

Clinical Paper
Craniofacial Anomalies

Extracraniofacial anomalies in Treacher Collins syndrome: A multicentre study of 248 patients

C. A. Beaumont^a, D. J. Dunaway^b,
B. L. Padwa^c, C. Forrest^d,
M. J. Koudstaal^{a,b,c},
C. J. J. M. Caron^{a,b}

^aThe Dutch Craniofacial Center, Department of Oral and Maxillofacial Surgery, Erasmus University Medical Center, Sophia's Children's Hospital, Rotterdam, the Netherlands; ^bThe Craniofacial Unit, Great Ormond Street Hospital, London, UK; ^cThe Craniofacial Centre, Boston Children's Hospital, Boston, MA, USA; ^dThe Center for Craniofacial Care and Research, SickKids Hospital, Toronto, Canada

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Abstract. Treacher Collins syndrome (TCS) is a congenital malformation of the craniofacial structures derived from the first and second pharyngeal arches. The craniofacial deformities are well described in the literature. However, little is known about whether there are associated extracraniofacial anomalies. A retrospective study was conducted using data from four craniofacial units. Medical charts were reviewed for the presence and type of extracraniofacial anomalies, as well as age at diagnosis. A possible correlation between the severity of the phenotype and the presence of extracraniofacial anomalies was assessed using the Hayashi classification. A total of 248 patients with TCS were identified; 240 were confirmed to have TCS, of whom 61 (25.4%) were diagnosed with one or more extracraniofacial anomalies. Ninety-five different extracraniofacial anomalies were found; vertebral ($n = 32$) and cardiac ($n = 13$) anomalies were most frequently seen, followed by reproductive system ($n = 11$), central nervous system ($n = 7$), and limb ($n = 7$) anomalies. No correlations between tracts were found. Extracraniofacial anomalies were more prevalent in these patients with TCS compared to the general population (25.4% vs 0.001–2%, respectively). Furthermore, a positive trend was seen between the severity of the syndrome and the presence of extracraniofacial anomalies. A full clinical examination should be performed on any new TCS patient to detect any extracraniofacial anomalies on first encounter with the craniofacial team.

Keywords: Treacher Collins syndrome; Mandibulofacial dysostosis; Congenital heart defect; Urogenital abnormalities; Central nervous system; Congenital limb deformities; Retrospective study.

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Treacher Collins syndrome (TCS) is a rare congenital craniofacial condition. It affects 1 in 50,000 live births.^{1,2} The disorder is caused by abnormalities in

the development of the first and second pharyngeal arches, resulting in craniofacial malformations.¹ TCS is an autosomal dominant disorder.² Mutations in the

TCOF1 gene, and in a smaller percentage in *POLR1D* and *POLR1C*, are found to be responsible for the resulting phenotype.² However, in some patients no mutations in

these genes are detected. In more than 60% of the patients with TCS there is no previous family history and the condition is thought to arise as a result of a de novo mutation.^{2,3} The severity of the phenotype varies among individuals but is in general characterized by bilateral hypoplasia of the facial skeleton, absence of the ears, down-slanting palpebral fissures and eyelid colobomas, cleft palate, and dental hypoplasia.⁴⁻⁶ The deformity results in an abnormal facial appearance, and patients diagnosed with TCS frequently undergo multiple reconstructive procedures.¹ Consequently, patients often suffer from aesthetic and/or psychological problems.⁷

Functional difficulties in patients with TCS have been well described. Over 90% of the patients are diagnosed with unilateral or bilateral conductive hearing loss as a result of external auditory canal abnormalities and/or middle ear deformities.⁸ Furthermore, underdevelopment of the facial skeleton (i.e., maxilla, mandible, and zygomatic arches) can result in breathing difficulties including obstructive sleep apnoea (OSA). The prevalence of OSA in patients with TCS is higher than in a population without facial malformations: 46% versus 2.2–3.8%, respectively.⁹⁻¹¹ The most severely affected patients are at risk of life-threatening airway compromise after birth, resulting in the need for intubation or tracheostomy.⁹ Other affected orofacial functions include reduced jaw opening (63%), malocclusion (94%), and feeding difficulties (68%).¹² Feeding difficulties are common in patients with craniofacial syndromes as well, although the prevalence in TCS is not well described.¹³

The treatment of patients with TCS might be challenging due to the severity of the phenotypic expression, and necessitates a multidisciplinary approach. An objective assessment is needed to describe the clinical features, plan the treatment, and evaluate the outcome. Hayashi et al. described a grading system for classifying TCS patients^{13,14}. Using this system, clinical features can be scored according to the degree of severity in each region and patients are then classified into three different grades. This grading system includes the typical craniofacial malformations that have been well documented in the literature.^{1,5,8,13,15}

However, little is known about whether extracraniofacial anomalies are common in patients with TCS. Extracraniofacial anomalies are defined as congenital anatomical malformations in visceral systems outside the head region, including the circulatory, pulmonary, urinary, and reproductive systems, and vertebral/spine

anomalies. Extracraniofacial anomalies are seen in other congenital craniofacial disorders (craniofacial microsomia, CFM) that arise from defects in the first and second pharyngeal arches.¹⁶⁻¹⁸ A recent study found a correlation between CFM and reported prevalence rates for extracraniofacial anomalies ranging from 10% to 26.1%.¹⁷ TCS shares many characteristics with CFM. It is hypothesized that extracraniofacial anomalies occur more frequently than expected in patients with TCS.¹⁹⁻²⁴ There appear to have been no retrospective cohort studies focusing on the presence of extracraniofacial anomalies in TCS. Knowledge of the prevalence of extracraniofacial anomalies in TCS patients is important for (prenatal) screening and early intervention if needed.

