Molar incisor malformation in six cases: description and diagnostic protocol

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Objective. The term molar-incisor malformation (MIM) has recently been presented in the scientific literature, where it is described as a condition with localized impaired root development. Here we present 6 recently discovered cases referred to our departments.

Study Design. The patients were enrolled in the study after referral and were examined clinically and radiologically. Two extracted teeth were further examined with micro–computed tomography or microscopy.

Results. Affected teeth were first permanent molars with hypoplastic roots, narrow pulp chambers, and a hypercalcified dentine layer cervical to the pulp chamber. Two of the cases also had cervical constrictions on the upper incisors. The patients were 8 to 12 years of age and healthy, but had experienced serious medical conditions of the head and neck region in their first year of life. Some of the cases had been referred because of acute infection and pain.

Conclusion. In 5 out of 6 patients, severe health problems in the head and neck region early in life may have been associated with root malformation in molars and incisors. Patients with MIM need to be followed closely, and extractions should be planned at the right time to avoid unnecessary infection and pain in addition to orthodontic problems. (Oral Surg Oral Med Oral Pathol Oral Radiol 2017;124:52-61)

The formation of permanent first molars and incisors starts around the time of birth, and serious medical insults to the child during the first 2 to 3 years of life may affect tooth development. Molar-incisor hypomineralization (MIH) is a well-known but poorly understood condition affecting the mineralization of permanent first molars and incisors in 2.4% to 40% of individuals, according to worldwide prevalence studies.[1] Recently, a new condition has been described that affects the roots of the same teeth. So far, only 6 publications, all published within the last 2 years, have described the condition.[2-7] In these publications, the terms root malformation, molar-incisor malformation (MIM), and molar root-incisor malformation have all been used to describe the phenomenon.

From these publications, the condition is characterized by disturbances in root development of all first permanent molars. The roots are very slender and malformed and are sometimes absent. In some patients, there are constrictions located in the cervical part of the crown of the permanent incisors. There are also cases in which the roots of the second primary molars are affected.

Tooth development is tightly genetically controlled, starting from thickening of the epithelium to form the dental lamina.[8] The cells proliferate to form the dental placode, which continues through the bud, cap, and bell stages, induced by signaling interactions between the epithelium and the mesenchyme. In the bell stage, cells differentiate into ameloblasts and odontoblasts, followed by matrix secretion and mineralization of the crown.[9] Root development, which is also tightly genetically controlled, extends from Hertwigs's epithelial root sheath (HERS). The HERS is formed from the cervical loop, which consists of the inner and outer enamel epithelium at the neck ring of the dental papilla.[10] The exact decisive component that triggers the HERS to initiate root formation is not well known, but Sakano et al. recently reported that the outer enamel epithelium cells had higher proliferative and migratory activity than the inner enamel epithelial cells before forming the HERS.[11] The HERS cells are then thought to initiate odontoblast differentiation from mesenchymal cells and to determine root size

Statement of Clinical Relevance

Molar incisor malformation is a newly recognized condition. The dental team should be aware of this condition in order to make the correct diagnosis and develop a control and treatment plan to avoid infection, pain, and early tooth loss in affected children.

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and shape.[12,13] Other authors have reported a novel cell population, the apical odontoblast, as being responsible for the initiation of root formation.[14] These cells lie apical to the HERS after crown formation and are dependent on the activation of β-catenin.[14,15] It is clear that disturbances in this finely tuned process might affect root development.

In this paper, we aim to describe 6 cases of root malformations that were recently referred to the Department of Paediatric Dentistry at the University of Oslo and to the Oral Health Centre of Expertise in Mid-Norway. The condition was unfamiliar, and differential diagnoses included a progressive resorptive process and a developmental defect. After observing the cases over time and performing histologic and micro−computed tomography (CT) examinations, we now know that all these cases demonstrate developmental disturbances of root development. There are no signs that indicate a resorptive lesion in any of the cases. We also hope to give a schematic guide to identify the condition in children with known serious medical conditions during the first years of life and a guide for describing and reporting the condition when discovered.

METHODS

Patients

These patients were all referred to our department or to the Oral Health Centre of Expertise in Mid-Norway from the public dental health service or from private general dentists. The patients' teeth and oral cavities were examined clinically and radiographically. Clinical images were taken at the first visit with a Canon EOS60 D camera with Canon MR-14 EX ring flash and a 100-mm Canon EF macro lens (Tokyo, Japan). Characterizations of the patients are summarized in Table I. Written informed consent was given by the patients' parents. Teeth are designated with the Universal Numbering System (the US tooth numbering system).

Histology

The extracted of the lower right first permanent molar from patient 1 was embedded in resin (Technovit 7100) without decalcification after rehydration and then sectioned in the buccolingual direction. Images were obtained with a Canon EOS60 D camera with Canon MR-14 EX ring flash and a 100-mm Canon EF macro lens, and a Zeiss SteREO Discovery.V8 stereomicroscope with an Axiocam 105 color camera (Carl Zeiss Meditec AG, Jena, Germany). Then 10-μm sections were made and mounted on glass slides. For visualization, hematoxylin was applied to the undecalcified surface for 3 minutes, slides were washed in distilled water and air dried, and eosin was applied for 3 minutes before washing and drying. The sections were evaluated under a Leica DMRBE microscope (Leica Mikrosysteme Vertrieb GmbH, Mikroskopie und Histologie, Wetzlar, Germany) and images were taken with an Olympus DP50 camera (Olympus Corporation, Tokyo, Japan) fitted to the microscope.

