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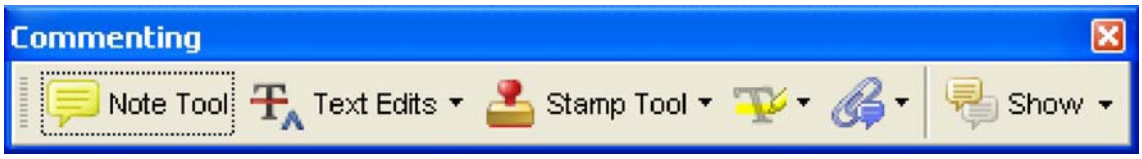

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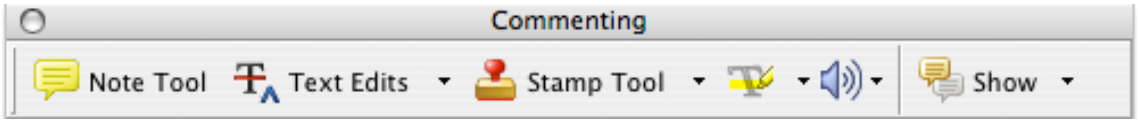

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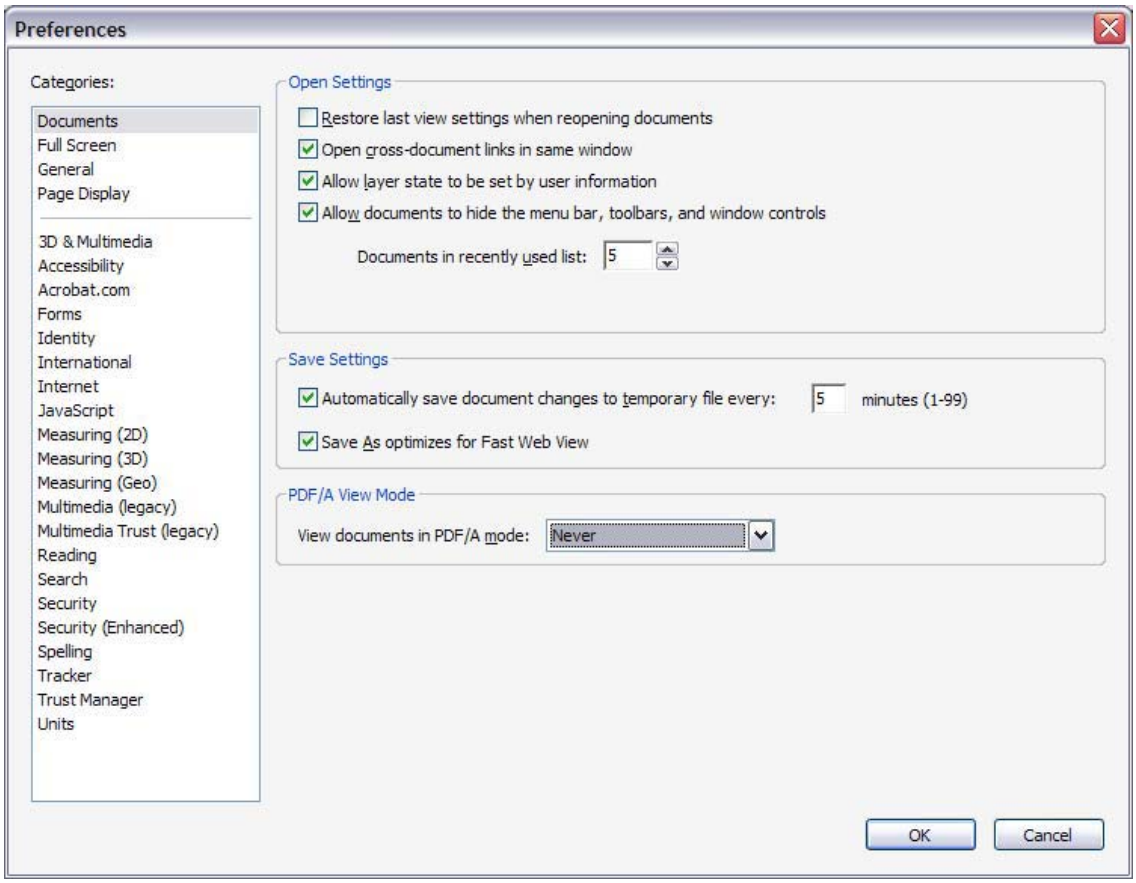

