Oculodentodigital Dysplasia: Disease Spectrum in an Eight-year-old Boy, His Parents and a Sibling

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Oculodentodigital dysplasia is an extremely rare autosomal dominant pleiotropic disorder, caused by mutations in the Connexin 43 gene (GJA1). Described here is a previously undiagnosed case of an 8-year-old boy with enamel and dentin hypoplasia and typical faces. In this presentation, many typical clinical and radiographical features of this condition are present. The characteristic features include a typical face, premature loss of primary teeth and odontodysplasia of permanent teeth, clinodactyly, ocular signs, and CNS involvement. To our knowledge, the case that we report here is the first case with mamelon-shaped tip of the tongue and enlarged midpalatal raphe.

Keywords: *Oculodentodigital dysplasia, clinodactyly, odontodysplasia.*
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INTRODUCTION

Oculodentodigital dysplasia (ODDD) or Meyer-Schwickerath syndrome is a highly penetrant autosomal dominant disorder, with variable expression.[1] ODDD is caused by mutations in the *GJA1* gene located on human chromosomes 6q22–q23, encoding the gap junction protein Connexin 43 (Cx43).[2,3] It is characterized by a wide spectrum of symptoms including craniofacial defects (microcephaly, thin nose), ophthalmological anomalies (microphthalmia, microcornea, glaucoma, cataract, iris abnormalities), dental abnormalities (microdontia, anodontia, multiple caries, early tooth loss) and anomalies of hand and foot (syndactyly, camptodactyly and clinodactyly due to hypoplasia or aplasia of the middle phalanges).[4] Neurological symptoms such as mental delay, ataxia, spasticity and hearing impairment may also be present.[4] Described here is a previously undiagnosed case of an eight-year-old boy with enamel and dentin hypoplasia and typical faces, and to the best of our knowledge, it is the first case with a mamelon-shaped tip of the tongue and an enlarged midpalatal raphe.

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CASE REPORT

An eight-year-old boy was referred for the treatment of dental abscess of lower left first premolar to the Department of Pediatric Dentistry, Tabriz University of Medical Sciences. Clinical examination revealed brachiocephaly with frontal bossa, long narrow nose with hypoplastic nasal alae, telecanthus, prominent epicanthal folds, short palpebral fissures, microphtalmia, converged strabismus and ptosis of both eyes (Figure 1). Further examination identified curly dry and spare hair, eyebrows and eyelashes. Patient's profile demonstrated a dish face, retruded lips, and round gonial angle of the mandible. Relatively short stature, bulky mandible, missing phalanges of fifth finger in hands, clinodactyly, and hyperkeratotic palms were also noted (Figure 2).

Medical history indicated extended prenatal period and delayed walking. The patient's dental history revealed infection of multiple primary and permanent teeth leading to the extraction of all primary as well as a number of permanent teeth. Intra-oral examination demonstrated dome-shaped palate, enlarged midpalatal raphe with a bony consistency, mamelon-shaped tip of the tongue and large widened alveolar crests (Figure 3a,b). The dental findings were teeth with size smaller than normal and yellowish hypoplastic enamel,

and early eruption of permanent premolars (Figure 4). Panoramic radiograph showed evidence of generalized rarefaction of mandibular base, 'ghost' appearance of shortened teeth, unclear lamina dura, decreased thickness of dentin, and lack of contrast between enamel and dentine. The pulp chambers of the permanent teeth were markedly enlarged; they had greater apicoocclusal height and lack of constriction at the level of the CEJ, giving it a rectangular shape, and hence, resembling the features of taurodontism in molars and premolars. Permanent dental buds appeared closer to the alveolar crest. Moreover, periapical radiolucency of lower left first premolar was noted (Figure 5a). The extent of involvements was a clue to suspect a syndromic nature of the condition by the dental team, and hence, the details of family history were checked.

