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Early craniofacial signs of cleidocranial dysplasia

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Summary. *Objectives.* Early diagnosis of CCD is essential for a timely introduction of the appropriate treatment approach. Since certain symptoms first fully manifest only during the pubertal growth spurt, their indicatory signs are often overlooked. The aim of this study is to describe the initial craniofacial findings in patients with CCD in order to categorise their reliability for early detection.
Method. 14 patients with CCD between the ages of 6 and 11 years who were referred to the University of Regensburg over a 4-year period were included in this study. The patients were examined clinically and radiologically and their dental status was determined. Typical signs of CCD were analysed according to such classic criteria as the 'quatermoon'-physiognomy described in the literature. The clinical findings were compared to medical data and case history.
Results. Early signs were registered for each patient. While some signs could be found in all patients, others were variably expressed. The typical extraoral symptoms were only rarely exhibited in our patient population.
Conclusion. As various indicators of CCD are age related, their expression should be taken into account for early diagnosis. Apparent signs only manifest during the growth spurt when the ideal timeframe for beginning treatment has already past. The symptoms described should serve as early markers to aid the general and paediatric dentist in planning appropriate treatment or referring patients to specialised centres.

Introduction

Cleidocranial dysplasia (CCD; MIM 119600) is a congenital disorder affecting the skeletal and dental system [1]. Mutations in the runt-related transcription factor 2 (*RUNX2*) gene (OMIM 600211), located on chromosome 6p21, have been shown to underlie CCD [2]. *RUNX2* is considered a master gene in the formation of bone and dental tissue. Major indicators of CCD include hypoplasia or aplasia of clavicular bones, resulting in the ability of the patient to approximate their shoulders; narrow and abnormally shaped pelvic and pubic bones as well as deformations in the thoracic region. The most prominent signs, however, are osseous malformations in the cranial base and the skull. Due to disturbed bone formation and delayed maturation, the skull is formed by a large number of Wormian bones which develop from multiple supernumerary centres of ossification. The absence of the nasal bone, bossing of the frontal bones, prominent chin and maxillary hypoplasia typify the characteristic appearance of those afflicted with this syndrome. In 1908 the Swedish physician Hultkranz described this as 'quatermoon' physiognomy: 'The nasion-alveolar line appears more upright than usual (…) if a protruding forehead and the strong prognathic mandible is added, the result is a concave facial profile, a quatermoon physiognomy' [3].

More than 100 other anomalies have also been associated with these major clinical features of the condition [1]. According to the patients, however, the major cause of restriction in their quality of life

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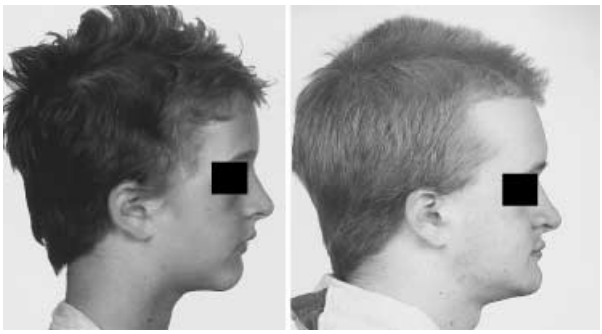

Fig. 1. Extraoral findings before (left; aged 13 years) and after (right; aged 18 years) the pubertal growth spurt, in the same patient, demonstrating the age-related manifestations. Due to the growth inhibition of the midface, the prominence of the chin is further pronounced.

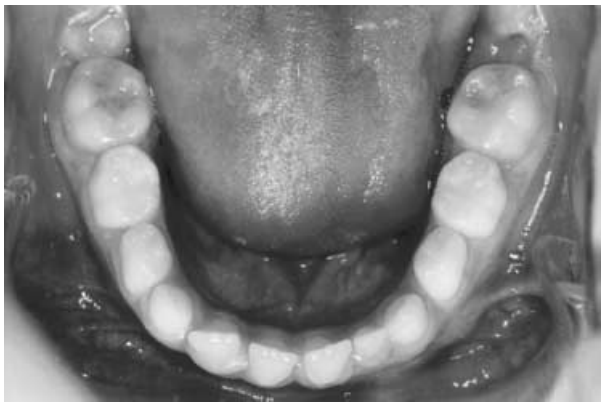

Fig. 2. Intraoral signs in a 10-year-old patient; erupted second molars, persisting primary dentition and spacing in the lower incisor area.

is the dental disturbances [4]. With the development of up to 63 supernumerary teeth, limited eruption force, impaction of permanent teeth, multiple follicular cysts and altered jaw development, early diagnosis is crucial to a timely introduction of an appropriate treatment regimen [5–7]. As seen with skeletal growth, the dentition is delayed by approximately 18–36 months [5]. Thus determining the ideal time for initiation of treatment is a function of comparing appropriate root development on the one hand, and obstructed eruption of the permanent dentition by supernumerary teeth on the other [6]. Ideally, diagnosis should therefore be made before age 9. Furthermore, an interdisciplinary treatment approach involving orthodontics, maxillo-facial surgery and prosthodontics is obligatory.

