# Dental and Maxillofacial Signs in Leri-Weill Dyschondrosteosis

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One of the most common causes of short stature is a defect of the short stature homeobox-containing (*SHOX*) gene, which is located in pseudoautosomal region 1 on the distal end of the short arm of chromosomes Xp22.33 and Yp11.32. More than 300 different mutations in the *SHOX* gene responsible for short stature syndrome have been described. The phenotypic expression of *SHOX* haploinsufficiency is remarkably varied. The 3 typical clinical presentations, from least to most severe, are idiopathic short stature without skeletal malformations, Leri-Weill dyschondrosteosis (LWD), and Langer mesomelic dysplasia, which is believed to represent the homozygous form of LWD. Despite a higher prevalence in women, suggesting the potentiating action of high estrogen levels on the effects of *SHOX* deficiency, the syndrome was initially believed to have an autosomal pattern of inheritance. In reality, heterozygous *SHOX* mutations can be transferred from the Y to the X chromosome and vice versa. This phenomenon is called "the jumping *SHOX* gene" and corresponds to a pseudoautosomal dominant inheritance. LWD is characterized by mesomelic short stature and Madelung deformity defined by an upward and medial displacement of the radial joint surface, which restricts range of motion. Less specific dysmorphic signs associated with LWD, such as short hands and feet, scoliosis, or muscular hypertrophy, have been described. When reviewing the dental and maxillofacial signs, only limited and summary data (micrognathia and high arched palate) have been published in the literature. This report presents a case of LWD that highlights many other noteworthy dental and maxillofacial signs that are important to clearly identify and appropriately treat.



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One of the most common causes of short stature is a defect of the short stature homeobox-containing (*SHOX*) gene, which is located in pseudoautosomal region 1 on the distal end of the short arm of chromosomes Xp22.33 and Yp11.32.[1] More than 300 different mutations in the *SHOX* gene responsible for short stature syndrome have been described.[1,2] The phenotypic expression of *SHOX* haploinsufficiency is remarkably varied. The 3 typical clinical presentations, from least to most severe, are idiopathic short stature without skeletal malformations, Leri-Weill dyschondrosteosis (LWD), and Langer mesomelic dysplasia, which is believed to represent the homozygous form of LWD.[3,4] Despite a higher female prevalence, suggesting the potentiating action of high estrogen levels on the

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effects of *SHOX* deficiency,[5,6] the syndrome was initially believed to have an autosomal pattern of inheritance.[7] In reality, heterozygous *SHOX* mutations can be transferred from the Y to the X chromosome and vice versa. This phenomenon is called "the jumping *SHOX* gene" and corresponds to a pseudoautosomal dominant inheritance.[6]

LWD is characterized by mesomelic short stature and Madelung deformity defined by an upward and medial displacement of the radial joint surface, which restricts range of motion.[8] Less specific dysmorphic signs associated with LWD, such as short hands and feet, scoliosis, or muscular hypertrophy, have been described.[9] For dental and maxillofacial signs, only limited and summary data (micrognathia and high arched palate) have been published in the literature.[1,9] This report presents a case of LWD that highlights many other relevant dental and maxillofacial signs that are important to clearly identify and appropriately treat.

## Report of Case

A 24-year-old man with LWD was referred by his orthodontist for assessment of oral and maxillofacial malformations to the Department of Oral and Maxillofacial Surgery (OMS) of the University Hospital of Lille (Lille, France). His history disclosed that he was born at term without complications and subsequently was diagnosed with LWD because of mesomelic short stature and slight forearm deformity without mobility impairment consistent with Madelung deformity. The finding of the *SHOX* gene mutation confirmed the LWD diagnosis. He also had celiac disease and underwent surgery for a pectus excavatum.

He was referred to the authors' clinic primarily for dentofacial anomalies and more particularly for a Class III jaw discrepancy. In addition to short stature (height, 150 cm; weight, 42 kg; body mass index, 18.7 kg/m$^2$), he had morphologic facial and nonfacial anomalies. Observation of his global facial morphology showed hypotelorism and remarkable anomalies of the orbitopalpebral region that included a marked left unilateral moderated ptosis associated with an antimongoloid palpebral fissure. A small pigmented spot was noted at the lower part of the right eye sclera (Figs 1, 2).

