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The neurocranial and craniofacial morphology in children with solitary median maxillary central incisor (SMMCI)

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Structed Abstract

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Objectives – The purpose of this study was to describe the neurocranial and craniofacial morphology on profile radiographs of children with single median maxillary central incisor (SMMCI).

Design – Cephalometric analyses of neurocranium and craniofacial morphology on profile radiographs.

Setting and Sample Population – Department of Orthodontics, School of Dentistry, University of Copenhagen. Thirteen children with SMMCI, 12 girls and one boy (7–17 years of age).

Outcome Measure – Cephalometric measurement were compared with normal standards using a paired *t*-test and Wilcoxon signed rank test.

Results – The size of the neurocranium (especially the length of the anterior cranial base), the maxillary prognathia, the maxillary inclination, the mandibular prognathia and the inclination of the mandibular incisors are significantly reduced in SMMCI. The mandibular inclination, the vertical jaw relationship, the alveolar bone prognathia in the upper jaw and the mandibular angle are significantly enlarged in SMMCI.

Conclusion – The present study showed that occurrence of SMMCI is a sign of a developmental anomaly associated with deviations in neurocranial size and shape and in craniofacial morphology.

Key words: cephalometry; dentition; growth; holoprosencephaly; neuro osteology; syndrome

Introduction

Solitary median maxillary central incisor (SMMCI) is a rare developmental anomaly in the dentition. The prevalence of live-born children with SMMCI is determined to be 1:50 000 (1). The occurrence of a single maxillary central incisor with normal crown width located exactly in the middle of the upper jaw was first described in 1958 (2).

The morphology of the single central incisor deviates from the morphology of a normal central incisor by having a symmetrical dental crown and by developing and erupting exactly in the mid-axial region of the maxillary dental arch in the primary as well as in the permanent dentition (1, 3–7).

Most likely, SMMCI is caused by an early defect in the fronto-nasal developmental field at 35–38 days gestational age (8). This developmental deviation involves the mid-sagittal structures of the head, e.g. the cranial base, the maxilla with the central incisors, the nasal cavity with the nasal septum and in some cases also the brain (9). The most severe malformation in this developmental field is holoprosencephaly (HPE), which is a complex malformation developing in early prenatal life and involving the frontal part of the brain and face (10, 11). The designation *HPE* comes from Greek *holos* = undivided and *prosencephalon* = frontal brain. The name thus indicates that the two brain halves in the frontal part of the brain are either fused or not separated during development.

Holoprosencephaly occurs with a prevalence of 1:16 000 liveborn, while the prevalence of HPE among spontaneous abortions is 1:250 (12). The degree of severity of prenatal HPE varies and is classified from severe to mild as follows: *cyclopia* with or without the proboscis (mid-axially placed eye and no nose), *ethmocephaly* (no nose), *cebocephaly* (mid-axially placed nose with only one nostril) and *premaxillary agenesis* (8).

In postnatal life, milder types of HPE are diagnosed with smaller facial malformations, such as hypotelorism, hyposmia (reduced sense of smell), eye defects, high palate, bilateral cleft lip with rudimentary premaxilla, one centrally placed incisor occasionally associated with reduced growth and mild mental retardation (4, 13, 14). The association between the clinical sign of one single maxillary central incisor and the neurological observation of a brain defect is not known in detail. Not all SMMCI cases are classified as HPE, but the exact phenotypic criteria for distinguishing SMMCI cases with minor HPE symptoms from SMMCI cases without these symptoms are not defined.

In HPE, the prosencephalon is malformed (8). Also the cranial base area in front of the pituitary gland/sella turcica and the facial bones are malformed (4, 15, 16). In all categories of prenatal HPE an abnormal shape of the neurocranium was observed (17). In all cases, the cranial bases displayed a round shape instead of an oval shape as in normal foetuses (15).