The difficulties involved in early diagnosis are a result of the genetic and developmental characteristics of the disorder. Many cases occur spontaneously, with approximately one out of three patients having unaffected parents [8,9]. The clinical variability ranges from nearly unrecognizable to full-blown cases. The most striking CCD marker, the abnormal shoulder mobility, is often not even expressed [8]. As the majority of the craniofacial findings are age related and become obvious only during adolescence (Fig. 1), the most favourable treatment time, which is limited by root development and bone quantity, is frequently missed. Although most of the abnormalities discussed in this paper have been published previously, the description of early findings has often been limited to case presentations [7,10–12].

The aim of this study is to provide a comprehensive description of the early craniofacial findings in a patient group with orthopaedic and molecular-genetically confirmed diagnosis of CCD to aid dentists in making more accurate early diagnosis.

Patients and methods

This study included 14 untreated patients from 12 families with CCD at our clinic. The age varied between 6 and 11 years with an average of 9·9 years. As there is no sex-predilection in CCD, details of the cohort were not differentiated by gender [13,14]. All participants were clinically examined with the intention of providing a surgical-orthodontic treatment approach. Therefore, the soft tissue was described according to the sagittal localization of the forehead, maxilla and mandible using lateral photographs taken under defined conditions as described by Proffit and coworkers [15]. The dental status was analysed based primarily on the examination of two frequently found signs of CCD: abnormally large spacing in the lower incisor area due to a wide alveolar bone and the 'second molar sign' – eruption of the second molars despite persisting primary dentition (Fig. 2). Although the manifestation of these signs in combination with the delayed dental development is rarely found in non-CCD patients, they are commonly expressed in CCD patients. Fulfilment of these criteria was determined based on the patient's dental status. The occurrence of supernumerary teeth and tooth germs was diagnosed on panoramic X-rays. In addition, the contours of the ascending rami were evaluated as described by McNamara and colleagues (Fig. 3) [16], where the ascending rami are narrow, with near parallel-sided anterior and posterior borders, sometimes tapering towards the

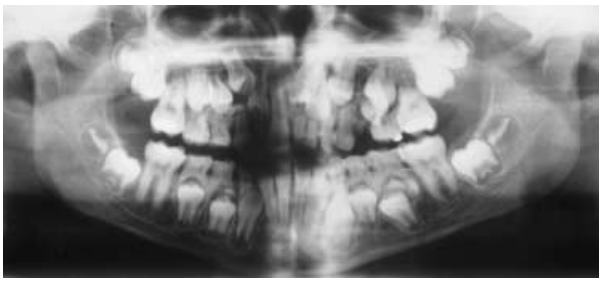

Fig. 3. Panoramic findings of a 10-year-old patient: (a) persistent deciduous teeth and multiple supernumerary germs, (b) parallel-sided ascending rami.

condyle and coronoid process, which often faces upwards and posteriorly. On the cephalometric radiograph, deformation of the sphenoid bone and gonion angle or the confirmed absence of a nasal bone and the presence of Wormian bones were also considered, as reported previously (Fig. 4) [17,18].

Results

The frequent description of frontal bossing in the literature could only rarely be diagnosed in our patient group. A hypoplastic midface and a prognathic mandible were found in 35% and 57% of our patients respectively. A combination of both of these signs occurring together with frontal bossing, leading to the 'quatermoon'-physiognomy was present in only one case (7%) [3]. Intraorally, the situation was quite different. The presence of the second permanent molar with a primary dentition was recorded in 80% of the patients and wide spacing in the lower incisor area was found in all cases. Supernumerary tooth germs and parallel-sided ascending rami were also invariably present; in one patient, there were two upper left canines. On the cephalometric radiographs,