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Craniofacial characteristics in cri-du-chat syndrome

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Objective. The purpose of this study was to analyze craniofacial characteristics from lateral head profile radiographs of patients with cri-du-chat (CdC) syndrome.
Study design. The craniofacial morphology of 10 CdC patients was evaluated using standard cephalometric methods, measuring 39 craniofacial variables on cephalometric x-ray images.
Results. The principal characteristics were skeletal class II malocclusion, caused by mandibular retrognathism, dental biprotrusion, and a small upper airway. Additionally, 70% of patients had a steep palatal plane angle; the cranial base angle was flattened, also in 70% of patients.
Conclusions. Results indicated that the deletion of 5p had an impact on the cranial base, maxilla, mandible, and upper airway, causing distinctive features to become apparent through irregular growth. **(Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010;xx:xxx)**

The cri-du-chat (CdC) syndrome, first described by Lejeune et al.,[1] is characterized by partial deletion of the short arm of chromosome 5. The size of the deletion ranges from the entire short arm to region 5p15 and 3 (5 to 40 Mb) only.[2,3] Its frequency is estimated to be between 1:15,000[4] and 1:50,000[5] of live-born infants, but the prevalence found by Niebuhr[4] in 6000 individuals with mental retardation was approximately 1:350. Furthermore, Schinzel's data[6] suggest that it is the most common autosomal deletion syndrome in humans.

The syndrome is characterized by a high-pitched monochromatic cry like the mewing of a distressed kitten, probably because of anomalies of the larynx and epiglottis as well as neurological, structural, and functional alterations.[4] Additional clinical features are severe psychomotor and mental retardation, growth delay, and hypotonia.[2,4] Although the characteristic cry is usually considered diagnostic for the syndrome,[2] the catlike cry has been found without the typical dysmorphic and severe developmental features of the syndrome in individuals with the limited 5p15.3 deletion.[2,7] Craniofacial abnormalities include microcephaly, slight hypertelorism, epicanthal folds, downslanting palpebral fissures, strabismus, malformed ears, and hypodontia.[8,9]

Even though the clinical features are well known as the result of descriptions by several authors,[2,7,10] little is known about craniofacial development. There are some studies based on anthropometric data, such as skull size, inner canthal distance, and retrognathia.[4,11,12] More recently, Kjaer and Niebuhr[13] investigated the cranial base of patients with CdC syndrome using profile radiographs and found that the condition involved a malformation of the cranial base. They pointed out that this particular cranial base region develops around the notochord, at the location where the rhombencephalic-derived brainstem, pons, and cerebellum develop dorsally and where the neurons migrate ventrally to the larynx. They suggested that a cranial developmental field, originating at the notochord location, is involved in the manifestations of CdC syndrome.

Cephalometrics involves the use of lateral head radiographs to measure the skull and facial bones with respect to specific reference points. It is useful for evaluating and quantifying growth and development features, such as the relationship between the jaws, and between the jaws and the cranial bones. The purpose of

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this study was to analyze craniofacial characteristics on lateral head profile x-rays in patients with CdC syndrome.

MATERIAL AND METHODS

Sixteen patients from the Spanish Cri-du-chat Association and diagnosed with CdC syndrome by their respective reference hospitals belonging to the Public Health Service were selected from among patients who had undergone some procedure in the Department of Oral and Maxillofacial Surgery at the Faculty of Dentistry, University of Seville (Spain). Six of these individuals were excluded because the images showed poor quality and motion artifacts; excluded subjects were those with severe mental retardation who were unable to remain still during the x-ray exposure. As a result, 10 patients—2 males and 8 females with a mean age of 23.9 ± 6.7 years—were selected for the analysis. The present study was carried out with the full knowledge and written consent of each subject and in accordance with the ethical principles governing medical research and human subjects, as laid down in the Helsinki Declaration (2002 version, http://www.wma.net/e/policy/b3.htm). The data have been treated with absolute confidentiality. Methods of gathering and storing data are subject to the Spanish Organic Law governing personal data protection. The Experimental Ethics Committee at the University of Seville independently approved the procedure.