The extraoral examination showed hypoplasia of the mid and lower thirds of the face with decreased global facial height associated with maxillary and mandibular retrognathia (Figs 3-6). He had thin lips and prominent low-set ears. Facial asymmetry with a deviation on the right side of the chin was noted.

The intraoral examination showed a dental and skeletal Class III malocclusion in the context of upper and lower jaw retrognathia confirmed radiologically. The shortness of the mandible involved the ramus and corpus and was associated with an open mandibular angle. Dental examination showed yellowish brown

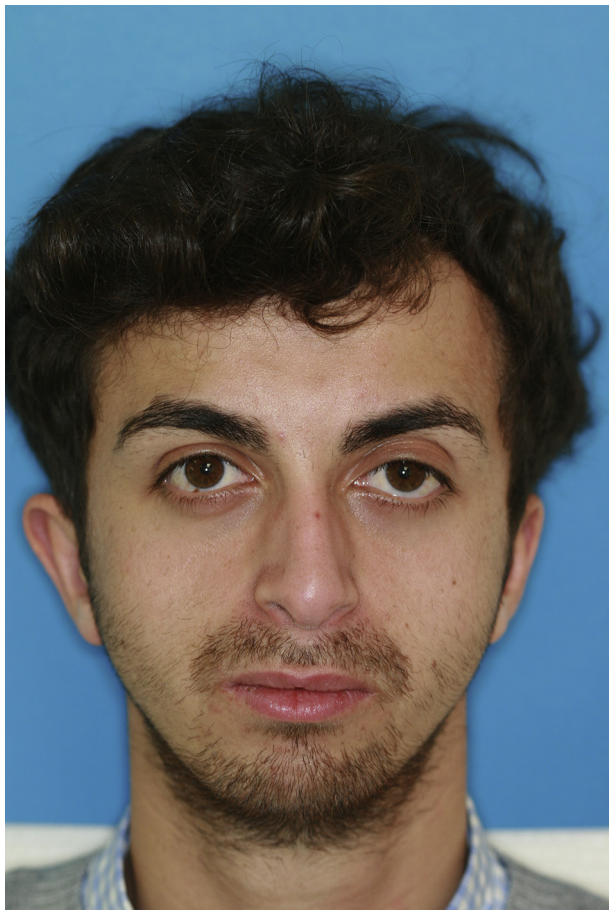

**FIGURE 1.** Facial image showing hypotelorism and left unilateral moderated ptosis associated with an antimongoloid palpebral fissure.

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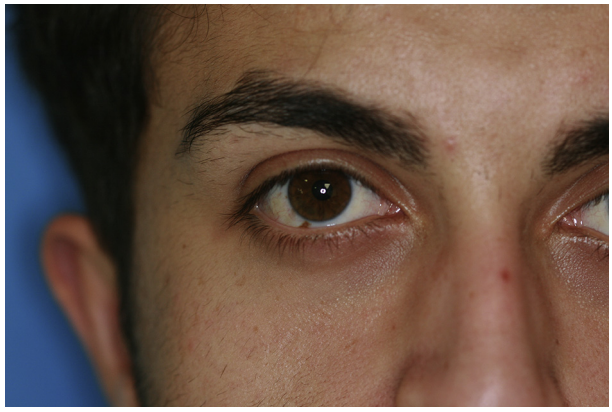

**FIGURE 2.** Image focused on the orbital region displaying a small pigmented spot at the lower part of the right eye sclera.