The patient's five year old brother was examined shortly after his elder brother's evaluation. The sibling had frontal bossa, clinodactyly, hyperkeratosis of hands, mild enamel hypoplasia of primary teeth, and bi-rooted right upper primary canine (Figure 5b). The patient's parents who are second cousins revealed clinodactyly. Considering all observed signs of the family, oculodentodigital dysplasia could be

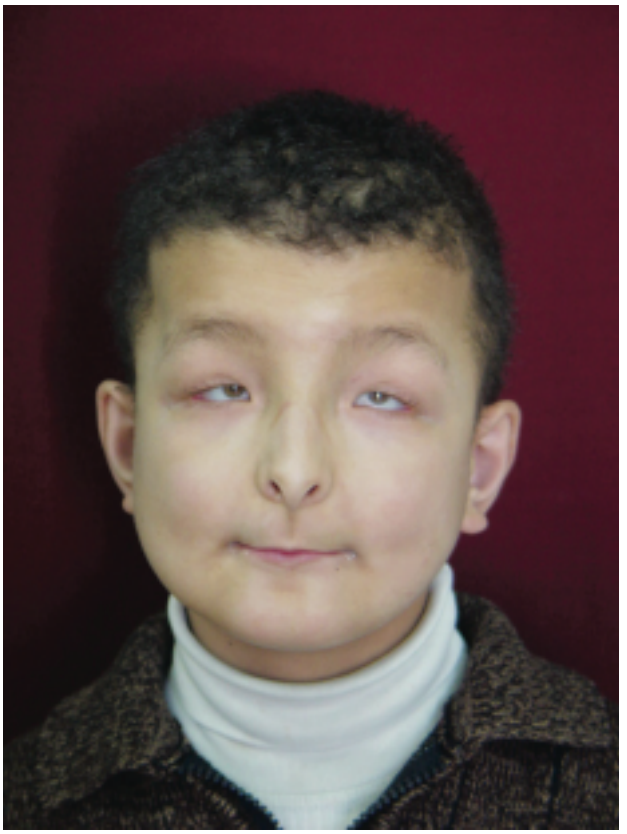

Figure 1. Extraoral frontal photograph showing frontal bossa, long narrow nose with hypoplastic nasal alae, converged strabismus, ptosis of eyes, microphtalmia, curly and spares hair, eyebrows and eyelashes.

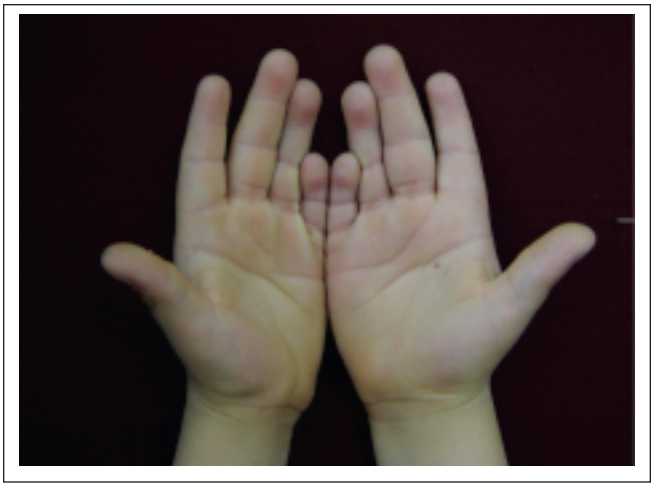

Figure 2. Hands photograph showing missing finger phalanx in the fifth fingers of hands, clinodactyly and hyperkeratotic palm of hands.