All subjects were photographed and examined intra- and extraorally for general medical and dental findings. The protocol included generating lateral cephalometric digital x-ray images, at 70 kV, 12 mA, with an exposure time of 0.80 seconds (Odontorama PC, Trophy, Cedex, France). Specific software (Nemotec, Madrid, Spain) was used for the digital images from which craniofacial and dental measurements were taken. Anatomical landmark coordinates were defined and summarized as shown in Table I. Craniofacial bones and relationships were measured after being classified into 4 groups: airway analysis, skeletal problems, dental problems, and esthetic problems. This classification provides useful information for determining which, if any, developmental field is affected in CdC syndrome. In each group, angular and linear measurements were assessed and quantified for this purpose, as shown in Table II. Measurements obtained from subjects with the CdC syndrome were compared with standard measurements provided by the specific software we used, and standard deviations calculated on the basis of standardized age, sex, and race norms. Cephalometric analysis methods by Steiner,[14,15] Ricketts,[16] Jaraback and Fizzel,[17] and McNamara[18] were used to obtain standard measurements. The measurements referred to previously correspond to the most representative and widely used methods according to orthodontic and craniofacial researchers. The correspondence between cephalometric analyses and measurements used are also shown in Table II. Intraobserver error was calculated for the sample, which was twice tested. It was calculated in the following way: SE = $\sqrt{(\Sigma d2/2n)}$, where d is the difference between the double measurements and n is the number of paired double measurements. It was evaluated using the Student *t* test for paired samples, with absence of significance regarded as indicative of concordance between mean values. The data obtained were analyzed using SPSS 17.0 software for Windows (LEAD Technologies, USA).

RESULTS

The accuracy of intraobservational error was 0.41 mm for linear measurements and 0.63° for angle measurements. There were no statistically significant differences between original and repeat measurements ($P > .05$).

Airway analysis emphasized the reduced volume in the upper respiratory tract (Table III). The great majority of the facial pattern measurements included shared mesofacial characteristics. However, there are parameters that demonstrate an obvious vertical component in the growth of study subjects, such as a decreased upper gonial angle and an increased lower gonial angle. By contrast, we also found an increased anterior facial height (the distance between the nasion and menton landmarks). In contrast, standard measurements were found for lower facial height (ans-xi-pm) and antero-inferior facial height (Na-me) (Table III).

An inclined palatal plane was found to be a standard feature of the analyzed subjects. Statistical frequencies for this variable show that only 30% of subjects had standard measurements and 70% had a marked slope. These data represent one of the most characteristic features of CdC syndrome (Table IV).

Measurements of the anterior and posterior cranial base showed that both were reduced compared with established age, sex, and racial norms. However, in 70% of cases, the cranial base angle (s-na-ba) was large (Table V) when compared with age-related standards for normal individuals.[19-21] Sagittal skeletal features are all consistent with skeletal class II malocclusion caused by mandibular retrognathism (Table III).

With regard to dental cephalometric data, we found dental biprotrusion, protruding lower incisors, and outward-protruding upper incisors (Table III).

The main esthetic problem observable from the cephalometric tracing was the presence of a short upper lip with a right nasolabial angle. The lower lip normally protruded (Table III).