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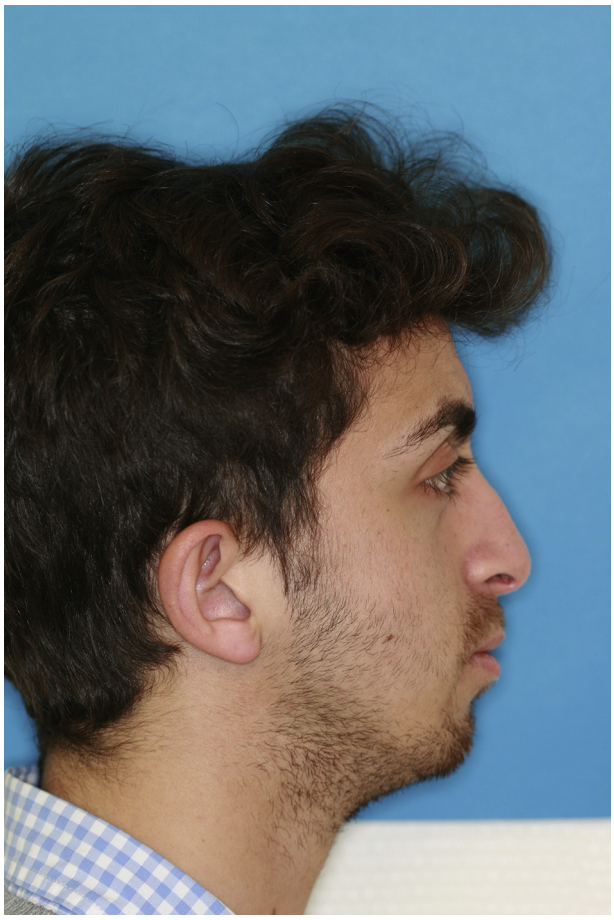

**FIGURE 3.** Right profile displaying a hypoplastic midface and lower third of the face with decreased global facial height. Note the thin lips and prominent low-set ears.

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enamel with dyschromia that was particularly pronounced on the canines and premolars, which were very conical. The cervical enamel and tips of tooth cusps were less affected (Figs 7-9).

The extrafacial examination showed Madelung deformity, short hands, brachydactyly, and partial webbing between some fingers (Figs 10, 11).

## Discussion

*SHOX* haploinsufficiency leads to short stature with a variable phenotype that is frequently nonspecific in young children.[3,9] Indeed, the main malformations associated with LWD concern mesomelic disproportion of the limbs and Madelung deformity, which has a variable time of onset, often appearing in the second decade and worsening with puberty.[1,10,11] The delayed development of clinical signs and the lack of specific and constant features associated with LWD lead to diagnostic difficulties.

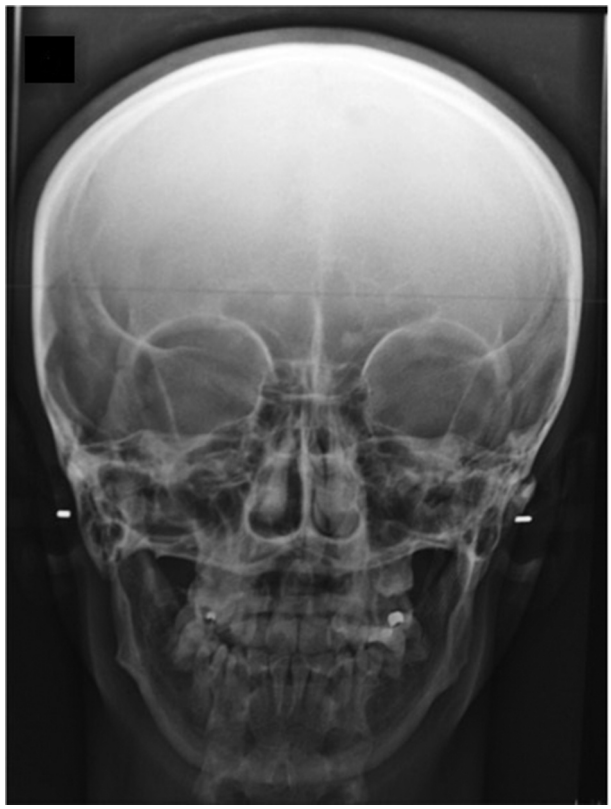

**FIGURE 4.** Frontal radiograph evaluation showing facial asymmetry.

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### PHENOTYPE OF *SHOX* HAPLOINSUFFICIENCY AND LWD

*SHOX* deficiency is associated with different phenotypic expressions of increasing severity: idiopathic short stature without skeletal malformations, LWD, and Langer mesomelic dysplasia. Heterozygous mutations of the *SHOX* gene cause idiopathic short stature without apparent skeletal malformations and LWD that is characterized by wrist deformity and mesomelic short stature.[1,3,7,9] The prevalence of *SHOX* deficiency accounts for approximately 80% of genetic causes of LWD and 2 to 16% of causes of idiopathic short stature. Loss of the 2 *SHOX* alleles causes the complete lack of *SHOX* and an extreme phenotype of osteodysplasia known as Langer mesomelic dysplasia.[1,7]

