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A Heliövaara
K Hurmerinta

Craniofacial cephalometric morphology in children with CATCH 22 syndrome

Authors' affiliations:
Arja Heliövaara, Kirsti Hurmerinta,
Department of Plastic Surgery, Cleft Center, Helsinki University Central Hospital, HUS, Finland

Correspondence to:
Dr Arja Heliövaara
Department of Plastic Surgery
Cleft Center
Helsinki University Central Hospital
PO Box 266
FIN-00029 HUS
Finland
Tel.: +358-9-471 87247
Fax: +358-9-471 87654
E-mail: arja.heliovaara@mbnet.fi

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Structured abstract

Authors – Heliövaara A, Hurmerinta K

Objectives – To evaluate cephalometrically the craniofacial, pharyngeal and cervical morphology in children with CATCH 22, and to compare and quantify the findings with age- and sex-matched controls.

Design – A retrospective case–control study.

Setting and Sample Population – Forty-one children (20 girls) with CATCH 22 were compared with age- and sex-matched controls from lateral cephalograms taken at the mean age of 8.5 years (range 5.8–12.9). The deletion of 22q11 was verified by fluorescence *in situ* hybridization techniques. Thirteen of the children with CATCH 22 had palatal clefts.

Outcome measure – Linear and angular measurements were obtained from lateral cephalograms. A Student's *t*-test and a paired Student's *t*-test were used in the statistical analysis. Standard deviation scores (SDS) were calculated to quantify the variation.

Results – Children with CATCH 22 had obtuse cranial base angles and long anterior cranial bases. Their faces were long with increased facial convexity. The maxillae were long but both jaws were retrognathic and the lower jaws posteriorly diverged. The pharynges were wide in the nasopharyngeal area and narrow in the hypopharyngeal area. The development of the hyoid bones was delayed, and hyoid bone and atlas lengths were reduced. The morphology of the children with CATCH 22 with and without a palatal cleft was similar. Despite several statistically significant differences between the children with CATCH 22 and the controls, the SDS did not exceed ±2 for any of the measurements.

Conclusion – Children with CATCH 22 have several minor distinctive morphological features in the craniofacial, pharyngeal, and cervical areas.

Key words: 22q11 deletion; CATCH 22; cephalometrics; craniofacial morphology; pharynx

Introduction

Deletion of chromosome 22q11 is a frequent cause of birth defects, with an incidence of 1 in 4000–5000 live births (1,2). The deletion has been reported in association with more than 80 different birth defects and malformations occurring in many combinations and with widely differing severity (2). The deletion 22q11 (OMIM 188400, 3) is linked to DiGeorge syndrome (DGS), velocardiofacial (or Shprintzen, CATCH 22) syndrome, conotruncal anomaly face syndrome, Cayler syndrome, and Opitz GBBB syndrome. Although published estimates vary, it is likely that 5–10% of the deletions are inherited (2). The 22q11 deletion syndrome can be inherited in an autosomal dominant fashion or result from a *de novo* deletion or translocation (4). The deletion of 22q11 is diagnosed by fluorescence *in situ* hybridization (FISH) techniques.

The CATCH 22 acronym outlines the main clinical symptoms that are caused by defects in chromosome 22q11, which are cardiac abnormality, abnormal facies, T-cell and immune deficit due to thymic hypoplasia, cleft palate and hypocalcemia due to hypoparathyroidism (5). Some form of congenital heart defect is found in 75% of patients with 22q11 deletions (6). A variety of cardiac malformations are seen, in particular affecting the outflow tract. Deletions of 22q11 may be involved in 5% of all newborns with heart defects (1), and it is the single most important cause of heart malformations after Down syndrome (7). Hypocalcemia is seen in 10–20% of patients, usually presenting between birth and 3 months of age with a variety of symptoms including seizures, tremors, and rigidity (8,9). A cleft of the secondary palate is present in more than 85% of patients (1). Velopharyngeal insufficiency (VPI) is common both in patients with and without a palatal cleft.

Learning disabilities are seen in almost all individuals with 22q11 deletions (8,9). Ceponiene et al. (10) have found auditory sensory impairment in children with CATCH 22 syndrome when studying the neurofunctional bases of their language and learning disabilities. Other typical findings include speech and language deficits (11), and behavior and personality problems (12,13). Short stature is reported in 35–40% of individuals with 22q11 deletion (9).