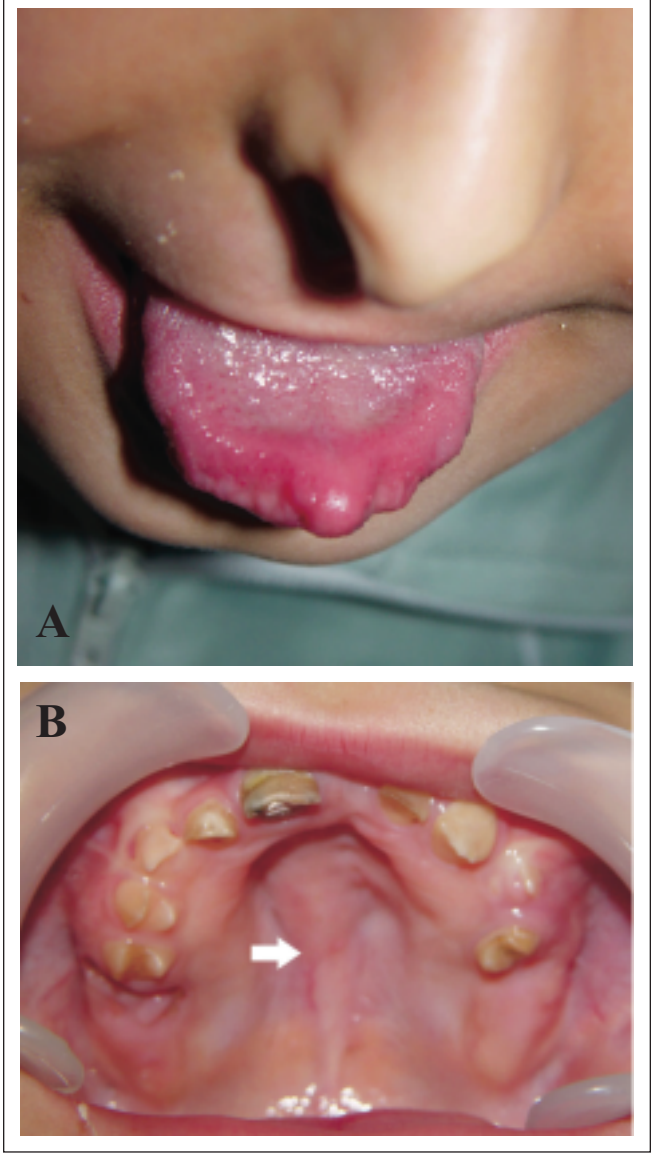

Figure 3. Photographs showing mamelon-shaped tip of the tongue (a) and enlarged alveolar crest as well as abnormal midpalatal raphe (white arrow) (b).

suspected, and therefore, the patient was referred to a pediatric hospital for further evaluations. The patient's ophthalmologic examination revealed microphtalmia, microcornea, congential cataract, chronic uveitis, glaucoma and reduced vision. Conventional radiography of both hands revealed agenesia of second phalanges of fifth fingers of hands and

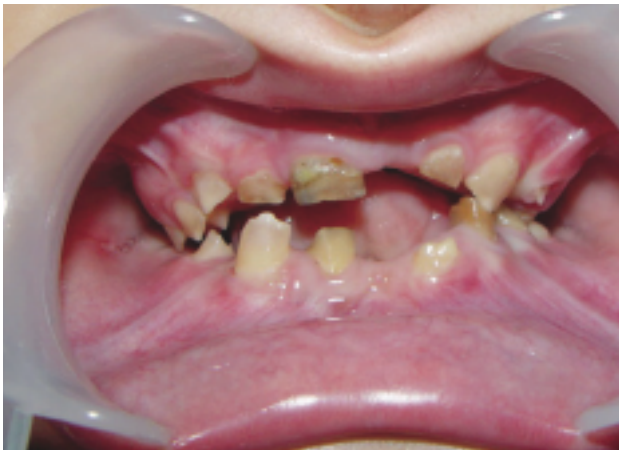

Figure 4. Dental photograph showing displastic teeth with a yellowish appearance.