With the exception of short stature, the delayed expression of clinical signs of these syndromes can considerably delay diagnosis. The characteristic skeletal deformity of LWD *SHOX* deficiency is known as the Madelung deformity, which is sometimes slightly present. This deformity appears relatively late in childhood and is a cluster of anatomic changes in the forearm, including bowing and shortening of the radius, prominence of the ulnar head, and palmar

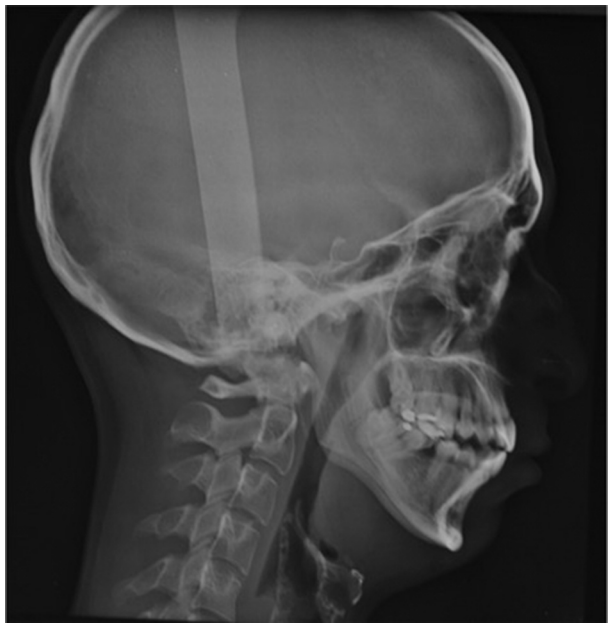

**FIGURE 5.** Lateral radiograph showing maxillary and mandibular retrusion associated with a decreased global facial height.

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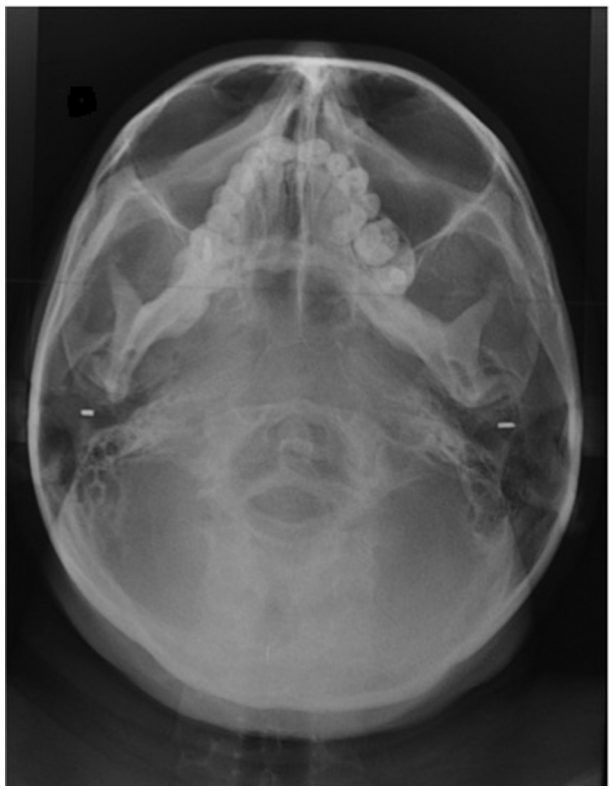

**FIGURE 6.** Inferior radiograph highlighting maxillary and mandibular discrepancy.

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and ulnar deviation ("pyramidal configuration") of the carpal bones.[8,12] The malformation is associated with a Vickers ligament, which can be considered an abnormally short volar radioulnar ligament.[12] Less specific malformation signs have been succinctly described in association with LWD and other *SHOX* haploinsufficiency syndromes. These features, specifically shortening of the fourth and fifth metacarpals, high arched palate, micrognathia, increased carrying angle of the elbow, scoliosis, and muscular hypertrophy, are notably similar to those described in Turner syndrome, which is associated with the loss of 1 *SHOX* gene owing to an aberration of the X chromosome.[1,9]

