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CASE REPORT

Oral and Dental Findings of the Longest Surviving Patient with Hoyeraal-Hreidarsson Syndrome

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ABSTRACT

Hoyeraal-Hreidarsson syndrome (HHS) is a severe multisystem disorder associated with premature mortality, due to bone marrow failure. Because HHS is a very rare disease and almost all cases die before 7 years of age, the dental development and dental findings of HHS patients are still not clear. According to our knowledge only twenty seven cases were reported up to now and we did not find any report focusing on the dental evaluation of HHS patients. Therefore, in this report, we aimed to present the dental findings of a twenty-year old patient with HHS.

Keywords: Hoyeraal–Hreidarsson syndrome, Dyskeratosis congenita, Aplastic anaemia, Immunodeficiency, Cerebellar hypoplasia, Oral and dental findings

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INTRODUCTION

Hoyeraal-Hreidarsson syndrome (HHS) is a severe multisystem disorder characterized by prenatal growth retardation, microcephaly, mental retardation, psychomotor retardation, immune deficiency, facial dysmorphism, cerebellar malformation, ataxia, bone marrow failure, progressive pancytopenia, aplastic anaemia, mucocutaneous lesions, oral aphthous ulcers, aplastic alopecia, and nail dystrophy (1-6).

This syndrome causes significant mortality and morbidity with bone marrow failure and immunodeficiency are the most serious manifestation of the condition, occurring in more than 80% of patients. The natural history of HHS terminates with a death secondary to complications of bone marrow failure or infection that generally occurs in the first decade of life (7). Although the pathogenesis and genetic basis is presently unknown (8), researchers have speculated that HHS may be a severe form of X-linked dyskeratosis congenita (DKC) (3,9,10). In this study, we reported the case of a 20-year old boy who represents the longest surviving case of HHS who is still alive and described some important oral and dental findings of the syndrome that have not been previously reported.

CASE REPORT

A 20-year-old Turkish boy who is the

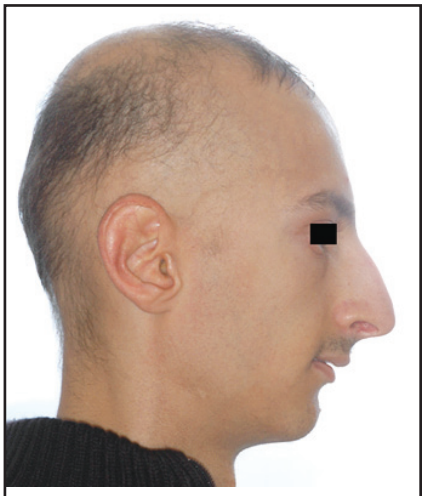

Figure 1. Showing alopecia and microcephaly of the patient

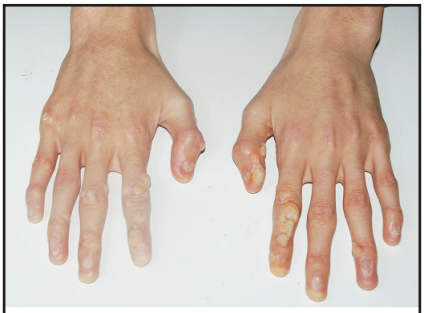

Figure 2. Nail dystrophy with complete loss of nail plate and skin abnormalities

ongest surviving patient with HHS was referred to our department for treatment of his dental and periodontal problems. On physical examination, he showed microcephaly, thin face with micrognathia, retrognathia, growth failure, slow psychomotor development, high palate, low-set ears, and general muscular atrophy. He presented with speech problems and mild learning difficulties. Alopecia (figure 1) and significant nail dystrophy was also noted in the patient (figure 2). The patient also had cerebellar ataxi, nystagmus dysmetria, dysdiadochoki-