Facial dysmorphism is pronounced in individuals with 22q11 deletion (4,14). The face in velocardiofacial syndrome (VCF) is usually long with vertical excess, malar flatness, and mandibular retrusion (15–17). The nose is prominent, with squared nasal root, hypoplastic alae nasi, and narrow nasal passages (15,16). The ears are low set and deficient in vertical diameter. The philtrum is long with a thin upper vermilion border, and the mouth is often held open (14,18). Microcephaly occurs in 40% of individuals with deletion of 22q11 (18,19).

Although the facial features of 22q11 deletions are well characterized, only one study describing the cephalometric morphology of VCF is available. Arvystas and Shprintzen (15) studied the cranial base angle in 13 children with VCF, ranging in age from 3 to 11 years. They found that children with VCF have obtuse angulation of the cranial base, which may help to explain the facial features of retrognathia, malar flatness, and the prominence of the nasal root. However, their study only gives information of the cranial base of 13 children with VCF. As facial dysmorphism is pronounced in children with CATCH 22 it is plausible that the craniofacial cephalometric morphology of these children is also affected. The aim of this study was to evaluate cephalometrically the craniofacial, pharyngeal and cervical morphology in children with CATCH 22 syndrome, and to compare and quantify their morphology with age- and sex-matched controls.

Materials and methods

The sample comprised 41 children with CATCH 22 syndrome who had attended the Cleft Center, Department of Plastic Surgery, Helsinki University Central Hospital during the years 1980–2005. In all patients the deletion of 22q11 was verified by FISH techniques. The mean age of the children was 8.5 years (range 5.8–12.9). Half of the children (20/41) were girls. Thirteen of the children had palatal clefts, seven had isolated cleft palates, and six submucous cleft palates. Submucous cleft palates were verified in the Cleft Center either

clinically or by nasopharyngoscopy. Twenty-two of the children with CATCH 22, 10 with and 12 without a palatal cleft, had had surgery to treat VPI.

The primary operations on the cleft palate were performed at the Cleft Center at the age of 9 months with modifications of Veau-Wardill-Kilner and Cronin techniques. Velopharyngeal surgery was carried out using superiorly based flaps, modified Honig flaps (n = 17), and Hogan flaps (n = 2) at a mean age of 5.8 years (range 4.2–7.1). In two cases, augmentation pharyngoplasty with cartilage transplanted into the posterior pharyngeal wall had been done. According to the hospital records eight children with CATCH 22 (one with and seven without a palatal cleft) needed surgery because of VPI after the cephalometric evaluation.

Craniofacial morphology was assessed using standardized lateral cephalometric radiographs, taken with the head positioned according to the Frankfort horizontal plane, with molar teeth occluded and lips in repose. Twenty-seven landmarks were identified and digitized using Numonics and Digital-X-metrics software programs (Smart System Oy 1996, Turku, Finland). For linear measurements, the enlargement (10%) was corrected. Cephalometric values of the children with CATCH 22 were compared with the values of 41 healthy age- and sex-matched controls collected from the normative Finnish database of the Department of Orthodontics, University of Helsinki. The difference in age between each of the comparative pairs was less than 6 months. In order to calculate the error of the method, 20 (N) randomly selected cephalograms were redigitized within a 2-week period and the distance (d) between the first and second tracing was calculated using the formula $\sqrt{(\sum d^2/2N)}$. The range of error between registrations was 0.9 mm for linear measurements and 1.1° for angular measurements. The reference points and landmarks are shown in Fig. 1.

A Student's t-test was used to compare the children with CATCH 22 with and without clefts. A Student's paired t-test was used to compare the children with CATCH 22 with age- and sex-matched controls. The standard deviation scores (SDS) were calculated to quantify the cephalometric measurements: SDS = mean value of the CATCH 22 measurement minus the mean value of the norm divided by the standard deviation of the norm.

The research protocol was approved by the Helsinki University Central Hospital.