Table I. Anatomical landmarks used

Point	*Definition*
Sella (S)	Point representing the center of the pituitary fossa
Nasion (Na)	Most anterior point of the frontonasal suture on the midplane
Basion (Ba)	Most postero-inferior point of the clivus
Articulare (Ar)	The intersection between the external contour of the cranial base and the dorsal contour of the condylar head or neck.
Tangent-gonion (tgo)	The point of intersection between the base and the ramus tangents through gnation and articulare
Menton (Me)	The lowest point of the jaw at the level of the midsagittal plane of the symphysis
Condylion (Co)	The uppermost point of the mandibular condyle
A point (A)	The most posterior point on the anterior contour of the upper alveolar process
Gnation (Gn)	The most inferior point on the mandibular symphysis
Pogonion (Pg)	The most anterior point on the mandibular symphisis
Apex superius (As)	The apex of the root of the most prominent maxillary central incisor
Incisor surperius (Is)	The midpoint of the incisal edge of the most prominent maxillary central incisor
Incisor inferius (Ii)	The midpoint of the incisal edge of the most prominent mandibular central incisor
Apex inferius (Ai)	The apex of the root of the most prominent mandibular central incisor
Psps point (psp)	The most posterior point on the soft palate
Ppws point (ppws)	Closest point on the posterior to pharyngeal wall to psp point
Pbt point (pbt)	Intersection of the posterior border of the tongue and the inferior border of the mandible
Ppwi point (ppwi)	Closest point on the posterior to pharyngeal wall to pbt point
Pm point (pm)	The point where the curvature of the anterior border of the symphysis changes from concave to convex
Xi point (Xi)	A point located at the center of the ramus
Pterigomaxillare (Pt)	The intersection point of the inferior border of the foramen rotundum and the posterior wall of the pterigomaxillary fissure
Gonion (Go)	The lowest, most posterior point on the gonial angle of the mandible
Porion (Po)	The most superior point on the radiolucency of the external and internal audigory meati. It is located posterior to the mandibular condyle and posterior clivus.
Orbitale (Or)	The most inferior point on the lower border of the bony orbit
CF point (CF)	The intersection point of the FH plane (Frankfort horizontal plane: a line connecting the Po and Or points) and the PTV plane (Pterygoid vertical plane: a line perpendicular to the FH plane thorugh the PT point).
Anterior nasal spine (ANS)	The apex of the anterior nasal spine
Posterior nasal spine (PNS)	The most posterior point on the bonu hard palate in the midsagittal plane
Stomion superius (Sts)	The lowest midline point of the upper lip
B point (B)	The deepest point on the contour of the mandible
Soft tisue pogonion (Pģ)	The most prominent point on the soft tissue contour of the chin in the midsagittal plane
Labrale superius (Ls)	The point denoting the vermillion border of the upper lip in the midsagittal plane
Labrale inferius (Li)	The point denoting the vermillion border of the lower lip in the midsagittal plane
Subnasale (Sn)	The point in the midsagittal plane where the base of the columella of the nose meets the upper lip
Columela nasal medium (Nm)	Geometric center on columela to de subnasal point to the tip of the nose
Center of cranium (Ce)	The intersection point of the Ba-Na plane and the facial axis plane
Condyle (Dc)	The point in the center of the condyle neck along Ba-N plane

DISCUSSION

Cri-du-chat syndrome was first described in 1963 by Lejeune et al.,[1] who comprehensively explained the common clinical manifestations. Since then, the literature has referred to patients with CdC as expressing craniofacial features that include hypertelorism, antimongoloid obliquity of the palpebral fissures, and a moon face. Radiological features, such as microencephaly and faulty long bone development have also been described. Many authors have reported on the clinical and radiological findings associated with this syndrome[8,10,13,22-25]; none, however have measured craniofacial features involving the maxillary and mandibular bones.

In CdC syndrome, the monotonous, high-pitched cry like a cat is probably the most characteristic and striking clinical feature.[26] This has also been found in certain kinds of disorders or neurological diseases.[4] Morphologic laryngeal alterations, such as a small floppy, curved epiglottis,[27] laryngeal hypoplasia, a narrow, diamond-shaped or quadrangular larynx, or an abnormal air space in the posterior area during phonation,[28] have all been said to result in this characteristic cry. Airway analysis found a narrow upper airway volume, confirmed by computed tomography studies.[22] Nevertheless, subsequent studies established that such anatomical alterations were not necessarily present in every patient and the existence of some other organic or functional factor was not being considered.[4] Thus, the statistical frequency of a markedly inclined palatal plane, found in 70% of the subjects, suggests that it is a characteristic feature and probably involved in the