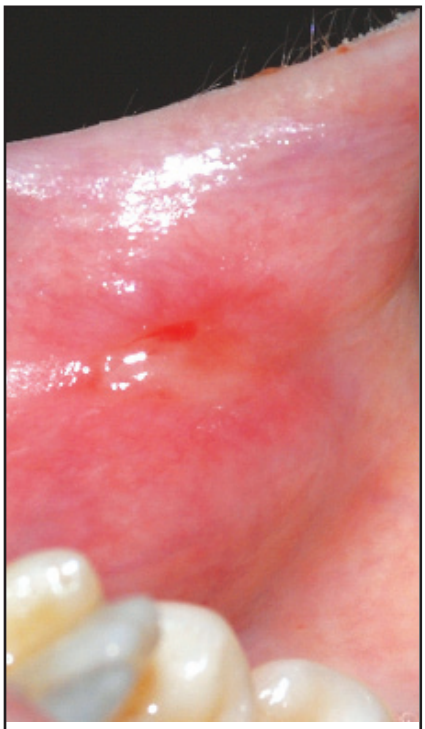

Figure 5. Ulceration of patient's right buccal mucosa

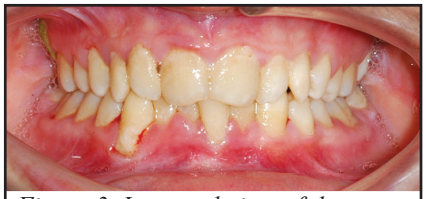

Figure 3. Intraoral view of the patient

nesia, hypoplasia of the cerebellum and cerebellar vermis. Oral examination revealed local gingival recession and marginal gingivitis. His oral hygiene was insufficient with heavy plaque and considerable calculus accumulation on the teeth surfaces (figure 3). Oral findings demonstrated pale tongue (figure 4), oral ulcerations (figure 5), dental caries, short-blunted roots, gingival bleeding, and tooth mobility. Leukoplakia was not diagnosed in the oral cavity. On panoramic radiographic examination, it was observed that root development was delayed. Panoramic examination also revealed presence of retained deciduous dentition. The short and blunted roots of the mandible and maxillary teeth -especially the premolars and second molars- showed symptoms of taurodontism (figure 6). According to the patient's previous panoramic radiograph which was taken at his fifteen years, delayed teeth eruption was also discussed at that time (figure 7). In cephalometric tracing, mandibular retrognathism was found according to Steiner and Mc Namara analyses.

This case report was carried out after obtaining a written informed consent from the parents of the patient. The

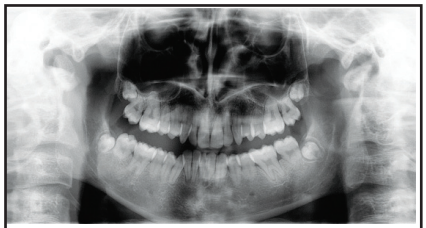

Figure 6. Panoramic radiograph of a 20-year-old male with HHS showing decreased root/crown ratios in the posterior teeth and taurodontism

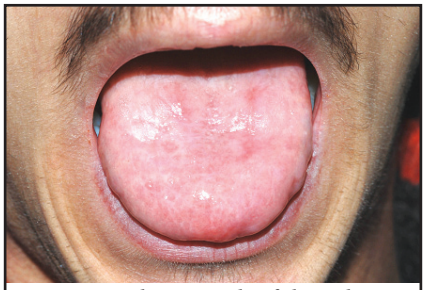

Figure 4. Photograph of dorsal surface of pale tongue

dental treatment plan included prevention protocol such as cleaning, fluoride varnish application after restorative treatment, meticulous oral hygiene instructions and the restoration of the permanent first and second molars. Gingival recessions required the consultation of a periodontist. After establishing optimal oral health, oral hygiene instructions were given to the patient and his parents. The aim of the dental treatment applied to this patient was to enable him to survive free from potential dental, gingival and acute infections. In addition, periodic follow-up visits were recommended in order to monitor oral mucosa ulcers and leukoplakic lesions.

Hematological findings showed pancytopenia and hypogammaglobulinemia now and he had requires regular transfusions. Bone marrow transplantation has not been applied since a suitable bone marrow match has not been found.