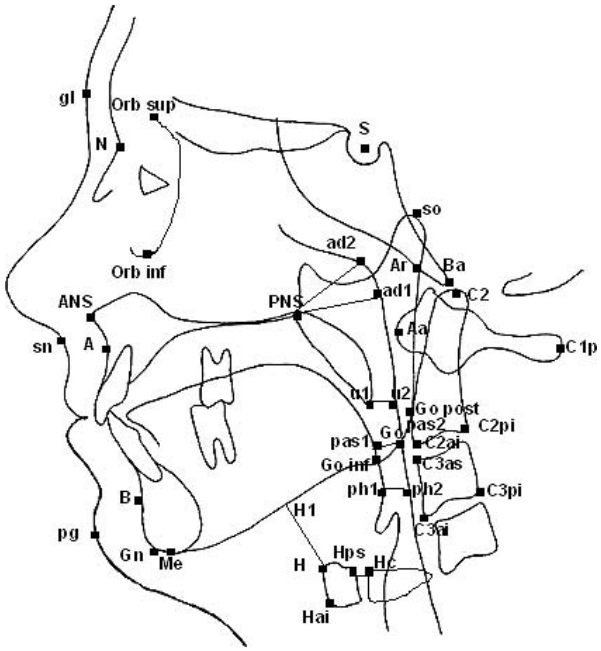

Fig. 1. Cephalometric landmarks used in this study. Abbreviated and full names and definitions. A: subspinale, the most posterior point of the anterior contour of the upper alveolar process; Aa: atlas anterior, the most anterior point of the atlas; ad1: the intersection of the line PNS-Ba and the posterior nasopharyngeal wall; ad2: the intersection of the line PNS-so and the posterior nasopharyngeal wall; ANS, anterior nasal spine, tip of anterior nasal spine; Ar: articulare, the intersection between the posterior border of the mandibular condyle and the lower border of the cranial base; B, supramentale, the most posterior point on the anterior contour of the lower alveolar process; Ba: basion, the lowest point on the anterior border of the foramen magnum; C1p: the most posterior point of atlas; C2: the most superior point of Dens; C2ai: the most anterior and inferior point of Dens; C3as: the most anterior and superior point of the third cervical vertebra; C3ai: the most anterior and inferior point of the third cervical vertebra; C3pi: the most posterior and inferior point of the third cervical vertebra; gl: glabella, the most anterior point of the soft tissue of the forehead; Gn: gnathion, the most anterior and inferior point on the mandibular symphysis; Go: gonion, the midpoint of the angle of the mandible; Go inf: gonion inferior, the most inferior point at the angle of the mandible; Go post: gonion posterior, the most posterior point at the angle of the mandible; H: hyoid bone, the most anterior and superior point of the body of the hyoid bone; Hai: the most anterior and inferior point of the body of the hyoid bone; Hps: the most posterior and superior point of the body of the hyoid bone; Hc: most anterior and superior point of the cornu major of the hyoid bone; H1: the projection point of H, perpendicular distance of point H on the mandibular plane (line Me-Go inf); Me: menton, the most inferior point of the mandibular symphysis; N: nasion, the most anterior point of the frontonasal suture; Orb inf: Orbita inferior, the most inferior point of the orbita; Orb sup: orbita superior, the most superior point of the orbita; pas1: the intersection of the line B-Go and the anterior pharyngeal wall; pas2: the intersection of the line B-Go and the posterior pharyngeal wall; pg: pogonion, the most prominent point of the soft tissue chin; ph1: the point of the tongue base that is closest to the posterior pharyngeal wall; ph2: the point on posterior pharyngeal wall that is closest to ph1; PNS: posterior nasal spine, the tip of the posterior nasal spine; S: sella, the center of the sella turcica; sn: subnasale, the point at which the columnella merges with the upper lip; so: midpoint of the distance from points S to Ba; u1: uvula, the most inferior tip of the soft palate; u2: the point on the dorsal pharyngeal wall that is closest to u1.

Results

Because the Student's *t*-test did not reveal any significant differences between the craniofacial, pharyngeal and cervical measurements of the children with CATCH 22 with and without a palatal cleft, the children with CATCH 22 were pooled for further analysis. The measurements of the children with CATCH 22 and the controls, and the comparisons using the Student's paired *t*-test are shown in Table 1. The children with CATCH 22 had obtuse cranial base angles. Their anterior cranial bases were long and the posterior cranial bases were short. Their faces were long with increased facial convexity. Maxillary lengths were increased, but both jaws were retrognathic and the lower jaws posteriorly diverged. The pharynges were wide in the nasopharyngeal area and narrow in the hypopharyngeal area. Hyoid bone and atlas lengths were reduced. The hyoidal gaps, which reflect the fusion of the hyoidal segments, the hyoidal cornu major and the base, were larger than those of the controls. Despite several statistically significant differences between the children with CATCH 22 and the controls, the SDS did not exceed ±2 for any of the measurements.