The present case highlights more dental and maxillofacial signs possibly associated with LWD. Some also seen with increased frequency in Turner syndrome have been described in the literature, such as micrognathia and high arched palate associated with LWD.[9] Despite a Class III dental occlusion, the patient presented mandibular and maxillary retromicrognathia, which is of *SHOX* deficiency. Some other novel signs identified in this case are listed in Table 1.

## ETIOPATHOGENESIS OF DENTAL AND MAXILLOFACIAL SIGNS IN LWD

There were discreet features, including high arched palate, Madelung deformity, micrognathia, and shortening and bowing of the forearm, that were considerably more common in pubertal children with LWD than in those with the diagnosis of idiopathic short stature.[9] These deficiencies in patterns of postnatal bone growth likely reflect the effects of *SHOX* haploinsufficiency on the growth plate, which is associated with marked disorganization of chondrocyte proliferation.[9,13] There is a dose-dependent relation between the number of active copies of the *SHOX* gene and the level of disorganization of the growth plate, resulting in altered bone height development. In other words, *SHOX* haploinsufficiency is associated with short stature, whereas *SHOX* excess, as seen in sex chromosome polyploidy, is associated with tall stature.[13] In addition, the *SHOX* gene is expressed during fetal life in the developing skeleton and is specifically expressed in bone marrow fibroblasts and proliferating hypertrophic chondrocytes.[9,14] The embryonic and developmental roles of the *SHOX* gene were investigated in an interesting *SHOX* loss-of function zebrafish model.[15] The translational blockade of *SHOX* mRNA delays embryonic growth after organogenesis and affects craniofacial bone formation and mineralization. In this model, the predominant domains of *SHOX* expression were the mandibular arch, pectoral fin, anterior notochord, rhombencephalon, and mesencephalon, suggesting that *SHOX* is very much involved in craniofacial bone and neural

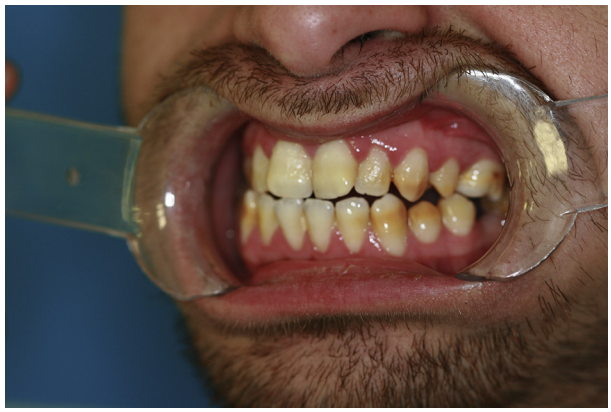

**FIGURE 7.** Intraoral image showing a left dental Class III malocclusion and yellowish brown dental enamel dyschromia that is particularly pronounced on the canines and premolars.

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development. Because many studies have substantiated that the in vivo osteogenic role of the *SHOX* gene is evolutionarily conserved between human and zebrafish, it is easy to juxtapose these observations with the role of human *SHOX* gene expression in the development of the midportion of the buds and in the first and second pharyngeal arches.[14,15] The *SHOX* gene is expressed in embryos and multiple types of organs and tissues in adults, suggesting a consecutive need for this gene from the embryonic to the adult stage. An attractive model to explain this notion is that mesenchymal stem cells (MSCs), or differentiating MSCs distributed to various tissues, express the *SHOX* gene.[16] Many cell lineages derived from MSCs express the *SHOX* gene in human adults, such as chondrocytes, osteocytes, and adipocytes.[17]