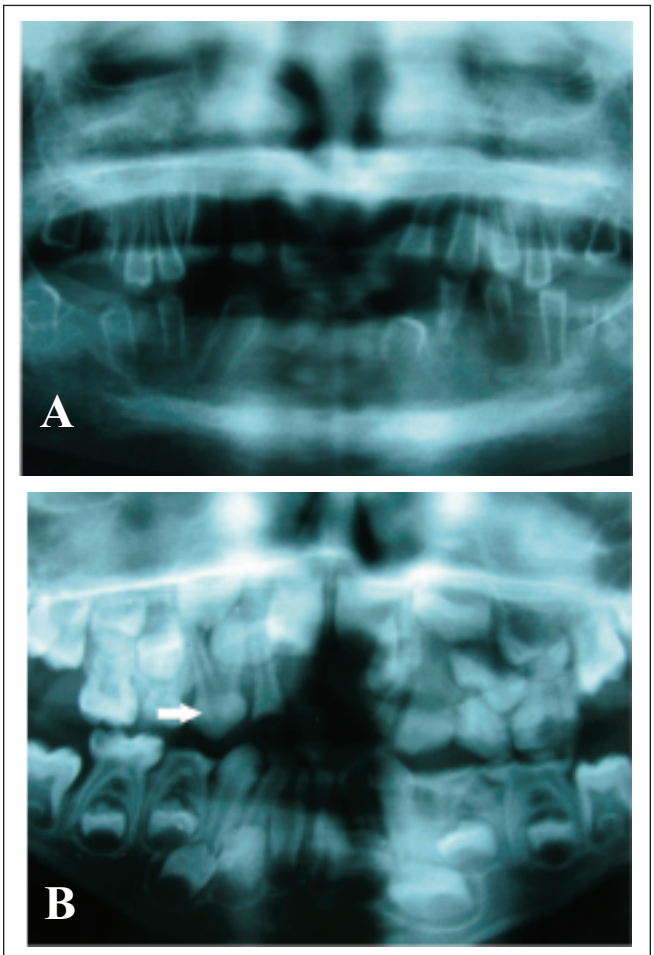

Figure 5. (a) Panoramic radiograph of the patient showing 'ghost' appearance of shortened teeth, generalized enlarged pulp chambers, decreased thickness of dentin, permanent dental buds closer to the alveolar crest, and periapical radiolucency of lower left first premolar; (b) panoramic view of the sibling showing bi-rooted upper right primary canine (white arrow).

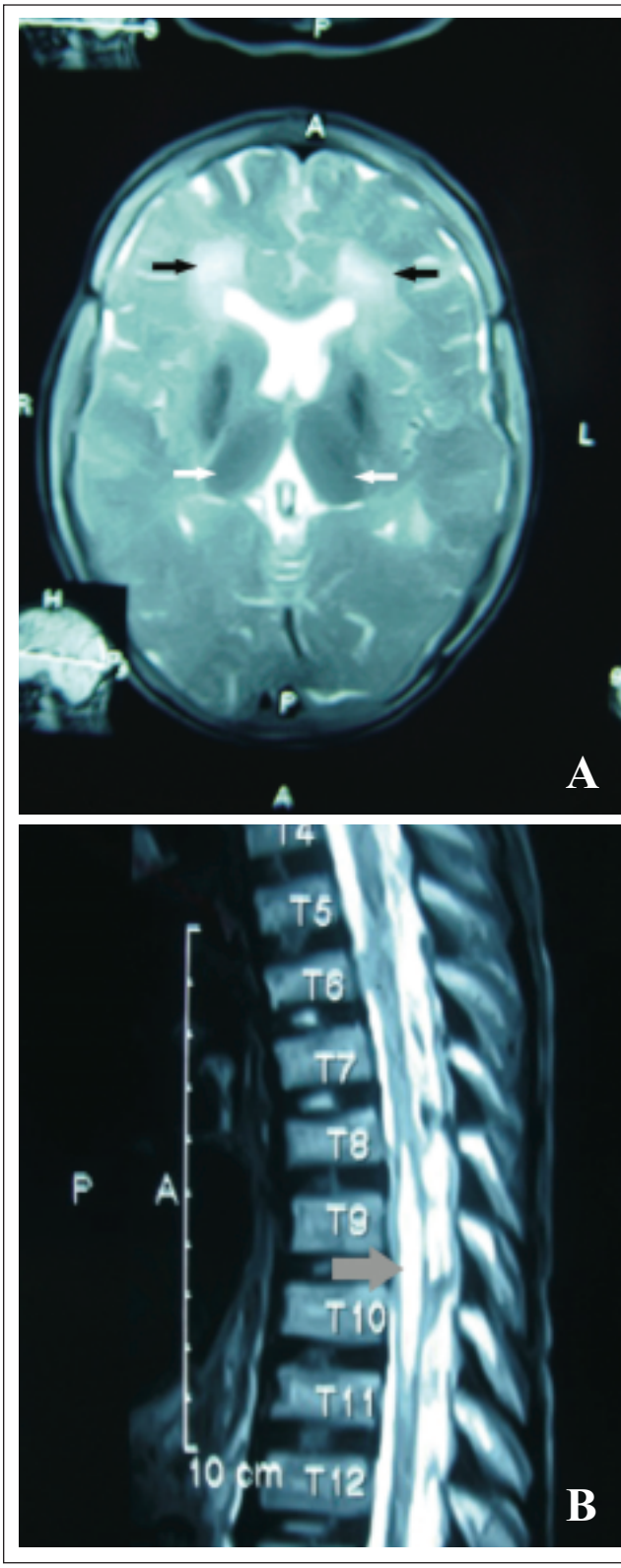

Figure 6. (a) Brain MRI showing abnormal high signal intensity on paraventicular white matter (black arrow). Bilateral symmetrical hyposignal intensities are noted on both putamens (white arrow); (b) Spinal cord MRI showing syringohydromyelia (gray arrow).

osteopenia of the wrists. In the comprehensive neurological assessment, malfunction of reflexes including spastic paraparesis and walking problem were observed. Further evidence provided by MRI of the brain showed abnormal high signal intensity on paraventicular white matter and bilateral symmetrical hyposignal intensities on both putamens (Figure 6a). MRI revealed syringohydromyelia and mild expansion of the thoracic cord at the level of T8 through T11 vertebrae. No abnormalities were noted at the cervical spinal cord (Figure 6b).