Micro-CT

The left mandibular first molar from patient 1 was scanned in a SkyScan 1172 (SkyScan, Aartselaar, Belgium) micro-CT with an image pixel size of 11.95 μm and an image resolution of 2000 × 1048 pixels. The 360° scans were obtained at 100 kV, 100 μA at 0.4° rotation steps with an additional aluminum (1 mm) and copper (0.05 mm) filter in the beam path.

The scans were reconstructed using the standard SkyScan reconstruction software (NRecon, v1.6.10.1). The following parameters were applied: smoothing of 2 pixels, beam-hardening correction of 25%, ring artifact reduction of 12, and an output attenuation coefficient range of 0.00 to 0.1.

RESULTS

Cases

A summary of the patient cases is given in Table I.

Patient 1

This 8-year-old female patient was referred to the university clinic because of painful lower first permanent molars on both sides with abnormal roots. The pain had been intermittent for 2 to 3 months, gradually worsening and occasionally preventing her from sleeping. The clinical and radiographic examination revealed narrow and underdeveloped roots, obstructed pulp cavities, and bone destruction down to the furcation areas (Figure 1). The right mandibular first molar demonstrated an apical radiolucency and a radiolucent area along the mesial surface of the mesial root all the way from the cervical to the apical margins (Figure 1). No marginal pockets deeper than 3 mm were probed at the time of examination, but the referring dentist had discovered marginal pockets deeper than 3 mm on both teeth earlier. The upper first permanent molars also showed underdeveloped roots. No bone loss was detected on the radiographs of the upper jaw. The 2 lower first primary molars showed taurodontism. The patient was healthy but had a medical record of brain blood clot at birth, which was treated with an anticlotting agent and antibiotics for 4 weeks under hospitalization. She had experienced occasional epileptic seizures up to the age of 7 years. These were treated with midazolam. The most painful tooth, the lower left mandibular

Table I. Summary of patients included in the study

Patient no.	*Medical history*	*Clinical characterization*	*Affected teeth*	*Age (y)*	*Sex*
1.	Born with brain blood clot; antibiotic and anticlotting agents for 4 weeks. Epileptic seizures until the age of 7 y, treated with midazolam.	Short hypoplastic and twisted roots of lower permanent first molars. In addition, malformation of buccocervical part of crown of 19. Pain and swelling. Underdeveloped roots of upper molars, no infection. Taurodontic L and S.	3, 14, 19, 30	8	F
2.	Abdominal tumor detected by fetal ultrasound examination, surgically removed at 3 mo of age.	Swelling and pus from 30 with corresponding large radiolucency. Missing roots in 19 and 30, malformed roots 3, 14. Cervical constrictions in upper central incisors. White demarcated opacity on upper first molar.	3, 14, 19, 30, 8, 9	11	F
3.	Hospitalized several times up to 1.5 y of age due to brain abscesses and high fever. Hydrocephalus, 3 ventricle shunts.	Tiny wedge-shaped roots on first permanent molars, no roots on 3 second primary molars, 1 is missing. Enamel hypomineralization on molars and incisors.	3, 14, 19, 30, A, K, T	9	M
4.	Acute caesarean section, zygomatic cavernous hemangioma.	Deformed and narrow roots on first permanent molars. Cervical constrictions on upper incisors.	3, 14, 19, 30, 8, 9	9	F
5.	Difficult delivery: tight nuchal cord, birth asphyxia, intracranial hemorrhage. Cerebral palsy.	Fever, pain, swelling from 30. Root malformations and cervical constrictions in first permanent molars.	3, 14, 19, 30	12	M
6.	Seizures and ischemic stroke (left side of brain) 5 days after birth.	Pain and abscess in 19. Missing distal and narrow mesial roots in 19 and 30, narrow roots in 3 and 14.	3, 14, 19, 30	11	F

Dental notations in ISO system according to the Universal Numbering System (US tooth numbering system).

molar, was extracted the same day, and the following week. These teeth were examined further (Figures 2 and 3). This gave pain relief, and complete healing occurred.

Patient 2

This 11-year-old female patient was referred due to swelling and suppuration from the lower right first permanent molar. Radiographs revealed missing roots in the bilateral lower first permanent molars, accompanied by a 12 × 13 mm radiolucency occupying the whole area where the root of 30 would have been expected (Figure 4). The roots of the bilateral upper first permanent molars were malformed and short, and pulp chamber obliteration was seen. The upper central incisors showed constrictions in the cervical third of the crown, but the roots were normal. A white demarcated enamel opacity could be seen on the upper left first molar. Radiographic and clinical images are shown in Figure 4. An abdominal tumor had been detected by fetal ultrasound examination and was surgically removed at 3 months of age.

Patient 3

This 9-year-old male patient was referred for evaluation because of incomplete root development in the second primary and first permanent molars, in addition to

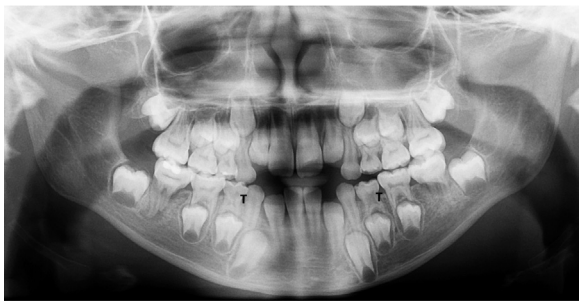

Fig. 1. Panoramic radiograph of patient 1 obtained at the first visit. All 4 first permanent molars demonstrate malformed roots. Lower left first permanent molar has a radiolucent area in the cervical/mesial part, and lower right first permanent molar has a radiolucent area along the entire mesial root and periapical to the distal root. Both lower first permanent molars have narrow pulp chambers. First primary lower molars on both sides are taurodonts and are marked with a T.