Table II. List of variables

			Mean	SD
Airway analysis				
Linear	ppws-pbt*	Width of the upper pharmyx	17.5	3
	ppwi-pm*	Width of the lower pharmyx	12.5	3
Aesthetic analysis				
Linear	ans-sts†	Superior lip length	27.6	2
	perp (sn-pg)-Ls‡	Protrusion of the superior lip relative to the sn-pg line	0	0
	perp (sn-pg)-Li‡	Protrusion of the inferior lip relative to the sn-pg line	0	0
Angular	nm-sn-Ls*	Angle between upper lip and nose	102	8
Skeletal analysis				
Linear	cf-go†	Lower posterior face height	64.6	2.5
	ans-me*	Lower anterior face height	78	4
	ar-goe§	Ramus length	56	5
	ce-na†	Cranial length	64.6	2.5
	si-ar§	Posterior cranial base length	38	3
	si-na§	Anterior cranial base length	83	3
	perp (na-pg)-a†	Maxillary prognathism relative to the na-pg line	−0.4	2
	co-a*	Total maxillary length	105	4
	co-gn*	Total mandibular length	135	4
	goe-me§	Length of the mandibular corpus	135	4
Angular	ba-na-pt gn†	Facial axis	90	3
	ans-xi-pm†	Inferior face height	47	4
	si na-go-gn‡	Angulation of the mandible to the anterior cranial base	32	4
	de-xi-pm†	Angulation of the mandibular corpus relative to the mandibular ramus	32	4
	ar-goe-me§	Total gonial angle	130	7
	ar-goe-na§	Superior gonial angle	53.5	1.5
	na-goe-me§	Inferior gonial angle	72.5	2.5
	na-cf-a†	Nasomaxillary height	59	3
	po.or-pns-ans†	Maxillary inclination relative po-or plane	1	3.5
	po.or-ba.na†	Cranial base angulation relative to po-or plane	29.4	3
	si-na-ba‖	Angulation between anterior and posterior cranial base	129	1
	si-na-a‡	Maxillary protrusion relative si-na line	82	2
	si-na-b‡	Mandibular protrusion relative si-na line	80	2
index	(name)-(si.goe)§	Anterior facial height take away posterior facial height	63.5	1.5
	(si.na.a)-(si.na.b)‡	Maxillomandibular relationship relative to anterior cranial base	3	2
	(co.a)-(co.gn)*	Maxillomandibular relationship index	30	4
Dental analysis				
Angular	a.pg-as.is†	Proinclination of the maxillary incisors	28	4
	a.pg-ni-ii†	Proinclination of the mandibular incisors	22	4
	a.pg-is†	Protrusion of the maxillary incisors	3.5	2.3
	a.pg.ii†	Protrusion of the mandibular incisors	1	2.3
	as.is-ai-ii†	Angulation between maxillary and mandibular incisors	132	6

For definitions see:
*McNamara.[18]
†Ricketts.[16]
‡Steiner.[14,15]
§Jaraback and Fizzel.[17]
‖Riolo et al.,[20] Björk,[19] Solow and Sarnas.[21]

typical cat-like cry because of a skeletal deformity of the stomatognathic system.

Kjaer and Niebuhr[13] studied the cranial base in profile radiographs of patients with CdC syndrome to locate the developmental field affected by the syndrome. Their results showed an abnormal development of the cranial base, expressed as malformations in the bony contours of sella turcica and clivus, and a reduced cranial base angle. Our findings do not coincide with this last point. We found an increased cranial base angle in 70% of patients. Our results of skeletal class II malocclusion caused by mandibular retrognathism are consistent with the findings of several authors,[29-33] who reported an increased cranial base angle in class II patients, resulting in a more posterior position of the mandible and a more posteriorly positioned condylar neck.[34-37]

Data in the available literature emphasized decreased long bone development. This agrees with our findings,

Table III. Descriptive statistics of 39 craniofacial variables in Cri du Chat syndrome