The length of the anterior cranial fossa, expressed as the nasion-sella length, was reduced in HPE foetuses, and the crista galli was absent. The shortest nasion-sella distance was observed in foetuses with the most severe types of HPE (15). Kjær et al. (15) furthermore showed that a connection exists between the type of facial malformation and the number of malformed facial bones, which decreased with the decreasing degree of severity of HPE. The premaxilla and the frontal part of the sphenoid bone were affected in all types of HPE.

Prenatal malformations of the pituitary gland have been demonstrated on holoprosencephalic human foetuses (18). SMMCI is generally considered the mildest phenotype of HPE, and therefore it can be presumed that the two developmental anomalies have the same abnormal genotype. Genetic investigations of individuals with SMMCI have shown deletion on chromosomes 7 and 18 (7q36.1 and 18p−) (19, 20), the same chromosomal regions in which the HPE genes are located. The relation between genes responsible for the development of SMMCI and the genes implicated in the pathogenesis of HPE is still unknown. Recently, a new *SHH* mutation (Sonic Hedgehog), which may be associated with SMMCI, has been discovered (6, 21, 22).

Short stature was one of the first signs described in connection with SMMCI, and later investigations documented reduced production of growth hormone (3, 23, 24). As then, more investigations have shown that even though most SMMCI patients have a short stature, this is not the case for all patients (19).

Developmentally, the central incisors belong to the fronto-nasal field, originating from the neural crest cells that have migrated anteriorly from the upper part of the neural tube towards the mid-axial part of the forehead and face. Thus, the fronto-nasal field stretches mid-axially from the face between the eyes to the sella turcica (15). The anterior wall of the sella turcica is abnormal in SMMCI patients (5). A centrally located incisor is a pathological sign seen in the fronto-nasal field.

Therefore, the condition diagnosed in the mouth is associated with deeper-lying osseous malformations within the fronto-nasal field. Craniofacial growth has been described postnatally on two SMMCI patients (5).

The hypotheses of the present study are:

1. The neurocranial size and shape in patients with SMMCI deviate from the neurocranial size and shape of a normal population.
2. A change in the neurocranium occurs concurrently with change in the craniofacial morphology.

The purpose of this study was to express the neurocranial and craniofacial morphology in SMMCI patients cephalometrically.

Material and methods

The material consisted of profile radiographs from 13 patients with SMMCI, 12 girls and one boy (Fig. 1). The ages of the girls were 7 year 0 months, 8 years 11 months, 9 years 5 months, 10 years 7 months, 10 years 8 months, 11 years 1 month, 11 years 2 months, 11 years 2 months, 11 years 9 months, 12 years 1 month, 12 years 4 months and 17 years 0 months. The boys' age was 14 years 10 months. The material was referred from orthodontic specialists in Denmark to the Department of Orthodontics, Copenhagen School of Dentistry. All patients were of Caucasian ethnicity. Three patients from this material have previously been included in two studies on the face, the palate and the craniofacial morphology in children with a single central incisor (16, 25). None of the patients were genotyped.

All profile radiographs were taken, at the ages mentioned above, with a film to focus distance of 180 cm and a 10 cm distance from the mid-sagittal plane to the film. The enlargement was 5.6% in the mid-sagittal plane.

Reference points and lines

The cephalometric reference points and lines used were defined according to Björk (26) and Solow (27) (Table 1). The points were marked directly on the profile radiographs, and measurements of the size of the neurocranium and the craniofacial morphology were performed.

Cephalometric variables

The variables for assessing the neurocranial and craniofacial morphology are defined according to Axelsson et al. (28) and Björk (26) (Tables 2 and 3).

Reference material

The size of the neurocranium was assessed according to age-related standard values from Axelsson et al. (28). The distances measured are illustrated in Fig. 2a. Craniofacial morphology was analysed according to standard values from Björk (26). The angles measured are illustrated in Fig. 2b.