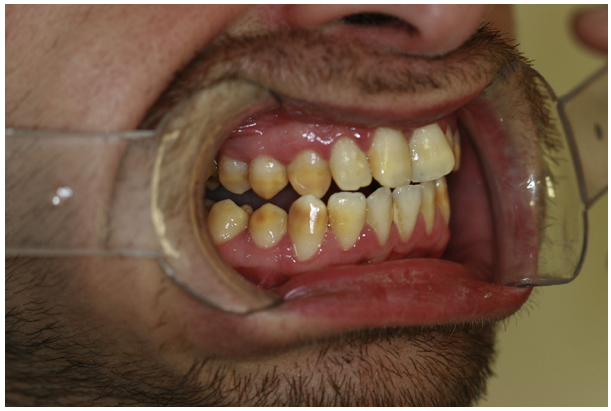

**FIGURE 8.** Intraoral image showing a right dental and skeletal Class III malocclusion and yellowish brown dental enamel dyschromia that is particularly pronounced on the canines and premolars.

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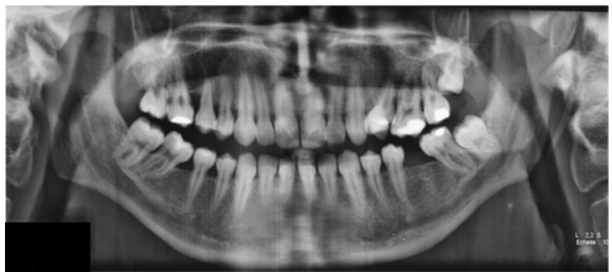

**FIGURE 9.** Panoramic radiograph showing missing teeth because of infections. Note the enamel anomalies.

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The enamel dysplasia in the present case is the first described observation of this kind associated with LWD. The enamel dyschromia was particularly visible on the canines and premolars of this patient. This alteration of enamel calls into question a potential interactive role of the *SHOX* gene in amelogenesis and dentinogenesis, because MSCs, widely distributed to various tissues, express *SHOX*.[16] A dentin sialo-

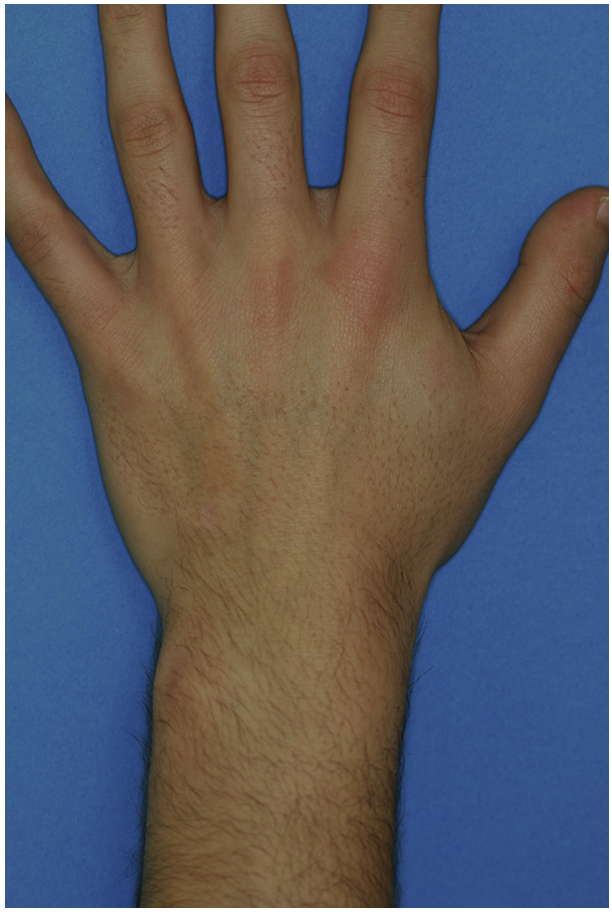

**FIGURE 10.** Left wrist and hand showing shortness of the hands, brachydactyly, and partial webbing between some fingers.