Discussion

The present study confirms earlier findings and provides new information about the distinctive craniofacial, pharyngeal, and cervical morphology of children with CATCH 22. Several statistically significant differences were found between children with CATCH 22 and controls. However, the SDS did not exceed ±2 for any of the measurements. It is of interest that even if CATCH 22 with a palatal cleft is a combination of a cleft and a syndrome, it seems to be associated with similar craniofacial morphology as CATCH 22 without a palatal cleft. On the other hand, the number of children with CATCH 22 with palatal clefts was small.

Our findings concerning the cranial base are in agreement with Arvystas and Shprintzen (15), who found that children with VCF have obtuse cranial base angles. In the present study, the anterior cranial base length was also larger, and the posterior cranial base length shorter. The differences in the size and angulation of the cranial base may partly explain mandibular retrognathia as well. It has been postulated that mandibular retrognathia in children with VCF can be a result of a posterior positioning of the entire mandibular complex in a posteriorly displaced cranial fossa (15). The fact that there were no significant differences in the size of the mandible in the present study adds validity to this statement. On the other hand, the children with CATCH 22 had greater maxillary length than the control children. This was not to be expected as children with cleft palates are reported to have shorter and more retruded maxillas than those without clefts (20). It is possible that the larger anterior cranial base length in children with CATCH 22 may also affect the length of maxillae.

A long face with vertical excess is one of the most typical facial features of children with CATCH 22 (15–17). Our study confirms these findings. The more vertical growth pattern and the differences in cranial base angulation, anterior facial height and mandibular inclination might reflect different modes of respiration between the children and more 'mouth-breathers' in CATCH 22 children. This is supported by the habitual open mouth posture of the children with CATCH 22. Associations between functional patterns and craniofacial morphology have been shown (21). Several factors may impair nasorespiratory function in children with CATCH 22. In patients with clefts, maxillary growth deficits constrict the nasal floor, reduce airway size, and increase nasal airway resistance (22), which can lead to mouth breathing. Furthermore, secondary procedures for VPI, such as a pharyngeal flap, increase the prevalence of mouth breathing (23).

In the present study, 22 of 41 of the children with CATCH 22 had had velopharyngeal surgery prior to the cephalometric evaluation, and eight needed velopharyngeal surgery after the cephalometric evaluation. The goal of surgical treatment in patients with VPI is to provide velopharyngeal competence either by improving velar function or by restricting the passage between the oropharynx and nasopharynx. The possible harmful effects of velopharyngeal surgery in patients with and without clefts include immediate or persistent airway obstruction, snoring and sleep apnea (24–26). In this study, the symptoms of apnea could not be registered retrospectively. However, obstructive sleep apnea occurs in 50% and hypotonia is observed in 70–80% of infants with 22q11 deletions (19). Long and McNamara (27) have reported more vertical facial growth direction after velopharyngeal flaps (VPP), whereas others have

Table 1. **The means, standard deviations, and the *p*-values of the cephalometric variables in paired Student's *t*-test between the children with CATCH 22 and the controls. The standard deviation scores (SDS) are given only for the values that were larger than 1 or less than −1**