Statistical methods

To compare the measured variables for the neurocranium in this study with the reference material (28), the measured variables of the SMMCI patients were corrected for radiographic enlargement (Enlargement factor 0.947) and age was interpolated. Based on the calculated normal material aged adjusted averages, the standard deviations were calculated. Accordingly, the *z*-score was calculated. To compare the measured variables for the craniofacial morphology in this study with the reference material (26), no correction for enlargement was necessary. To compare the mean differences between the variables of the SMMCI patients and the reference material, a paired *t*-test and Wilcoxon signed rank test was performed. The results

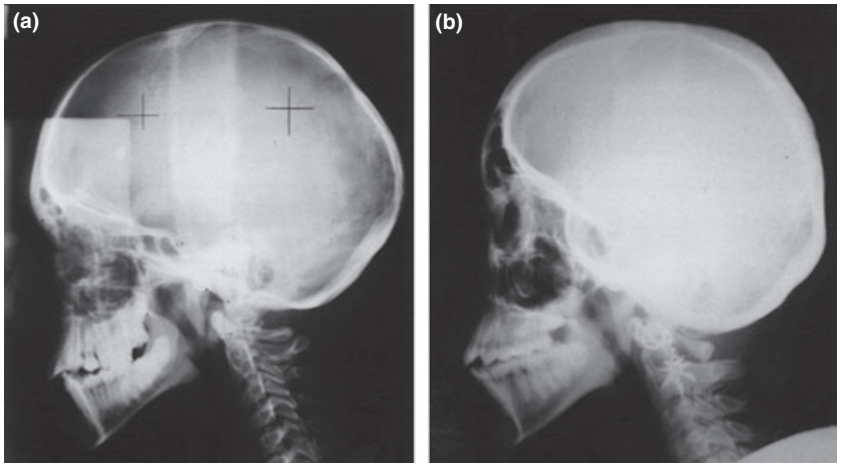

Fig. 1. (a) Profile radiograph of a girl with SMMCI aged 10 years 7 months. (b) Profile radiograph of a girl with SMMCI aged 17 years 0 months.

Table 1. **Definition of reference points and lines analysed on each profile radiograph (26, 27)**

Reference points and lines	Description
Articulare (ar)	The point of intersection between the contour of the external surface of the cranial base and the dorsal contour of processus condyloideus mandibulae
Basion (ba)	The most posterior–inferior point of the clivus
Bregma (br)	The point of intersection between the sagittal and the coronal suture
Chin line (CL)	The tangent to the chin through the infradentalis
Condylion (cd)	The most supero-posterior point on the condylar head
Frontalis (f)	A point on the surface of the frontal cranial bone determined by a perpendicular line on the middle of the line connecting nasion and bregma
Upper incisal line (IL_s)	The axis of the upper central incisor
Lower incisal line (IL_i)	The axis of the lower central incisor
Lambda (l)	The intersection between the lambdoid and sagittal sutures on the surface of the cranial vault
MBL	Mandibular base line. The line through pgn and ar
Nasion (n)	The most anterior point on the fronto-nasal suture
Opistochranion (opc)	The most posterior point on the surface of the cranial vault defined as the point farthest from the nasion
Sella (s)	Centre of the sella turcica
The mandibular line (ML)	The tangent to the lowest border of the mandibular base through the lowest point (gnathion, gn) of the symphysis mandibulae
The nasal line (NL)	The line through apex of spina nasalis anterior (sp) and pterygomaxillaris (pm)
The nasion-sella line (NSL)	The connection line between n and s
(OL_s)	The occlusal plane of the upper jaw from is (incision superius) to dms (the most inferior point on the disto-buccal cusp of the first upper molar)
(OL_i)	The occlusal plane of the lower jaw from ii (incision inferius) to dmi (the most superior point on the disto-buccal cusp of the first lower molar)
Pogonion (pg)	The most anterior point on the chin
Prognathion (pgn)	The point on the mandibular symphysis farthest from cd
Prosthion (pr)	The most anterior–inferior point on the alveolar process of the upper jaw
RL	Ramus line. The tangent to the posterior border of the mandible
Supramentalis (sm)	The deepest point on the anterior contour of the alveolar process of the mandible
Subspinalis (ss)	The deepest point on the anterior contour of the alveolar process of the maxilla

from the tests were considered to be significant at p-values < 0.05. The statistical analyses were performed using SAS Statistical Programme Package (SAS Institute Inc., Cary, NC, USA, 1982, 1988).