hypersensitivity to cold, probably because of MIH on all first permanent molars. The clinical and radiographic examination revealed very tiny wedge-shaped roots on all 4 first permanent molars and roots that were <1 mm long on the second primary molars (Figure 5A). The upper left primary molar was already missing, and mesial drift of the upper left first permanent molar had occurred. In addition, he had MIH affecting the maxillary central incisors and first permanent molars

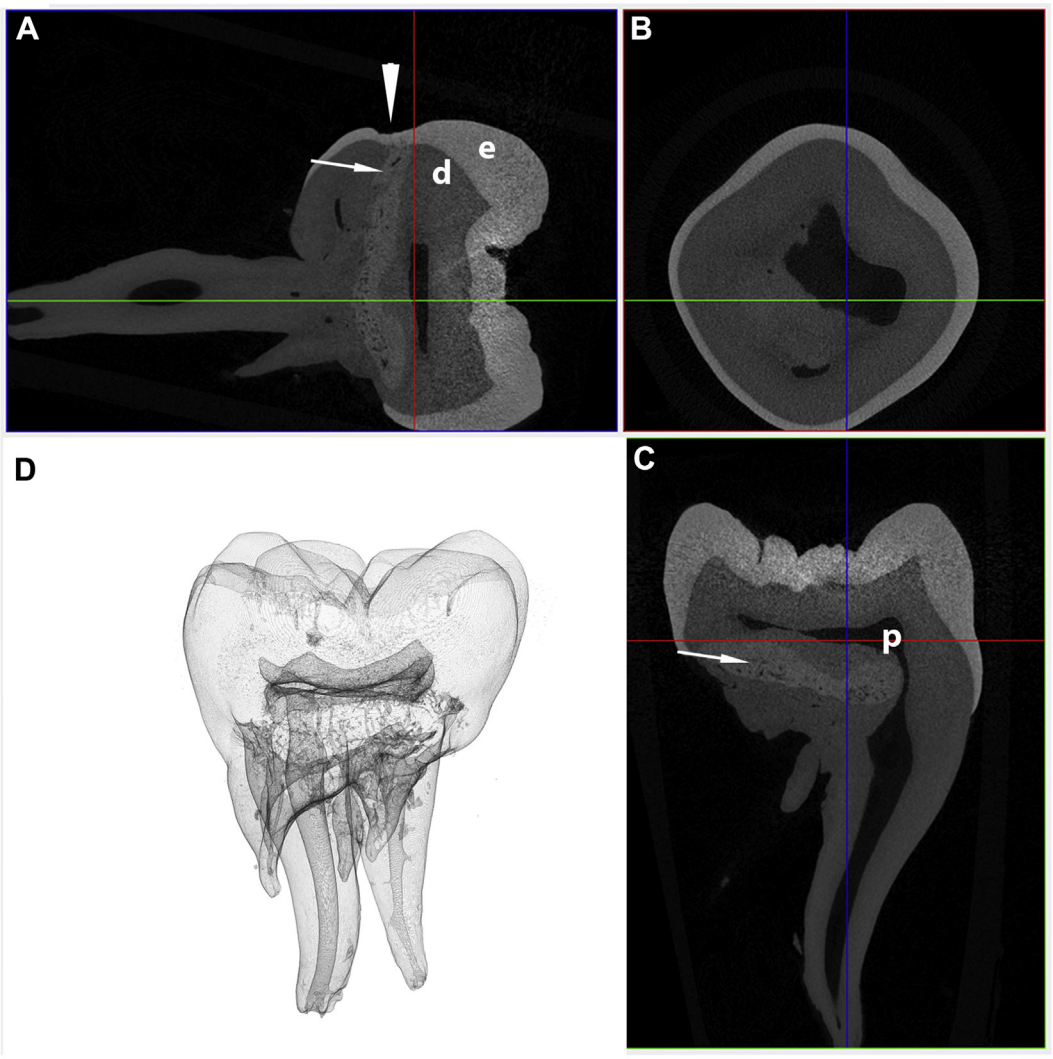

Fig. 2. Micro−computed tomography scan of the lower left first permanent molar from patient 1. The scan shows (**A**, **C**) 2 vertical and (**B**) 1 horizontal section in addition to (**D**) a 3-dimensional reconstruction. The colored lines indicate the direction of the sections. **A**, Vertical section. Cervical constriction (*arrowhead*). Cervical to the pulp chamber is a normal dentin layer (*white d*) and a more densely calcified area (*arrow*). e, enamel. **B**, Horizontal section through the tooth at the level of the red line in (**A**) and (**C**) by the floor of the pulp chamber. **C**, The pulp chamber (p) is partially obstructed, connected to one of the root canals only. The more densely calcified area is seen cervical to the pulp floor (*arrow*). **D**, A 3-dimensional reconstruction of the scans from the whole tooth. Numerous oddly formed roots and root canals are seen.

(Figure 6A-C). The patient was born full term, but 10 days after birth he experienced multiple brain abscesses. He was then hospitalized and underwent surgery and antibiotic therapy several times. He also experienced episodes of high fever and was hospitalized several times until he was 18 months old. His mother had used a selective serotonin reuptake inhibitor during pregnancy.

Patient 4

This 9-year-old female patient was referred because of atypical roots on her molars and maxillary incisors. She had no symptoms from the teeth and was otherwise healthy. Radiographs showed narrow, short roots with partly obliterated pulp chambers and hypercalcified and malformed cervical areas on all first permanent molars (Figures 5B and 6D-F). The upper central incisors had constrictions in the cervical area, but the roots appeared normal. The patient was born full term by acute caesarean section due to placental abruption. She had a cavernous hemangioma in her left cheek and was hospitalized the first 11 days after birth.