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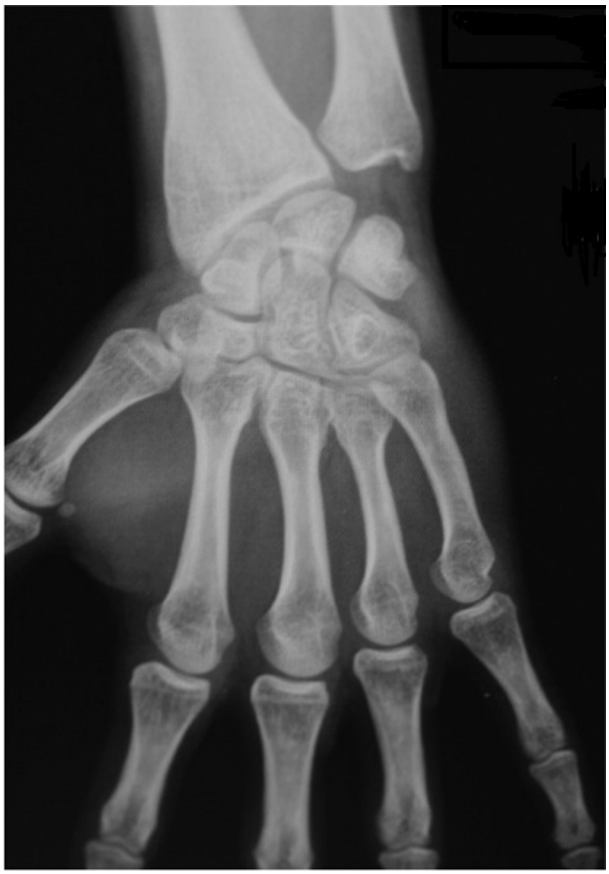

**FIGURE 11.** Left wrist radiograph showing Madelung deformity and brachydactyly.

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phosphoprotein (*DSPP*) knockdown model in human dental pulp stem cells showed markedly disturbed mineral formation and involvement in dentinogenesis imperfecta.[18] Mutations in several genes have been identified to cause amelogenesis imperfecta, including *AMELX*, *MMP20*, *ENAM*, *FAM83H*, *WDR72*, *KLK4*, *COL17A*, and *C4orf26*, genes that contribute to different clinical phenotypes.[19] No studies have established the precise mechanisms linking *SHOX* to amelogenesis or dentinogenesis and surely deserve further investigation.

**Table 1. DENTAL AND MAXILLOFACIAL SIGNS ASSOCIATED WITH LERI-WEILL DYSCHONDROSTEOSIS**

| | Dental and Maxillofacial Signs |
|---|---|
| Rappold et al[9] | Micrognathia |
| Binder[1] | High arched palate |
| Present case | Facial anomalies: moderate ptosis, antimongoloid palpebral fissure orientation, low-set ears |
| | Dental and skeletal anomalies: hypotelorism, decreased facial height, jaw discrepancy, bimaxillary retrognathia, enamel dysplasia |

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### TREATMENT OF PATIENTS WITH SHOX HAPLOINSUFFICIENCY AND LWD

Short stature, when diagnosed young, requires growth hormone therapy, which has been approved for growth promotion in individuals with *SHOX* mutations by the US Food and Drug Administration and the European Medicines Agency.[1,20] Surgical interventions, such as removal of the Vickers ligament in combination with dome osteotomy, have been described to treat the Madelung deformity. These surgeries concern particularly severe cases with painful wrist impairment.[4,6,8] These treatments do not interfere with maxillofacial management. LWD has no particularity in terms of anesthesiology.[1]

Given the effect of LWD on facial growth and dental and maxillary development, there is reason to believe that these patients need to be systematically referred to an OMS department. Interest in early recognition of the syndrome concerns occlusal anomalies, which are well described in patients with *SHOX* haploinsufficiency and require specific attention and surgical treatment. There are clinical benefits from early diagnosis for surgical and orthodontic treatments, facial growth, dental eruption and follow-up, feeding, or speech functions.

*SHOX* haploinsufficiency is responsible for various phenotypic syndromes. LWD is one of them and is classically described by the association of short stature, mesomelic disproportion of the limbs, and Madelung deformity. Other clinical signs involving craniomaxillofacial and dental abnormalities are less well documented and, if recognized early, could expedite a diagnosis. These are micro-retrognathia, decreased facial height and possible hypotelorism, high arched palate, and enamel and dental dysplasia that can be firmly explained by the embryologic and postnatal effects of *SHOX* expression.

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