Reliability

The reliability of the variables describing the neurocranium and the craniofacial morphology was assessed by re-measurement of five lateral radiographs selected at random from the previously recorded radiographs. The radiographs were marked again after 2 weeks, and the differences between the two sets of recordings were calculated. No significant differences between the two sets of recordings were found.

Results

Neurocranium

1. The length of the anterior cranial base (s-n) was significantly shorter in the group with SMMCI.
2. The longest distance from the line ba-l to the outer contour of the occipital bone was significantly shorter in SMMCI.
3. The length br-l was significantly shorter.

Table 2. **Variables for assessing the neurocranium (28)**

Variable	Description
s-n-f	The prominence of the os frontale
n-s-ba	The cranial base angle
s-n	The length of the fossa cranii anterior
s-ba	The length of the fossa crani posterior
s-f	The distance from the sella to the os frontale
n-br	The distance from the nasion to the bregma
s-br	The distance from the sella to the bregma
ba-br	The distance from the basion to the bregma
br-l	The distance from the bregma to the lambda
s-l	The distance from the sella to the lambda
n-l	The distance from the nasion to the lambda
n-opc	The diameter of the neurocranium from the nasion to the ophistocranion
ba-l	The distance from the basion to the lambda
n-br to the os frontale	The longest distance from n-br o the os frontale
br-l to the os parietale	The longest distance from br-l to the os parietale
ba-l to the os occipitale	The longest distance from ba-l to the os occipitale
The diameter of the os frontale	The diameters of the os frontale, the os parietale and the os occipitale are defined as the distance from the point where the angle bisection of n-br, br-l and ba-l divides the inner ad outer contours of the each bone
The diameter of the os parietale	
The diameter of the os occipitale	

Table 3. **Variables for assessing the craniofacial morphology (26)**

Variable	Description
Sagittally	
Dento-aveolar	
pr-n-ss	Upper jaw – alveolar prognathia
CL/ML	Lower jaw – alveolar prognathia
IL_s/NL	Upper jaw – incisor inclination
IL_i/ML	Lower jaw – incisor inclination
Basically	
s-n-ss	Maxillary prognathia
s-n-pg	Mandibular prognathia
ss-n-pg	The sagittal jaw relation
ss-n-sm	The sagittal jaw relation measured to the sm point
Vertically	
Dento-alveolar	
NL/OL_s	Upper jaw zone
OL_i/ML	Upper jaw zone
Basically	
NSL/NL	Maxillary inclination
NSL/ML	Mandibular inclination
NL/ML	The vertical jaw relation
Cranial base	
n-s-ar	The cranial base laterally
n-s-ba	The cranial base angle
Mandibular base	
RL/ML	The jaw angle to ar
MBL/ML	The β-angle is the angle between MBL and ML