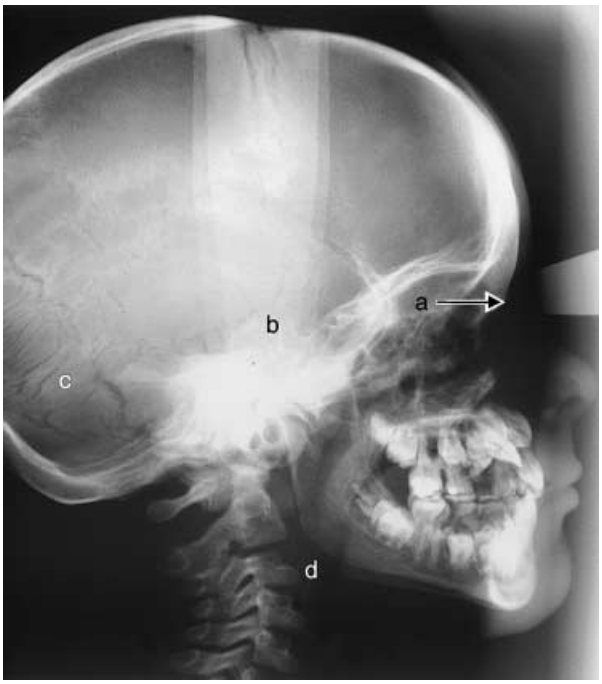

Fig. 4. Cephalometric radiograph of a 10-year-old affected boy: (a) missing nasal bone, (b) kyphotic sphenoid bone, (c) Wormian bones, ossification centres in the lambdoid suture, (d) markedly deficient gonion angle.

the markedly rounded gonion angle and the kyphotic sphenoid bone were present in all cases. The absence of nasal bones was inconsistent, while Wormian bones were always visible (Table 1).

Discussion

It was concluded from the present review that the second molar sign and spacing in the lower incisor area seems to appear consistently in patients with CCD. As the development of supernumerary teeth

Table 1. Early craniofacial signs with diagnosed proportions.

		Affected	Percentage
Extraoral signs	Frontal bossing	2/14	14
	Hypoplastic midface	5/14	35
	Prognatic mandible	8/14	57
	'Quatermoon'-physiognomy	1/14	7
Intraoral signs	Second molars sign	4/5	80
	Spacing of the lower front	10/10	100
Panoramic signs	Supernumerary germs	14/14	100
	Parallel-sided ascending ramus	14/14	100
Cephalometric signs	Missing nasal bone	9/14	64
	Kyphotic sphenoid bone	14/14	100
	Markedly rounded gonion angle	14/14	100
	Wormian bones	8/8	100

only ceases late in adulthood, the exact number of such teeth occurring was not taken into account in our study. Furthermore, the fact that CCD can also affect patients with no supernumerary teeth, or even missing teeth, has been described by Richardson and colleagues [19]. Over 20 syndromes and developmental conditions have been found to be associated with supernumerary teeth [20], potentially adding to confusion.

The skeletal signs can be divided into categories expressing variations in formation, size or occurrence. While deformations of the mandible or sphenoid bone are consistently expressed in all patients, signs of growth such as the sagittal jaw relationship are influenced by the pubertial growth spurt, and should therefore only be used as indicators in adults. The decelerated and retarded skeletal development might have a negative influence on the development of the classic 'quatermoon'-physiognomy, which may in turn affect its reliability as an early indicator. While the absence of nasal bones could not always be diagnosed, Wormian bones were invariably seen on X-ray. However, Wormian bones may also serve as an indicator of numerous congenital diseases and anomalies such as macrocephaly, trisomy 21 or osteogenesis imperfecta [21].

The signs and symptoms described here should serve as early markers to aid the general and paediatric dentist in planning appropriate treatment or referring patients to specialised centres. In addition, with the identification of the responsible gene, molecular-genetic analysis has become an indispensable diagnostic tool for early detection in cases where CCD is suspected [22]. In confirmed cases, genetic counselling for family planning should certainly be advised.