Patient 5

This 12-year-old male patient was referred after repeated episodes of fever, pain, and swelling from the

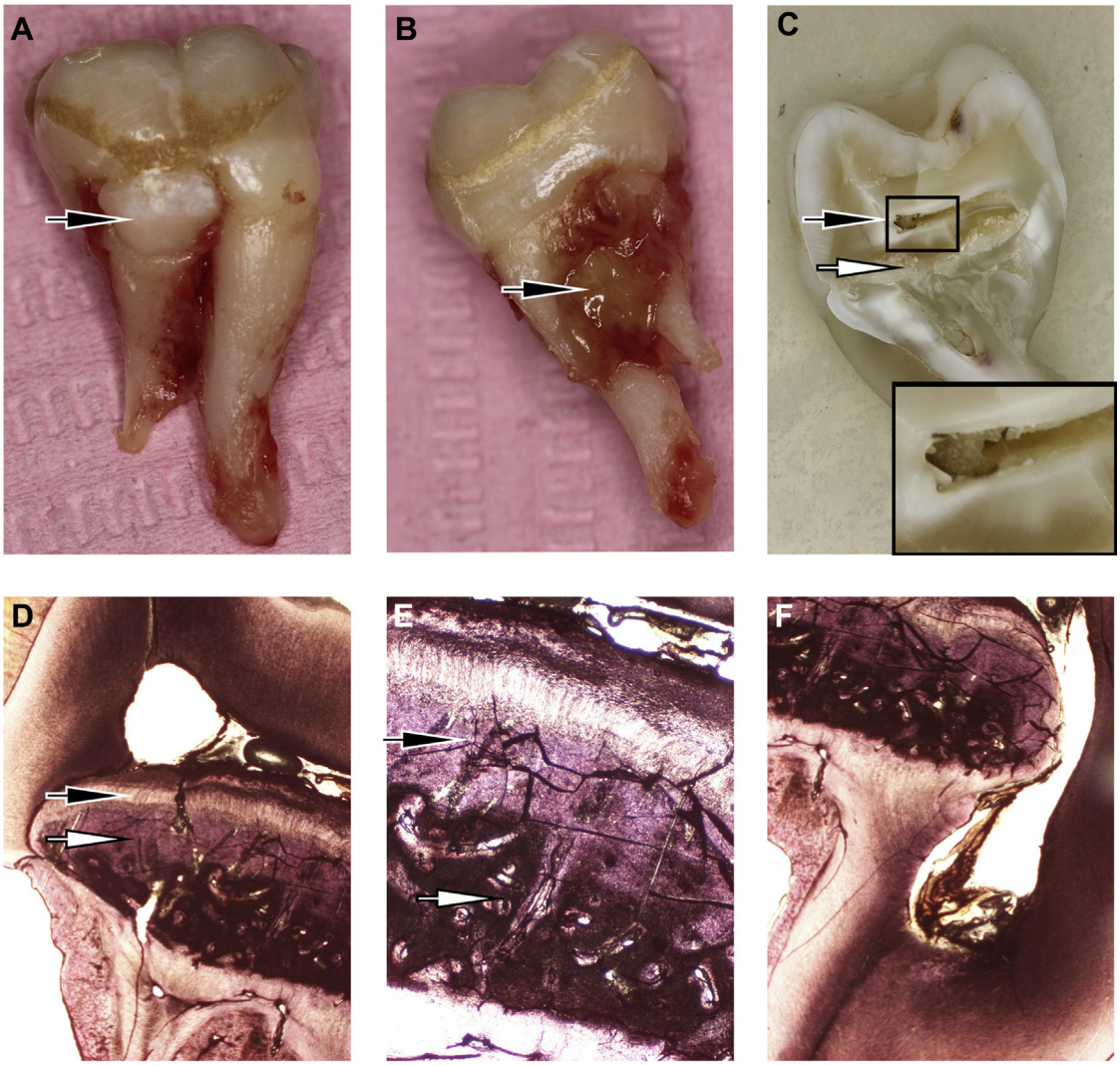

Fig. 3. Photographs of a complete and sectioned first permanent molar from patient 1. **A**, Buccal view of lower left first permanent molar (the same tooth as seen in Figure 2) immediately after extraction. At the cervical quarter of the buccal surface there is a prominence of enamel. The *arrow* points to this buccocervical prominence. **B**, Mesial view of lower left first permanent molar. Hyperplastic tissue nodule is seen between the short mesial roots (*arrow*). **C**, Buccolingual section of lower right first permanent molar embedded in resin. A narrow pulp chamber (*black arrow*) and an irregular dentin layer (*white arrow*) are seen. The insert is a larger magnification of the area in the *black box*. **D**, Hematoxylin and eosin−stained section showing a narrow pulp chamber, a layer of normal dentin (*black arrow*), and irregular dentin (*white arrow*). **E**, Larger magnification of the irregular dentin. One layer of irregular (*black arrow*) and one of globular appearance (*white arrow*) can be seen. **F**, Section from the opposite side of the pulp chamber in (**D**), showing a narrow pulp chamber, a layer of normal dentin, and irregular dentin. The hematoxylin and eosin−stained sections were examined under a Nikon microscope fitted with (**D**, **F**) 10 × and (**E**) 40 × magnification lenses.

lower right first permanent molar. Radiographs showed a cervical constriction and obliterated pulp chamber, but long, straight roots on both lower first permanent molars. There were apical radiolucencies on the mesial roots of both teeth. Clinical examination revealed an abscess with a draining sinus mesial to the roots of the lower right first permanent molar. The upper first molars showed the same cervical malformation, but their roots were shorter and narrower. His incisors were normal (Figures 5C and 6G-I). Due to complicated labor, the patient was born by vacuum-assisted delivery. He also had a tight nuchal cord, which caused asphyxia. Intracranial hemorrhage was present, and he had cerebral palsy. He presently uses methylphenidate.