Variable	*Mean*	*SD*	*Min*	*Max*	*Interpretation*
Airway analysis					
ppws-pbt*	22.44	7.23	12.6	38.6	Increased
ppwi-pm*	14.41	3.68	10.3	21	Decreased
Aesthetic analysis					
ans-sts†	22.81	3.45	18.2	30.4	Superior lip shorted
perp (sn-pg)-Ls‡	−0.35	3.30	−7.10	5.70	Normal
si-goe§	79.83	9.27	62.30	96.20	Mesofacial
na-me§	122.9	11.2	109.30	143.10	Dolichofacial
ans-me*	72.58	8.24	60.70	83.50	Brachyfacial
ar-goe§	52.35	8.6	34.60	62.50	Standar
cc-na†	61.22	3.8	54.80	66.60	Cranial base shorted
si-ar§	31.10	4.12	24.8	39.00	Posterior cranial base decreased
si-na§	70.99	14.16	33.10	82.60	Anterior cranial base decreased
perp (na-pg)-a†	26.20	2.09	22.50	29.70	Maxillary prognathism relative to the na-pg line
co-a*	89.27	6.53	82.80	101.70	Total maxillary length decreased
co-gn*	116.59	9.76	100.10	131.80	Total mandibular length decreased
goe-me	69.2	6.45	58.70	79.10	Length of mandibular corpus decreased
ha.na-pt.gn†	89.54	5.73	77.40	97.30	Mesofacial
ans-xi-pro†	48.17	5.83	40.50	59.50	Mesofacial
si.na-go.gn‡	35.02	7.78	27.30	50.50	Mesofacial
de-xi-pm†	32.96	6.6	25.20	42.30	Mesofacial
ar-goe-me§	128.2	9.4	112.10	142.10	Mesofacial
ar-goe-na§	51.05	5.44	43.30	59.70	Dolichofacial
na-goe-me§	77.15	7.74	68.80	92.70	Dolichofacial
na-cf-a†	54.28	3.47	49.70	59.70	Dolichofacial
po.or-pns-ans†	0.24	5.39	−7.10	8.00	Standar
po.or-ba-na†	26.2	2.09	22.50	29.70	Cranial base angulation decreased relative to po-or plane
si-na-ba‖	134.27	4.74	128.50	143.20	Increased angulation between anterior and posterior cranial base
si-na-a‡	83.26	3.51	78.40	90.30	Maxillary protrusion relative si-na line
si-na-b‡	77.68	3.41	71.40	82.90	Mandibular retrusion relative si-na line
(na.me)-(si.goe)§	89.54	5.73	77.40	97.30	Mesofacial
(si.na.a)-(si.na.ba)‡	5.59	2.17	3.00	9.30	Maxillary protrusion relative to anterior cranial base
(co.a)-(co.gn)*	27.3	7.07	17.10	43.10	Skeletal class II
Dental analysis					
a.pg-as.is†	43.17	7.24	32.70	54.10	Proinclination of the maxillary incisors
a.pg-ai-ii†	25.79	5.64	18.70	25.79	Normal inclination of the mandibular incisors
a.pg-is†	12.75	3.39	8.20	18.30	Protrusion of the maxillary incisors
a-pg.ii†	5.45	3.93	0.40	12.70	Protrusion of the mandibular incisors

For definitions see:
*McNamara.[18]
†Ricketts.[16]
‡Steiner.[14,15]
§Jaraback and Fizzel.[17]
‖Riolo et al.,[20] Björk,[19] Solow and Sarnas.[21]

Table IV. Frequency of (po.or-pns-ans) variable

Angulation	*Frequency*	*%*
Decreased	4	40.0
Increased	3	30.0
Normal	3	30.0

Table V. Frequency of (si-na-ba) variable

Angulation	*Frequency*	*%*
<131	1	10
131<×<131.9	2	20
>132	7	70

because our data show decreased length of the anterior and posterior cranial base. Furthermore, total maxillary length and mandibular corpus are decreased. Skeletal class II malocclusion is a common feature in CdC patients, the result of a protruding maxilla that makes the condition worse, because of the short anterior cranial base and mandibular retrognathism influenced by a larger cranial base angle.

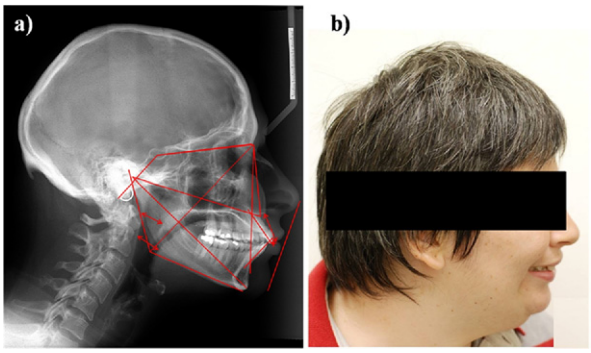

Fig. 1. Summary of the principal craniofacial characteristics of a patient with cri-du-chat syndrome. **a,** Profile x-ray of a patient with cri-du-chat syndrome with skeletal class II malocclusion caused by mandibular retrognathism with marked dental biprotrusion, decreased angulation, and maxillary height. A small upper airway can also be observed. **b,** Profile photograph of the same cri-du-chat patient.