Résumé. *Objectifs.* Le diagnostic précoce de la Dysplasie Cléido-Crânienne est essentiel à la mise en place en temps et en heure d'une approche thérapeutique adaptée. Du fait que certains symptômes ne se manifestent vraiment que durant la poussée de croissance pubertaire, leurs signes indicateurs sont souvent ignorés. L'objectif de cette étude est de décrire les caractéristiques crânio-faciales initiales chez des patients atteints de DCC afin d'évaluer leur fiabilité pour une détection précoce.
Méthodes. 14 patients avec DCC, âgés de 6 à 11 ans, adressés à l'Université de Regensburg sur une période de 4 ans, ont été inclus dans cette étude. Les patients ont été examinés cliniquement et radiographiquement et un bilan dentaire effectué. Des signes typiques de DCC ont analysés selon des critères classiques tels que la « physionomie en quartier de lune décrite dans la littérature. Les caractéristiques cliniques ont été comparées aux données médicales et à l'histoire des cas.
Résultats. Des signes précoces ont été enregistrés pour chaque patient. Alors que certains signes pouvaient être retrouvés chez tous les patients, d'autres étaient d'expression variable. Les symptômes typiques extra-buccaux ont rarement été trouvés dans la population exhibée.
Conclusions. Puisque différents indicateurs de DCC sont lies à l'âge, leur expression devrait être prise en compte pour le diagnostic précoce. Les signes apparents ne se manifestent que durant la poussée de croissance quand le moment idéal de début de traitement est déjà passé. Les symptômes décrits devraient servir comme marqueurs précoces pour aider les omnipraticiens et pédodontistes à programmer un traitement approprié ou adresser les patients à des centres spécialisés.

Zusammenfassung *Ziele.* Eine frühzeitige Diagnose der Cleidocranialen Dysplasie (CCD) ist wichtig, um zeitgerechte Therapiemaßnahmen einleiten zu können. Da bestimmte Symptome erst während des pubertären Wachstumsschubes erkennbar werden, werden frühe Symptome oft übersehen. Ziel dieser Studie ist es, frühe craniofaziale Befunde bei Patienten mit CCD zu beschreiben und ihre Wertigkeit für eine frühe Diagnosestellung einzuordnen.
Methoden. 14 Patienten mit CCD im Altern von 6 Jahren bis 11 Jahren, die über einen Zeitraum von 4 Jahren an die Universität Regensburg überwiesen worden waren, wurden in diese Studie einbezogen. Die Patienten wurden klinisch und röntgenologisch untersucht, ihr Zahnstatus wurde erhoben. Typische Symptome von CCD wurden analysiert entsprechend der klassischen Kriterien wie der charakteristischen Physiognomie (vorgewölbte Stirn, eingefallene Maxilla). Die Befunde wurden mit medizinischen und anamnestischen Daten verglichen.
Ergebnisse. Frühsymptome gab es bei jedem Patienten. Während manche Symptome durchgängig vorlagen, waren andere unterschiedlich ausgeprägt. Typische extraorale Symptome waren in unserer Stichprobe nur wenig vorhanden.
Schlussfolgerungen. Da viele Symptome der CCD altersabhängig sind, muss deren Ausprägung für die Frühdiagnose berücksichtigt werden. Offen ersich-

tliche Zeichen werden erst im pubertären Wachstumsschub sichtbar, wenn der Zeitpunkt für einen idealen Therapiebeginn bereits verstrichen ist. Die beschriebenen Symptome sollen als frühe Marker mithelfen, Zahnärzten eine angemessene Therapieplanung und Weiterüberweisung in spezialisierte Zentren zu ermöglichen.

Resumen. *Objetivos*. El diagnóstico precoz de la DCC es esencial para la introducción oportuna del enfoque de tratamiento apropiado. Puesto que ciertos síntomas primero sólo se manifiestan completamente durante el brote de crecimiento puberal, sus signos indicativos con frecuencia se pasan por alto. El objetivo de este estudio es describir los rasgos craneofaciales en pacientes con DCC para clasificar su fiabilidad para la detección precoz.

Métodos. Se incluyeron en este estudio 14 pacientes con DCC de edades entre 6 y 11 años que fueron referidos a la universidad de Regensburg durante un periodo de 4 años. A los pacientes se les realizó un examen clínico y radiográfico y se determinó su estado dental. Se analizaron signos típicos de DCC según los criterios clásicos de fisonomía-"quatermoon" descritos en la literatura. Los hallazgos clínicos se compararon con los datos médicos y la historia clínica.

Resultados. Para cada paciente se registraron los signos precoces. Mientras que algunos signos podían encontarse en todos los pacientes, otros se expresaron de forma variable. Los síntomas extraorales típicos se manifestaron sólo raramente en nuestra población de pacientes.

Conclusiones. Puesto que varios indicadores de DCC están relacionados con la edad, su expresión debería ser tenida en cuenta para el diagnóstico precoz. Los signos aparentes sólo se manifiestan durante el brote de crecimiento cuando la franja de tiempo ideal para el comienzo del tratamiento ya ha pasado. Los síntomas descritos deberían servir como marcadores precoces para ayudar al dentista general y al odontopediatra, a planificar el tratamiento apropiado o referir a los pacientes a centros especializados.

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