Patient 6

This 11-year-old female patient was also referred due to pain and swelling in the lower left first permanent molar. Radiographs revealed obliterated pulp chambers, missing distal roots, and thin mesial roots in the

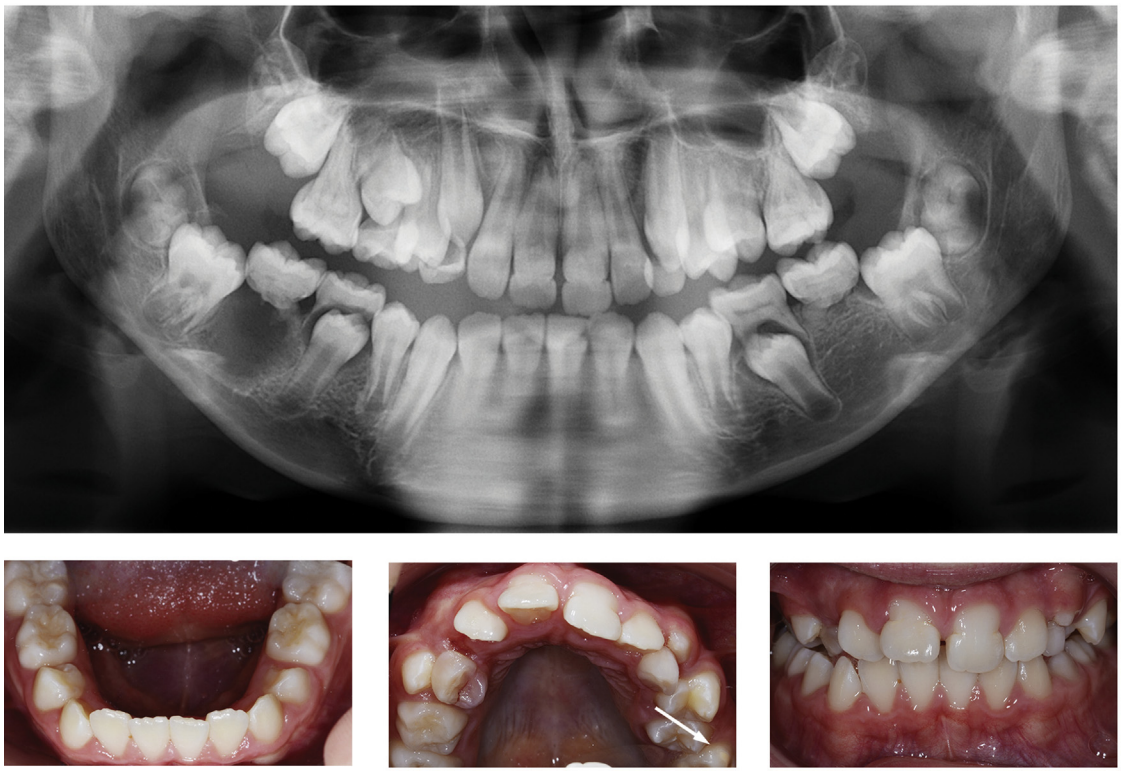

Fig. 4. Panoramic radiograph and clinical photographs of patient 2. The radiograph shows narrow, wedge-shaped roots on the upper permanent first molars and missing roots on the lower first permanent molars. Cervical crown constrictions can be seen on the upper permanent incisors. Clinical images show normal appearance of teeth in the lower jaw (*left*), a white demarcated enamel opacity on upper left molar (*arrow*, middle image), and cervical crown constrictions on upper incisors (*right*).

bilateral lower first permanent molars. The maxillary first molars had partly obliterated pulp chambers and somewhat narrow roots. The incisors were normal (Figures 5D and 6J-L). Five days after birth, she experienced seizures and an ischemic stroke on the left side of the brain.

Micro-CT evaluation of extracted molar

Two painful molars were extracted from patient 1. A panoramic radiograph obtained at the first visit is shown in Figure 1. The micro-CT scan of the lower left first permanent molar revealed a partly obliterated pulp chamber connected to 1 root canal only (Figure 2). The coronal dentin and enamel were of normal appearance. Cervical to the pulp chamber, a layer of dentin with normal density was seen, and then a denser layer appeared. The hypercalcified (denser) layer corresponded to a cervical enamel constriction. The 3-dimensional reconstruction showed numerous root canals not connected to the pulp chamber.

Morphologic appearance of extracted molars

Clinical images of the lower left first permanent molar from patient 1 were obtained directly after extraction (Figure 3A, B). This was the same tooth that was evaluated with micro-CT (Figure 2). The images showed a long distal root and short, bent irregular mesial roots (Figure 3A, B). A cervical constriction and a more prominent area apical to the constriction were seen on the buccal side (Figure 3A, arrow). Between the short mesial roots, a hyperplastic soft tissue nodule was seen (Figure 3B, arrow). The extracted lower left first permanent molar from the same patient was embedded in resin and cut in the buccolingual direction (Figure 3C-F). This section showed a narrow pulp chamber with small calcified rods extending from the walls (Figure 3C, black arrow and inserted enlargement). As seen in the hematoxylin and eosin (H&E)-stained sections, the floor of the pulp chamber consisted of a layer of normal-looking dentin (Figure 3D, black arrow). Cervical to the normal dentin layer, an irregular dentin layer appeared (Figure 3D, white arrow), similar to what was seen on the micro-CT scan. The H&E-stained sections showed that this dentin layer consisted of 2 layers, 1 irregular (Figure 3E, black arrow) and 1 of globular appearance (Figure 3E, white arrow). The same layers can be seen in a different view of the same tooth (Figure 3F). The hypercalcified dentin layer seemed to obturate the