The examination was performed on adult patients with a mean age of 23.9 ± 6.7 years. A changing phenotype is described in older CdC patients.[38,39] With advancing age, the phenotype becomes less striking. The face lengthens, the hypertelorism and epicanthus attenuate, and mandibular hypoplasia becomes less evident. Additionally, decayed teeth are described. These changes were not found in the results reported by Mainardi et al.[40] We found marked dental biprotrusion and skeletal class II malocclusion on the radiographic images; other studies were based on clinical follow-up pictures. Clinical pictures would mask real craniofacial and dentofacial relationships (Fig. 1).

F1

CONCLUSIONS

Based on cephalometric findings, CdC patients have a specific craniofacial morphology involving skeletal class II malocclusion caused by a protruding maxilla with marked dental biprotrusion. Anomalies of the cranial base, such as an increased cranial base angle, together with a marked palatal plane angle and a small upper airway, may play a part in some of the common clinical features of this syndrome, such as the characteristic catlike cry. Because there were no data about the topic before publication, the present study contributes to our knowledge of the cranial and dentofacial characteristics of CdC patients.

UNCITED REFERENCES

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AQ: 7

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AQ: 4

REFERENCES

1. Lejeune J, Lafourcade J, Berger R, Vialatte J, Boeswillwald M, Seringe P, et al. Trois Cas de deletion partielle du bras court d'un chromosome 5. C R Hebd Seances Acad Sci 1963;257:3098-102.
2. Overhauser J, Huang X, Gersh M, Wilson W, McMahon J, Bengtsson U, et al. Molecular and phenotypic mapping of the short arm of chromosome 5: Sublocalization of the critical region for the cri-du-chat syndrome. Hum Mol Genet 1994;3:247-52.
3. Simmons AD, Goodard SA, Gallardo TD, Overhauser J, Lovett M. Five novel genes from the cri-du-chat critical region isolated by direct selection. Hum Mol Genet 1995;4:295-302.
4. Niebuhr E. The Cri du Chat syndrome. Epidemiology, cytogenetics and clinical features. Hum Genet 1978;44:227-75.
5. Higurashi M, Oda M, Iijima K, Iijima S, Takeshita T, Watanabe N, et al. Livebirths prevalence and follow-up of malformation syndromes in 27,472 newborns. Brain Dev 1990;12:770-3.
6. Schinzel A, editor. Catalogue of unbalanced chromosome aberrations in man. Berlin: Walter de Gruyter; 1984.
7. Gersh M, Goodart SA, Pasztor LM, Harris DJ, Weiss L, Overhauser J. Evidence for a distinct region causing a cat-like cry in patients with 5p deletions. Am J Hum Genet 1995;56:1404-10.
8. Mainardi PC. Cri du Chat syndrome. Orphanet J Rare Dis 2006;1:33-42.
9. Kitsiou-Tzeli S, Dellagrammaticas HD, Papas CB, Ladas ID, Bartsocas CS. Unusual ocular findings in an infant with cri-du-chat syndrome. J Med Genet 1983;20:304-7.
10. Mainardi PC, Pastore G, Castronovo C, Godi M, Guala A, Tamiazzo S, et al. The natural history of Cri du Chat syndrome. A report from the Italian Register. Eur J Med Genet 2006; 49:363-83.
11. Weiss L, Reynolds WA. Osseus malformations associated with chromosome abnormalities. Orthop Clin North Am 1972;3:713-32.
12. Dallapiccola B, Pistocchi G, Forabosco A, Capra L. Skeletal changes in the "cri-du-chat" syndrome. Acta Genet Med Gemellol (Roma) 1973;22:39-44.
13. Kjaer I, Niebuhr E. Studies of the cranial base in 23 patients with cri-du-chat syndrome suggest a cranial developmental field involved in the condition. Am J Med Genet 1999;82:6-14.
14. Steiner CC. Cephalometrics for you and me. Am J Orthod 1953;39:729-55.
15. Steiner CC. Cephalometrics in clinical practice. Angle Orthod 1959;29:8-29.
16. Ricketts RM. Cephalometric analysis and synthesis. Angle Orthod 1961;31:141-56.
17. Jarabak JR, Fizzel JA, editors. Aparotologia del Arco de Canto com Alambres Delgados. Buenos Aires: Editorial Mundi; 1975. p. 613-1236.
18. McNamara JA. A method of cephalometric evaluation. Am J Orthod 1984;86:449-69.
19. Björk A. Cranial base development. Am J Orthod 1955;41:198-225.
20. Riolo ML, Moyers RE, McNamara JA, Hunter WS, editors. An atlas of craniofacial growth: cephalometric standards from the University School Growth Study, the University of Michigan. Ann Arbor: The University of Michigan; 1974.

