-	+	+	+	nd	nd	+	-	nd	+
Cerebellar malformation	+	+	+	+	-	+	+	+	+	+	+	+	+
Ataxi	nd	+	nd	+	-	+	+	+	+	+	+	nd	+
Bone marrow failure	+	+	+	+	+	+	+	+	+	+	+	+	+
Absence of megakaryocytes	+	+	+	-	nd	+	nd	+	+	+	+	+	+
Reccurent infections	-	+	+	+	+	-	+	+	-	nd	-	+	-
Low serum IgG	nd	+	nd	+	IgG_2	+	+	nd	nd	+	-	+	IgG_1 $C_3\uparrow$
B-cell depletion	nd	nd	nd	+	+	-	+	nd	nd	nd	+	+	-
T-cell dysfunction	nd	nd	nd	+	+	-	+	nd	nd	nd	+	-	+
Mucocutaneous lesions	nd	+	nd	nd	nd	nd	nd	+	+	+	+	+	+
Alopecia	nd	nd	nd	nd	nd	nd	nd	nd	nd	+	-	-	+
Nail dystrophy	nd	nd	nd	nd	nd	nd	nd	nd	nd	+	-	-	+
Age at death (mo)	23	42	23	41	89			36					
Age at report (mo)						36	31		51	50	84	9	153

+, present; -, absent; nd, not described; M, male; F, female

ratio of females to males was found 0.2 in Table 1. All cases had IUGR and growth failure for each case was noted in early infancy. Microcephaly and psychomotor retardation were also noted in all cases. Eventhoug cerebellar hypoplasia was present in all other cases, the absence in Ogha's case was attributed to the variability of HHS.[8] In addition, Akaboshi et al. reported that delayed myelination of cerebral white matter and hypoplastic corpus callosum were also important findings.[13]

Thrombocytopenia was the earliest symptom of progressive pancytopenia, except for Berthet's case.[7] Thrombocytopenia was appeared about nine years of age in our case, but in most cases had been appeared about one or two years of age. At that time, bone marrow findings showed an absence of megakaryocytes. Recurrent infection was observed in seven cases. However, in Hoyeraal's first case, immunodeficiency was not diagnosed probably because of early death.[5] Though our case showed immunodeficiency in laboratory data (IgG1 deficiency and T cell dysfunction), no recurrent infection occurred, indicating subclinical immunodeficiency. Also cases of Ogha, Berthet, Nespoli and Akaboshi showed immunological abnormalities such as IgG2 deficiency or B cell depletion and T cell dysfunction of lymphocytes.[7,8,10,13]

Several of the cases listed in Table 1 had mucocutaneous lesions, including aphthous stomatitis (including our case), skin abnormalities and alopecia.[5,13,16,18,20] In addition, case of Yahmaghi and ours had nail dystrophy as similar cutaneous lesions of DKC patient.[16]

In this report, we reviewed 12 case of HHS, including our case which is the longest survivor. We consider that, autosomal ressesive form of HHS represents similar features of DKC and IUGR, microcephaly, psychomotor retardation, cerebellar malformation with a long survival time but, X-linked form of HHS shows severe clinical symptoms which leads to early death in infancy in most cases.

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Key Words: Hoyeraal-Hreidarsson Syndrome; Dyskeratosis Congenita; Mental Retardation; Cerebellar Hypoplasia; Pancytopenia.

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