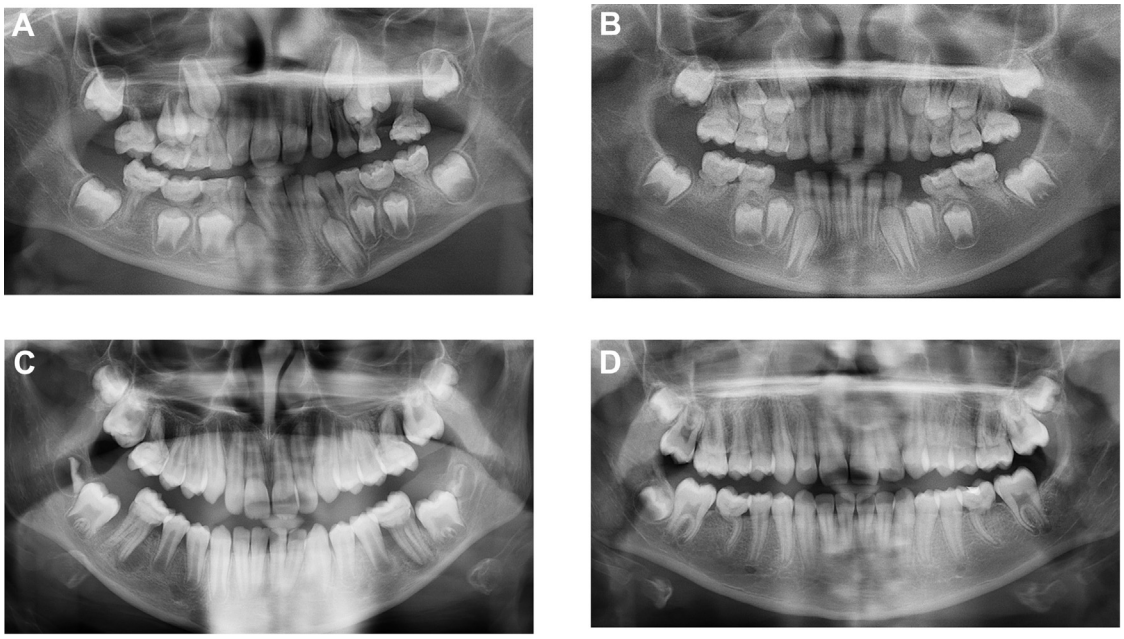

Fig. 5. Panoramic radiographs of patients 3, 4, 5, and 6. **A**, Patient 3. Small wedge-shaped roots on all 4 first permanent molars. Lower second primary molars have roots <1 mm long. Upper left second primary molar is missing. **B**, Patient 4. Small, malformed roots on all 4 first permanent molars. Cervical constrictions can be seen on upper permanent incisors. **C**, Patient 5. Small, wedge-shaped roots on upper first permanent molars. Malformed cervical area and long roots with apical radiolucency can be seen on both lower first permanent molars. **D**, Patient 6. Upper first permanent molars have narrow pulp chambers but normal root morphology. Lower first permanent molars show cervical malformation and missing distal roots.

connection between the pulp chamber and the root canals (Figure 3C, white arrow).

DISCUSSION

The prevalence of this newly described condition is so far unknown as the only descriptions are the case reports discussed here.[2-7] However, it is likely that this is not a new condition, and the fact that we are now aware of it helps us to detect the condition and treat affected individuals appropriately. Many of these teeth likely would have been extracted once they became symptomatic or demonstrated periodontal or apical infection, possibly in combination with acute pulpitis. The patient could have been misdiagnosed with a resorptive process. On the other hand, some of the systemic conditions these children experienced during their first years of life might have been so treatment-intensive that they would not have survived a couple of decades earlier. If so, one could speculate that the incidence of this condition could increase with improved perinatal health care.

There seems to be an association between the environmental stressors these children experienced early in life and their root molar malformations and incisor constrictions. This was also suggested by Wright et al.[6] and Luder.[16] However, the etiology of the condition remains unclear.

Initial mineralization of first permanent molars starts around birth. The crown is fully mineralized at the age of 3 years; then the furcation forms, followed by root development.[9] The timing of disease onset (the first year of life) and root development of the first permanent molars (around the age of 3 years) do not coincide, and this remains a puzzle. One explanation might be that the HERS is already formed long before root development starts; it awaits signals from the mesenchymal cells to differentiate and later disintegrate during root formation. Early disturbances in the epithelial-mesenchymal cross talk might affect the ability of these cells to differentiate properly into odontoblasts.

Both environmental and genetic conditions could impair root development. A study in mice showed that radiation of 10 and 20 Gy before the onset of root development disrupted the HERS and resulted in root malformation.[17] A genetic study using nuclear factor I-C (Nfic) knockout mice demonstrated disturbances in root patterning, leading to taurodontism in these mice.[18] The study also demonstrated that mesenchymal proliferation was impaired, causing short roots in the mutant mice. Wright et al.[6] suggested that neurologic conditions could be an etiological factor because many of the children in their study had conditions related to neurologic damage. This does not seem to be the case