21. Solow B, Sarnäs K-V. A comparison of the adult Swedish and Danish craniofacial morphology. Swed Dent J Suppl 1982;15: 229-37.
22. Arisaka H, Sakuraba S, Matsumoto M, Kitahama H, Furuya M, Yoshida K, et al. Airway evaluation by CT imaging for cri-du-chat syndrome. J Anesth 2006;20:258-9.
23. Collins MSR, Eaton-Evans J. Growth study of Cri du Chat syndrome. Arch Dis Child 2001;85:337-8.
24. James AE, Merz T, Janower M, Dorst J. Radiological features of the most common autosomal disorders: trisomy 21-22 (mongolism or down's syndrome), trysomy 18, trisomy 13-15, and the cri du chat syndrome. Clin Radiol 1971;22:417-33.
25. Torres CP, Torsatto MC, de Queiroz AM, Rosetti FC, Orsi I. Cri du Chat syndrome: a case report. Spec Care Dentist 2005;25: 286-8.
26. Rodríguez-Caballero A, Torres-Lagares D, Rodríguez-Pérez A, Hernández-Guisado J, Machuca-Portillo G. Cri du Chat syndrome: a critical review. Med Oral Patol Oral Cir Bucal 2010;15:e473-8.
27. Ward PH, Engel E, Nance WE. The larynx in the cri du chat (cat cry) syndrome. Laryngoscope 1968;78:1716-33.
28. Colover J, Lucas M, Comley JA, Roe AM. Neurological abnormalities in the "cri-du-chat syndrome. J Neurol Neurosurg Psychiatry:35:711-9.
29. Moss ML. Correlation of cranial base angulation with cephalic malformations and growth disharmonies of dental interest. NY State Dent 1955;24:452-4.
30. James GA. Cephalometric analysis of 100 Class II div II malocclusion with special reference to the cranial base. Dent Pract 1963;14:35-46.
31. Houston WJB. A cephalometric analysis of Angle Class II div II malocclusion in the mixed dentition. Dent Pract 1967;17:372-6.
32. Kerr WJS, Adams CP. Cranial base and jaw relationship. Am J Anthropol 1986;77:213-20.
33. Magalhães MH, da Silveira CB, Moreira CR, Cavalcanti MG. Clinical and imaging correlations of Treacher Collins syndrome: report of two cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007;103:836-42.
34. Bacon W, Eiller V, Hildwein M, Dubois G. The cranial base in subjects with dental and skeletal Class II. Eur J Orthod 1992;14:224-8.
35. Dibbets JMH. Morphological associations between the Angle classes. Eur J Orthod 1996;18:111-8.
36. Rothstein T, Yoon-Tarlie C. Dental and facial skeletal characteristics and growth of males and females with Class II division I malocclusion between the ages of 10 and 14—part. I: Characteristics of size, form and position. Am J Orthod Dentofac Orthop 2000;117:320-2.
37. Klocke A, Nanda RS, Kahl-Nieke B. Role of cranial base flexure in developing sagittal jaw discrepancies. Am J Orthod Dentofac Orthop 2002;122:386-91.
38. Van Buggenhout GJCM, Pijkels E, Holvoet M, Schaap C, Hamel BCJ, Fryns JP. Cri du Chat syndrome: changing phenotype in older patients. Am J Med Genet 2000;90:203-15.
39. Posmik R, Panasiuk B, Yatsenko SA, Stankiewicz P, Midro AT. A natural history of a child with monosomy 5p syndrome (cat-cry/cri-du-chat syndrome) during the 18 years of follow-up. Genet Couns 2005;16:17-25.
40. Mainardi PC, Perfumo C, Calì A, Coucourde G, Pastore G, Cavani S, et al. Clinical and molecular characterisation of 80 patients with 5p deletion: genotype-phenotype correlation. J Med Genet 2001;38:151-8.

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