	CATCH 22	SD	Controls	SD	*p*-value	SDS > 1 or <−1
Cranial measurements						
Cranial base angle, N–S–Ba (°)	136.9	6.4	132.3	4.7	0***	
Anterior cranial base, S–N (mm)	63.1	3.4	59.2	3.5	0***	1.1
Posterior cranial base, S–Ba (mm)	34.7	2.6	36.8	3.1	0.005**	
Facial measurements						
Facial height, N–Me (mm)	98.9	5.4	93.1	5.1	0***	1.1
Upper facial height, N/ANS–PNS (mm)	43.4	3	41.4	3.3	0.006**	
Lower facial height, ANS–Me (mm)	58	3.3	53.3	3.6	0***	1.3
Orbital height, Orb inf–Orb sup (mm)	31.9	3.8	29.4	3.7	0.008**	
Facial angle, S–N/Me–Go inf (°)	39.8	6.6	34.8	3.5	0***	1.4
Mandibular angle, ANS–PNS/Me–Go inf (°)	32.2	4.9	27.9	3.9	0***	1.1
Palatal angle S–N/ANS–PNS (°)	7.6	3.5	7.1	3.7	0.517	
Maxillary protrusion, SNA (°)	79.2	4.1	81	3.7	0.04*	
Mandibular protrusion, SNB (°)	74.2	4.6	76.8	3.1	0.009**	
Sagittal jaw relationship, ANB (°)	5.1	2.8	4.2	2.2	0.143	
Maxillary length, ANS–PNS (mm)	46.8	2.3	44	3.2	0***	
Mandibular length, Go–Gn (mm)	59.1	5.6	59	4.5	0.291	
Gonial angle, Me–Go inf./Ar–Go post. (°)	131.1	6.3	128.5	6.4	0.11	
Convexity angle, gl–sn/sn–pg (°)	17.6	6.4	12.1	4.2	0***	1.3
Pharyngeal measurements						
PNS–ad1 (mm)	19.7	4.1	17.9	4.1	0.049*	
PNS–ad2 (mm)	16.3	3.9	12.5	3	0***	1.3
u1–u2 (mm)	10.7	4.2	10.5	2.5	0.813	
pas1–pas2 (mm)	11.3	3.9	13.2	3.6	0.028*	
ph1–ph2 (mm)	9.7	3.6	11.1	3.5	0.091	
Hyoidal measurements						
H–H1 (mm)	10.1	4.8	10.3	4.1	0.929	
Hyoid height, H–Hai (mm)	4.7	1.3	5	1.6	0.433	
Hyoid length, H–Hps (mm)	3.7	1.2	5.1	1.3	0***	−1.1
Hyoidal gap, Hps–Hc (mm)	2.2	1.7	1.3	1.1	0.035	
Cervical measurements						
Dens height, C2–C2ai (mm)	24.8	2.9	25.5	12.7	0.743	
Atlas body length, Aa–C1p (mm)	34.3	3	38.2	4.2	0***	
C3 height, C3as–C3ai (mm)	5.5	1.4	5.6	0.9	0.188	
C3 length, C3ai–C3pi (mm)	11.2	3.7	10.7	2	0.466	

failed to substantiate the long-term effects on midfacial growth (28–30). In children with submucous cleft palate, VPP has been associated with narrowing of the lower pharyngeal airway dimensions (31).

In addition to the functional adaptations and surgical iatrogenesis, the obtuse cranial base angle, the dysmorphology of the midface and the vertebral column may interfere with nasopharyngeal growth in children with CATCH 22. Williams et al. (32) have found evidence of congenital hypoplasia of the adenoids in over four-fifths of patients with VCF syndrome. They suggested that this contributes to their hypernasal speech, because velopharyngeal closure during speech is normally aided by the

adenoids. A shortcoming of our study is that it was not possible to distinguish between patients with or without adenoidectomy and to evaluate the effect of adenoids on the size of nasopharyngeal airways. However, besides the morphologic dimensions of the nasopharyngeal port, velopharyngeal valving is dependent on the sensorimotor adequacy of the velum and its synergistic musculature (33).

Before the diagnostic use of the FISH hybridization techniques, delayed ossification of the hyoid bone was suggested to be a useful tool in the diagnosis of DGS during the first postnatal months (34). According to this study, ossification of the hyoid bone is delayed even in older children with CATCH 22 (mean age 8.5 years). In addition, the hyoid bone was short. The infants with clefts have also been shown to have significant hyoid bone abnormalities such as abnormal shape (35). The hyoid bone has an important role in respiration, deglutition, and speech. In children with CATCH 22, hypotonia of the velopharyngeal muscles, delayed development of the hyoid bone and nasal speech may be related. The hyoid bone has been shown to have a more superior and posterior position in patients with hyperdivergent vertical facial growth (36). Although our children with CATCH 22 showed hyperdivergent facial growth, no differences were observed in relation to the position of the hyoid bone.

In the cervical area, the heights of the second and third vertebrae were similar to the controls, but the atlases were short. This reflects the broad spectrum of the findings on CATCH 22 syndrome. A high prevalence of cervical vertebral anomalies has also been observed in children with clefts (37,38). Three-dimensional findings of the cervical spine of cleft infants have shown a significantly smaller height of vertebral bodies with larger intervertebral spaces and fusion of the posterior arches of the cervical spine (35).

The findings of the present study provide support for the concept that CATCH 22 syndrome is a part of a broad craniofacial anomaly with several minor distinctive morphological features in the craniofacial, pharyngeal, and cervical areas.

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