DISCUSSION

Hoyeraal-Hreidarsson syndrome (HHS) is a severe infantile variant

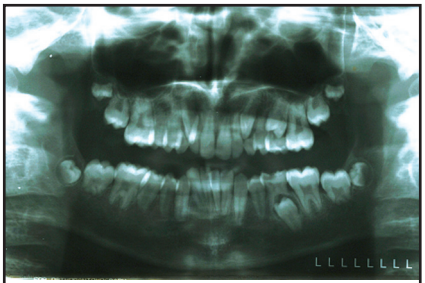

Figure 7. Patient's previous panoramic radiograph which was taken five years ago

of X-linked DKC (3). DKC is a rare inherited bone syndrome exhibiting marked clinical and genetic heterogeneity. This syndrome is characterized by mucocutaneous abnormalities, bone marrow failure and predisposition to cancer. The main causes of mortality in DKC are bone marrow failure/immunodeficiency (60–70%), pulmonary complications (10–15%) and malignancy (10%) (11). Mutations in the DKC1 gene on Xq28 have been identified in the X-linked form of DKC and in some HHS patients (12-15). Clinically there appear to be three patterns of inheritance for DKC autosomal dominant, autosomal recessive and X-linked recessive (16). In order to obtain background information on our patient's condition, DNA analysis was carried out on his family. The mother had a random X-chromosome inactivation pattern. This means that she is unlikely to be a carrier for X-linked DKC. DNA samples of his father were found to be normal. DNA sample of our patient was screened for the hTR gene (mutated in autosomal dominant DKC) and this again was found to be normal. Results from these analyses

Table 1. Oral and dental features of all patients with HHS

Number of cases	Reported Cases	Reported Year	Gender, M/F	age at onset, mo	age at death, mo	IUGR	micro-cephaly	Mental retardation	Oral Ulcerations	Dental and oral Findings
1	Hoyeraal HM,1970, (two cases)	1970	M	9	23	+	+	+	nd	nd
2		1970	M	5	43	+	+	+	+	nd
3	Hreidarsson S,1980(one case)	1980	M	6	23	-	+	+	+	nd
4	Berthet F,1994(one case)	1994	M	10	41	+	+	+	-	nd
5	Aalfs CM, 1995(one case)	1995	M	36	nd	+	+	+	nd	nd
6	Ohga S,1997(one case)	1997	M	77	89	+	+	+	nd	nd
7	Nespoli L,1997(one case)	1997	M	8	nd	+	+	+	+	nd
8	Mahmood F,1998(two cases)	1998	F	14	36	+	+	+	+	nd
9		1998	F	18	alive	+	+	+	+	nd
10	Knight SW,1999 (four cases)	1999	M	18	alive	+	nd	+	nd	nd
11		1999	M	32	36	+	nd	nd	nd	nd
12		1999	M	18	32	+	nd	nd	nd	nd
13		1999	M	7	alive	+	+	+	+	nd
14	Revy P,2000(one case)	2000	F	2	48	+	+	+	nd	nd
15	Yaghmai R,2000(two cases)	2000	M	8	alive	+	+	+	+	nd
16		2000	M	12	67	-	+	+	nd	nd
17	Akaboshi S,2000(one case)	2000	F	4	alive	+	+	+	+	nd
18	Cossu F,2002(one case)	2002	M	9	alive	+	+	+	+	nd
19	Sznajer Y,2003(four cases)	2003	M	12	24	+	+	+	+	nd
20		2003	M	1	48	+	+	+	+	nd
21		2003	M	7	36	+	+	+	+	nd
22		2003	M	6	30	+	+	+	+	nd
23	M'Kacher R,2003(one case)	2003	M	nd	nd	+	+	+	nd	nd
24	Ozdemir MA,2004(one case)	2004	M	19	alive	+	+	+	+	nd
25	Coman D, 2008(one case)	2008	F	24	nd	+	nd	nd	+	nd
26	Borggraefe I, 2009(two cases)	2009	M	8	72	+	+	+	+	nd
27		2009	M	36	nd	-	+	+	+	nd
28	OUR PATIENT	2010	M	19	alive	+	+	+	+	

Taurodontism, delayed tooth eruption,tooth mobility, dental caries, local gingival recession , marginal gingivitis,gingival bleeding,heavy plaque and considerable calculus, pale tongue, high palate, micrognathia,