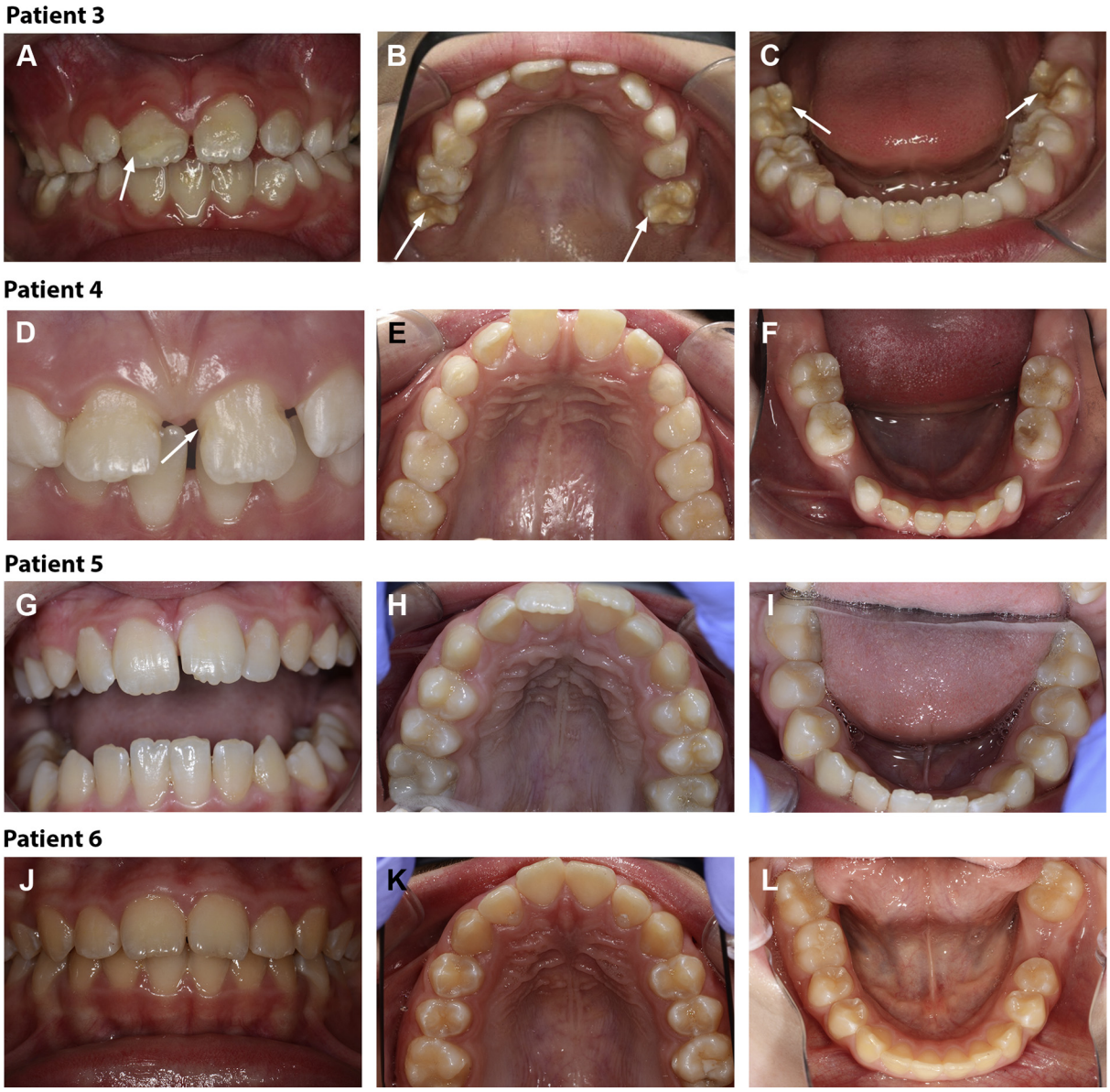

Fig. 6. Clinical images of patients 3, 4, 5, and 6. **A**, **D**, **G**, **J**, Frontal view of the teeth. **B**, **E**, **H**, **K**, Occlusal view of the upper jaw. **C**, **F**, **I**, **L**, Occlusal view of the lower jaw. **A**, *Arrow* shows white enamel opacity on patient 3. **B**, **C**, *Arrows* show brown and white enamel opacities on patient 3. **D**, *Arrow* shows cervical constriction on patient 4.

in our study. Even though most of our patients had conditions of the brain or head, these conditions seemed to be of a vascular nature, such as cranial hemorrhage or infarct. Several studies report the contribution of neural crest cells to dental mesenchyme, thereby suggesting a connection between brain tissue and teeth.[19,20] In the present cases, a relationship between brain damage and developmental disorders of the teeth would only be speculation. However, the patients might have a genetic predisposition favoring damage to both teeth and brain tissue.

In addition to root malformation with pulpal obliteration and cervical constriction, one of the patients had taurodontic first mandibular primary molars (Figure 1). The etiology of taurodontism may be both genetic and environmental and can be associated with syndromes including other oral aberrations.[16,21,22] A taurodont arises when the HERS fails to start the formation of the furcation bridges,[16] but this seems to be just a delay because a normal furcation will be formed later. This is in contrast to what is seen in MIM teeth, where the furcation is malformed at its normal location. We cannot exclude a possible common genetic cause or predisposition for the 2 different root anomalies seen in patient 1, but the 2 anomalies may appear simultaneously by coincidence. Even though most of