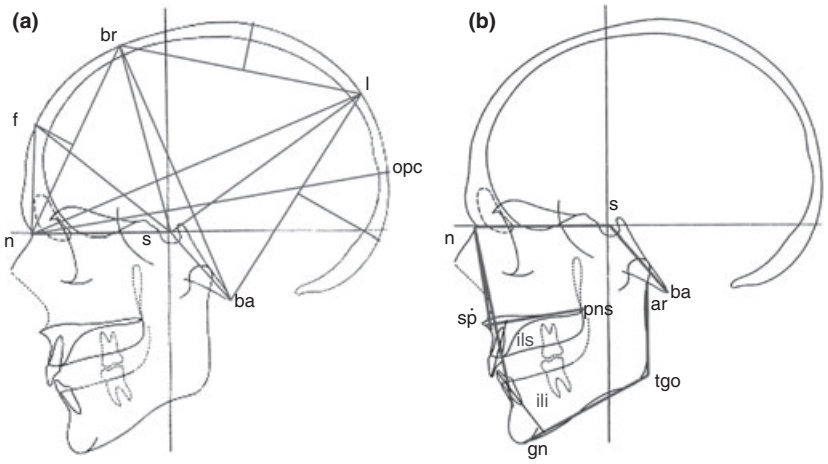

Fig. 2. (a) Reference points and reference lines used in the measurement of the neurocranium (28). The distances between the reference points are used to express the size and shape of the theka cranii. The figure is reproduced with permission from Axelsson et al., 2003 (28). (b) Reference points and reference lines used in the measurement of the craniofacial morphology. The cephalometric points and variables refer to Björk's analysis (26).

4. Both n-l (diameter) and n-opc (length) of the neurocranium were significantly shorter.
5. In the middle part of the neurocranium the length of br-l was significantly shorter.

These results are demonstrated in Table 4.

The cephalometric results showed that the neurocranium of patients with SMMCI is shorter in size in the anterior–posterior dimensions compared with normal values. The other measured variables were neither significantly shorter nor larger than the concurrent value in the normal material. Thus, the neurocranial shape differed from normal. In Fig. 3, the distances that were significantly shorter are illustrated with green for n-s and orange for n-opc, n-l, br-l and for the distance expressing the longest distance between the ba-l line and the outer contour of the occipital bone.

Thus, the first hypothesis of this study is confirmed.

Craniofacial morphology

From the mean *Z*-score and the belonging observed *t*-test and signed rank test (Table 5), the following is concluded:

1. The maxillary prognathia (s-n-ss) and inclination (NSL/NL) deviated significantly from normal. Both the maxillary prognathia (s-n-ss) and the maxillary inclination (NSL/NL) were significantly smaller in SMMCI.
2. The mandibulary prognathia (s-n-pg) and the inclination (NSL/ML) deviated significantly from normal. The mandibulary prognathia (s-n-pg) was significantly smaller, while the mandibulary inclination (NSL/ML) was significantly larger in SMMCI.
3. The vertical jaw relation (NL/ML) deviated significantly from normal. The vertical jaw relation (NL/ML) was significantly larger in SMMCI.
4. The upper jaw alveolar prognathia (pr-n-ss) was significantly larger in SMMCI.
5. The upper jaw zone (OL_s/NL) was significantly larger in SMMCI.
6. The jaw angle to the articulare (RL/ML) was significantly larger in SMMCI.
7. The β-angle to the articulare (MBL/ML) was significantly smaller in SMMCI.
8. The lower jaw incisor inclination (ML/IL_i) was significantly smaller in SMMCI.

Table 4. **The average *Z*-score, *t*-test sizes (*t*-values) and *p*-values for *t*-test and signed rank test for each measured variable (31)**

Variable	No of patients	No of measured variable	Mean *Z*-score	SD	*t*-value	*P-values* *t*-test	*P*-values Signed rank
Ba-br	13	12	−0.87	1.51	−1.99	0.0720	
Ba-l	13	11	−0.85	1.02	−2.76	0.0202	
Ba-l-oc	13	10	−1.19	0.69	−5.43	0.0004	0.0020
Br-l	13	11	−1.30	1.36	−3.18	0.0098	0.0137
Br-l-pa	13	11	−0.79	1.22	−2.14	0.0581	
n-br	13	12	−0.28	1.18	−0.38	0.4218	
n-br-f	13	12	−0.31	1.17	−0.90	0.3850	
n-l	13	11	−1.33	1.37	−3.22	0.0091	0.0068
n-opc	13	10	−1.36	1.26	−3.40	0.0079	0.0098
n-s-ba	13	12	0.55	0.79	2.40	0.0353	
s-ba	13	13	−0.63	1.32	−1.17	0.1123	
s-br	13	12	−0.17	2.27	−0.25	0.8048	
s-f	13	12	−1.41	1.69	−2.90	0.0144	
s-l	13	11	−0.82	1.16	−2.35	0.0404	
s-n	13	13	−2.27	2.00	−4.09	0.0015	0.0024
s-n-f	13	12	−0.31	0.90	−1.19	0.2599	
Th-f	13	12	0.60	1.29	1.60	0.1372	
Th-oc	13	10	1.21	1.76	2.18	0.0575	
Th-pa	13	11	0.22	2.15	0.33	0.7460	