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

concluded that our patient probably represents an autosomal recessive form of DKC whose genetic basis is presently unknown. Bone marrow failure is the principal cause of early mortality with an additional predisposition to malignancy and fatal pulmonary complications. Death usually occurs as a result of pancytopenia or the malignant transformation of mucocutaneous lesions (8). According to our patient's hematological examination, pancytopenia was detected subsequently. X-linked recessive, autosomal dominant and autosomal recessive forms of the disease are recognized. All clinicians should be aware of this rare genetic disorder so that early referral can be made and appropriate management may be applied.

The rare bone marrow failure syndrome DKC is a heritable disorder that is characterized by a triad of abnormal skin pigmentation, nail dystrophy and leukoplakic lesions in the oral cavity. Alopecia and skin lesions which entitled the name of the DKC appear later during the course of the disease (14). Our patient had abnormal skin pigmentation, nail dystrophy and alopecia consistent with these findings.

Several studies in the literature have described the oral and dental symptoms of DKC (3,5,8,9,17-24). These include gingival recession, gingival bleeding, gingival inflammation with edema, alveolar bone loss, periodontitis, extensive caries, smooth atrophic tongue mucosa, leukoplakia, lichen planus, hypodontia, short blunted roots, hypocalcification and thin enamel.

The most commonly seen oral symptoms in dyskeratosis congenita are oral leukoplakia (8,9) and alveolar bone loss (23,24), neither were detected in our patient. The dentists must be aware for the malignant transformation of the leukoplakic lesions in patients with DKC (25,26). According to our knowledge only 27 cases of HHS were reported up to now (1-5,7,12,14,15,19,20,27-32) (Table 1). The dental evaluation of these patients was not reported in any of these studies. In addition controlled studies of the associated oral and dental findings in HHS have not yet been reported. The clinical course and symptoms are still not clear because HHS is a very rare disease and almost all cases died before 7 years of age (except for case one at 12 years of age) (7). We consider that the dental and oral findings observed in our patient should be added to the previously described dental symptoms observed in HHS as they could be important in the diagnosis of the disease. The autosomal recessive form of HHS displays similar dental features of DKC. However, the X-linked form of HHS has severe clinical symptoms which in most cases lead to early death in infancy.

Among sixteen cases had oral ulcerations only one case had no oral ulcerations and eight cases were not related to oral ulcerations. In our case the patient had oral ulceration on his right buccal mucosa.

There is no effective and curative treatment for HHS(22). Allogeneic bone marrow transplantation appears to provide a long-term solution (33,34). We were able to identify only four HHS patients recorded in the literature who received a BMT (3,14,21,32). Knight *et al*. (3) reported the use of an unrelated BMT in a boy, and M'kacher *et al*. (21) reported the sibling matched transplantation in a 7-year-old boy. Unfortunately, no information was provided regarding the conditioning regimens. Cossu *et al*. (14) reported the particular patient encountered prompt and sustained engraftment, from an HLA matched elder sibling donor, at the time of publication 1-year post-BMT. Coman D *et al*. (32) reported a patient who was still alive during 37 months after hematopoietic stem cell transplantation. The patient reported here requires a regular transfusions replacement. Bone marrow transplantation has not been applied since a suitable bone marrow match has not been found.

In some patients standard treatments, such as chemotherapy regimens, and radiation therapy are not applicable due to the increased sensivity to these treatments (35). For these patients, preventive and interceptive precautions may be taken for early diagnosis. Patients with DKC or HHS should be kept under observation (36). In future gene therapy may provide an alternative treatment for the management of this fatal disorder (37).

CONCLUSION

HHS is a rare disorder and dentists and clinicians should be aware of its systemic and oral symptoms because of the poor prognosis. They also should be vigilant to diagnose this fatal condition in its early stages and advise appropriate haematological investigations.
It is important to be aware of the unexpected mucocutaneous malignant changes which can occur in this disorder. In addition, genetic counselling, early diagnosis and referral for the management of the dental and oral symptoms and educating the patient about the oral hygiene and dental problems seem very important.

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