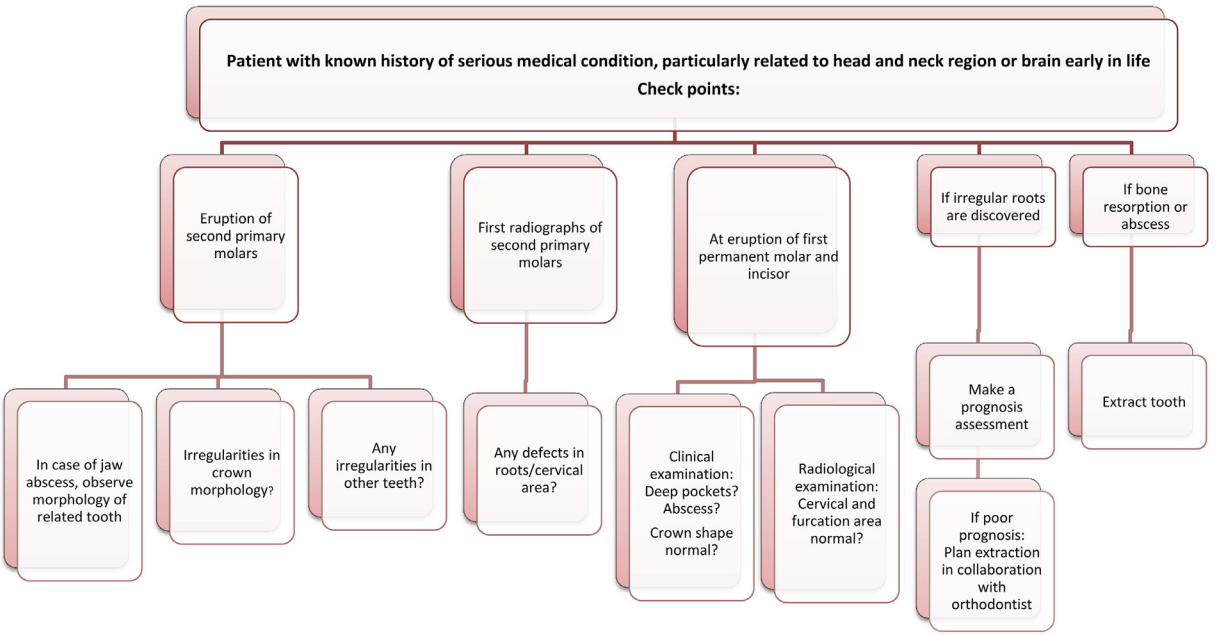

Fig. 7. Checkpoint chart for diagnostic use. The chart lists useful items to assist in discovering the condition when treating children with known serious medical conditions early in life.

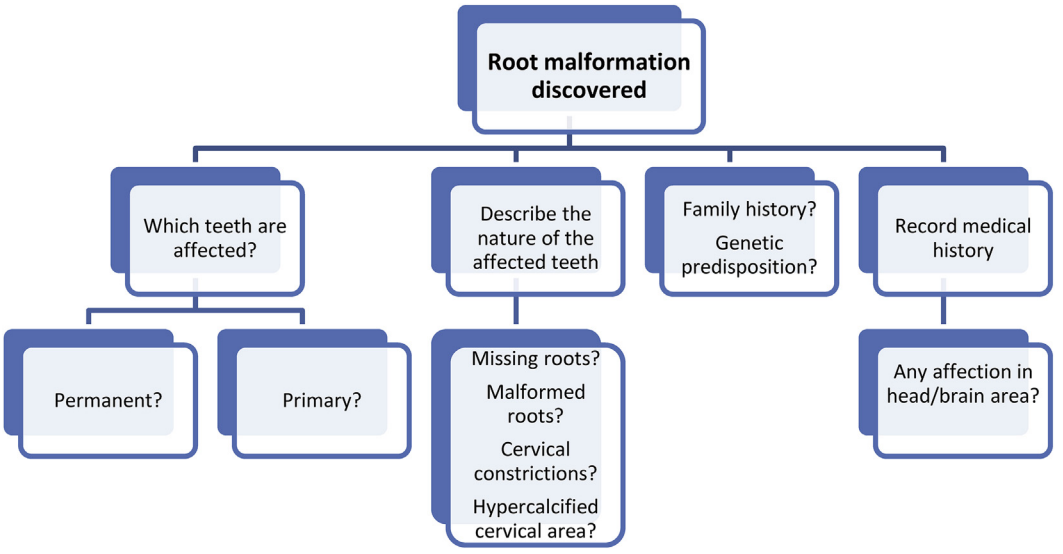

Fig. 8. Suggested workflow to apply when discovering a tooth with missing or malformed roots.

the MIM teeth looked normal in the mouth, there were exceptions. The affected incisors of patients 2 and 4 had interproximal constrictions (Figures 4 and 6D). Patient 2 showed a demarcated opacity on the upper left first molar (Figure 4), while patient 3 had demarcated opacities on both his first permanent molars and his incisors (Figure 6A-C), consistent with an MIH diagnosis.[23] Given that illness during the first 3 years of life might be an etiological factor in MIH, it is not surprising that some of these patients showed signs of MIH.[24]

The macroscopic, microscopic, and radiographic appearance of the teeth examined in this study (Figures 1-6) were comparable with the teeth described by Witt et al. and Lee et al.,[2,4] making us confident that we are describing the same condition. Further studies are needed to clarify the etiology and mechanisms of development. We suggest a diagnosis chart with checkpoints for the condition to use when treating children with a known history of a serious medical condition, particularly related to the head and neck region or the brain, early in life (Figure 7). We also

suggest a registration chart to use when root malformations are discovered (Figure 8). By actively looking for the condition and encouraging clinicians to do so, we hope to learn about the incidence and prevalence of the condition.

Children with MIM must be followed closely by the dental team. In cases of severe malformation with poor long-term prognosis, extractions should be planned to minimize the need for painful and complicated treatment later. Many of these cases would probably benefit from extraction, allowing the healthy second permanent molars to replace the first. Cooperation with an orthodontist in treatment planning would be wise, and advice on early extraction of first permanent molars can be found in the British clinical guidelines.[25]

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