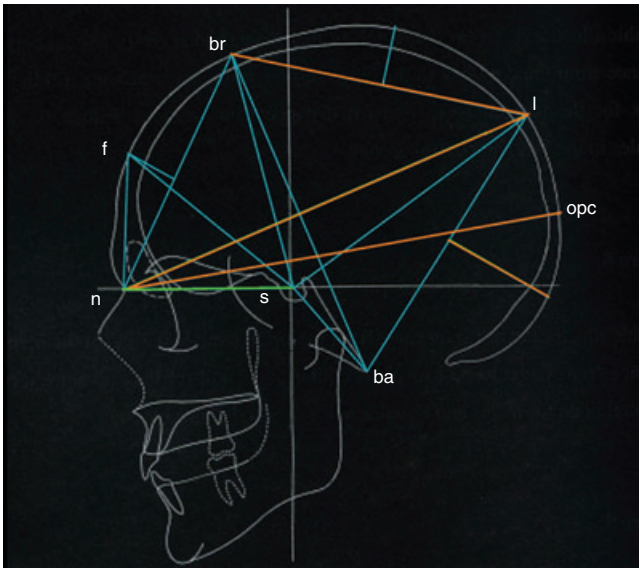

Fig. 3. Schematic drawing demonstrating in green and orange the distances in the neurocranium that were significantly shorter in SMMCI patients. The blue lines show the distances that were not significantly deviant from normal.

Table 5. **Mean *z*-score and the belonging observed *t*-test and signed rank test**

Variable	n	No of variables measured	Mean *Z*	SD	Pr > | *t* |	Signed rank
CL/ML	13	13	0.05	0.52	0.7272	
ML/IL_i	13	13	−1.12	0.74	0.0001	0.0017
NL/IL_s	13	13	−0.61	0.89	0.0300	
NL/ML	13	13	1.89	1.07	<0.0001	0.0002
OL_s/NL	13	13	2.29	1.09	<0.0001	0.0002
NSL/ML	13	13	1.24	1.17	0.0024	0.0034
NSL/NL	13	13	−1.28	1.53	0.0107	0.0183
OL_i/ML	13	13	0.31	0.77	0.1768	
Jaw angle	13	13	0.66	0.72	0.0063	0.0073
β-angle	13	12	−1.83	0.52	<0.0001	0.0005
n-a-ar	13	13	0.32	0.84	0.1916	
pr-n-ss	12	12	2.38	1.76	0.0007	0.0010
s-n-pg	13	13	−1.36	1.62	0.0106	0.0146
s-n-ss	13	13	−1.45	1.42	0.0032	0.0054
ss-n-pg	13	13	−0.14	1.94	0.8016	
ss-n-sm	13	13	−0.62	1.61	0.1926	

Conclusively, the SMMCI patients had a retrognathic and anteriorly inclined maxilla and a retrognathic and posteriorly inclined mandible. Furthermore, the incisor inclination in both the upper jaw and the upper jaw zone was increased.

Thus, the second hypothesis of this study is also confirmed.

Discussion

Solitary median maxillary central incisor is a rare abnormality with an aetiology that has so far not been precisely determined. Furthermore, there is little knowledge concerning the interrelation between SMMCI and HPE and on brain involvement in these two conditions.