Autosomal dominant trait of the syndrome was suggested by the genetic evaluation. To confirm the clinical diagnosis, a genome-wide search for location of the ODDD locus was performed using Short Tandem Repeat Polymorphisms (STRPs). Evidence of linkage between ODDD and markers from chromosome 6q22-q23 was detected.

DISCUSSION

Oculodentodigital dysplasia (ODDD) is a disorder with distinct clinical features affecting both ectodermal and mesodermal cell lineages. The developmental abnormalities in ODDD appear to be caused by impaired Cx43 function which forms intercellular 'communication' channels. These gap junction channels are vital for the control and coordination of many physiologic and developmental processes in human tissues, therefore its impairment may lead to various abnormalities in different tissues such as brain, heart, gonads, lens, cornea, skin and bone.[5]

We present here the dental characteristics and other clinical features of an 8-year-old boy with ODDD. The patient had a more severe phenotype compared to his parents who showed clinodactyly and his younger brother who had mild ocular and dental involvement in addition to clinodactyly. A key finding in ODDD is syndactyly type III affecting fingers V and IV, sometime also the fingers IV and III and the toes.[6] In this case report, however, the parents, the presented case and his male sibling had only clinodactyly. Vitiello et al[7] suggested that mutations in Cx43 can lead to a spectrum of different phenotypes including typical ODDD, isolated type III syndactyly, atypical ODDD without hand and/or foot syndactyly, and Hallermann–Streiff/ODDD phenotype. Clinodactyly seen in this case may be due to the variable expressions of the mutated *Cx43* gene.

The signs and symptoms of ocular involvement in this case are similar to that described in the literature.[1,8-10] Neurological symptoms have also been described as inconsistent but frequent features of ODDD and show a high degree of variability in expression within families. There seems to be a tendency for affected individuals to start to complain of stiffness and difficulty in walking with onset from the first decade to the sixth decade.[6,11,12] The slight difficulties in walking affecting the present case may tend to deteriorate as further neural conditions arise in the coming decades of life. Indication of neurological sings of the syndrome was not present in the younger sibling and they might not manifest until as late as the second decade of life.

The dental abnormalities observed in this case were hypoplastic teeth with average size, enlarged pulp chambers and taurodontism, decreased thickness of dentine, and lack of contrast between the thin enamel and dentine, which are similar to the signs of odontodysplasia.[13] There is only one case study in the literature that describes taurodontism in a patient with ODDD.[1] There were no signs of hypercementosis or pulp denticles as described in a previous report.[9]

In our patient, we also identified early eruption of premolars. The early eruption of premolars in the present case could be a result of bone loss due to primary teeth infections. Moreover, premature eruption of the permanent and probably primary teeth is likely caused by the proximity of tooth buds to the alveolar crest. The latter may be a result of the osteoblast dysfunction, delayed mineralization and decreased bone mass or skeletal abnormalities due to the loss-of-function mutations in *Cx43* gene.[5,14]

In the younger brother, we observed mild generalized hypoplastic enamel as well as bi-rooted upper right primary canine. The latter is a finding which is not mentioned in other reports and can be another manifestation of this syndrome or a separate phenotype, which warrants further investigation.

As illustrated in this report, generalized enamel hypoplasia in both primary and permanent dentition has been reported in patients with ODDD.[1] In our patient, pulpal and periapical infections in both primary and permanent teeth could be explained by the deficiency in the formation of enamel and dentine as well as enlarged pulp chambers of the teeth. Lack of timely treatment can result in loss of permanent teeth in the present case.

Dental treatment of ODDD is a challenging part of overall management of this syndrome as it may be possible to prevent some of the morbidity associated with tooth loss. The patient presented here is undergoing a comprehensive dental treatment provided by professionals from different disciplines of dentistry, and we intend to report the treatment process in a future paper.

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