The primary focus with regard to SMMCI has been on clinical descriptions of single cases and on the search for actual genes involved in the pathogenesis. Until now, interest in SMMCI has not been significant within the orthodontic field perhaps because of the low prevalence of the syndrome. The actual interest in SMMCI patients has been based on analyses of human holoprosencephalic cases, in which it has been revealed that the holoprosencephalic malformation is limited to the fronto-nasal developmental field (15, 18, 29). Also in SMMCI, the malformation is seemingly limited to the fronto-nasal field (4, 5, 16, 25).

The aim of the present study was to describe the neurocranium and the craniofacial morphology of children with SMMCI based on 13 patients. The first issue to be focussed on was whether a neurocranial malformation could be registered and, in a later study, to prove a possible relationship between the neurocranium and the brain diagnosis. The second issue was whether the former report on abnormal craniofacial profile in two SMMCI patients was statistically significant when 13 patients were analysed.

Gender distribution of SMMCI cannot be concluded based on this study. In the material of 13 patients referred to the Department of Orthodontics, Copenhagen, over a period of 12 years, there was only one boy. Therefore, the statistically determined results can only be used for girls.

Whether the registered neurocranial deviation is associated with brain malformations or mental retardation is not clarified as neuro-paediatric records were not available. It could be presumed that the larger the deviation of the neurocranium, the more affected the brain, as a result of the primary malformation in the area of fusion in the prosencephalon, but this cannot be concluded from the present study.

Another consideration was how the possible prosencephalic fusion influences the regional falx cerebri and its attachment to the anterior cranial fossa, the crista galli. In other words, it can be presumed that the shorter the distance s-n, the more deviant the crista galli and the less the separation between the two hemispheres.

Solitary median maxillary central incisor patients are often of short stature (3), and it is therefore likely that the previously registered malformation of the sella turcica in the neurocranium (5) and the prenatal malformation of the pituitary gland in HPE (18) are findings associated with the growth failure in SMMCI.

Concerning craniofacial morphology, it would be interesting to know whether the registered craniofacial deviations are associated with the size and shape of the neurocranium, particularly the short n-s distance. The present study cannot clarify this.

When assessing the craniofacial deviations in each patient, it must be noticed that the available control group was based on data from Swedish boys aged 12 and 20 years (26). This is not optimal, as the patients used in the present study were girls aged 7–17 years In future studies on girls with SMMCI, it would be preferable that a control groups of girls was used (30).

The most important result of this study is that SMMCI is not only a local deviation observed in the dentition. This shows that patients with SMMCI must be examined thoroughly when seen in the clinic. Also genotyping of the SMMCI patients is important, as there seems to be genetic (SHH mutations) and phenotypic similarities between SMMCI and HPE (21, 32, 33). Why patients with identical gene mutations can exhibit different clinical features as demonstrated in the variety of facial features observed in HPE, is an interesting question recently elucidated in experimental studies (34). From a genetic point of view, the present sample may be heterogeneous. SMMCI patients should be treated by an interdisciplinary team, including paediatrists, geneticists, neurologists, endocrinologists, dentists and specialists in orthodontics, prosthodontics and dental surgery.

From an orthodontic point of view, it should be kept in mind that the cephalometric analyses in the present study only deal with sagittal and vertical dimensions. In future studies, transversal dimensions should be analysed as well. This was not possible in the present study as a frontal radiograph was available in only one of the 13 referred cases. Former registrations of absence of the internasal suture and parts of the intermaxillary suture will prevent transversal expansion of the palate (5). Therefore, orthodontic treatment should not include maxillary expansion but solely tooth movement possibly combined with insertion of dental implants. In some cases, extraction of the central incisor and mesialization of the laterals were preferred (5). There is not always indication of orthodontic treatment if the patient and the parents are content with the child's dentition, and if the occlusion does not cause any functional and/or aesthetic problems.

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