The aim of this study was to provide an overview of the prevalence of extracraniofacial anomalies in patients diagnosed with TCS. Four different craniofacial units located in Boston, London, Rotterdam, and Toronto collaborated in this study, which made it possible to study one of the largest populations of this patient group worldwide.

Materials and methods

The data used in this retrospective study were collected by reviewing the patient records of patients diagnosed with TCS in craniofacial units at Great Ormond Street Hospital, London, UK; Erasmus MC, Rotterdam, the Netherlands; Boston Children's Hospital, Boston, Massachusetts, USA; and SickKids Hospital, Toronto, Canada. This study was approved by the institutional review boards by all four hospitals.

The medical records of patients who presented to the clinics between 1960 and 2016 and were diagnosed with TCS were reviewed. As the diagnosis of TCS is mainly based on clinical characteristics, patients with clinical and/or radiographic images or a clinical description suspected for TCS were included for further analysis. Deceased patients were also included. Patients were excluded if the diagnosis of TCS was not certain due to missing data or the presence of other craniofacial syndromes (e.g., Nager syndrome or craniofacial microsomia).

The medical records were used to document age, sex, presence of extracraniofacial anomalies, and severity of the phenotype. Extracraniofacial anomalies were categorized into cardiac, vertebral, central nervous system, pulmonary, gastrointestinal, renal, limb, and reproductive system anomalies. These subgroups were

chosen to cover most of the extracraniofacial tracts. Anomalies that could not be categorized into one of these subgroups were categorized as 'other'. Once categorized, the conditions were further reviewed for the type of anomaly, the age at which the anomaly was diagnosed, the type of treatment performed, and the age at which treatment was performed. For the data collection, each anomaly was counted once, although some patients had two or more anomalies. When no information on a history of extracraniofacial anomalies was found, patients were categorized as having no extracraniofacial anomaly.

A possible relationship between the phenotypic severity of the TCS and the presence of extracraniofacial anomalies was examined by classifying the patients with the Hayashi classification.¹⁴ The Hayashi classification scores the severity of deformities in several anatomical regions of the face, i.e., the malar bone, the lower eyelid, the mandible, the ear, the palate, and the nasal root, which possibly gives a more adequate assessment of the degree of severity than classifications only describing the severity of anomalies in one particular anatomical region, such as the orbitozygomatic complex or the mandible.^{25,26}

One examiner (CB) was trained in classifying the patients and performed all classifications based on both medical photography and radiography. The mean Hayashi score of subjects with extracraniofacial anomalies was compared to the mean Hayashi score of subjects without extracraniofacial anomalies.

All statistics consist of descriptive numerical and categorical data. Descriptive statistics were used to give an overview of the population studied. The statistical analyses were performed using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA). *P*-values of <0.05 were considered to be statistically significant.

Results

Study population

From 1960 to 2016, a total of 248 patients were diagnosed with TCS. The patients were born between 1941 and September 2015. Eight patients were excluded because of missing data and the presence of other craniofacial syndromes besides TCS. No additional information on extracraniofacial anomalies was found in the medical records of 179 patients. In total, 61 patients were diagnosed with at least

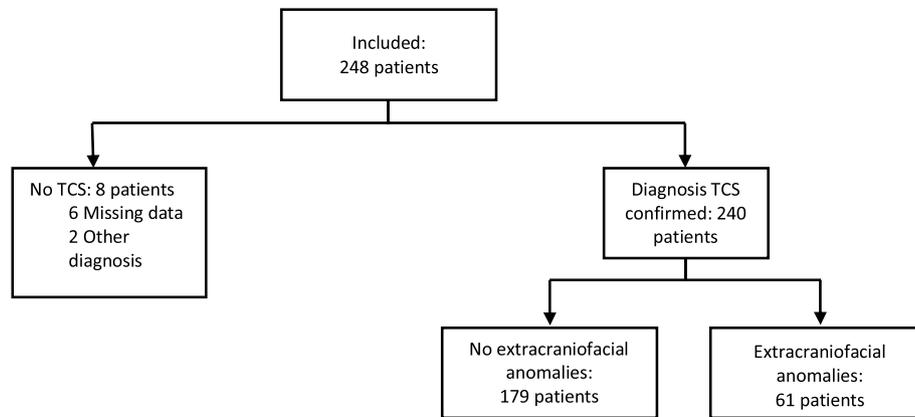


Fig. 1. Presence of extracraniofacial anomalies in Treacher Collins syndrome.

Table 1. Description of the study population.

	Total	Extracraniofacial anomalies	
		Yes	No
Sex			
Male	127	36	91
Female	113	25	88
Mean Hayashi score (SD)	8.8 (3.8)	10 (4.3)	8.1 (3.3)

SD, standard deviation.

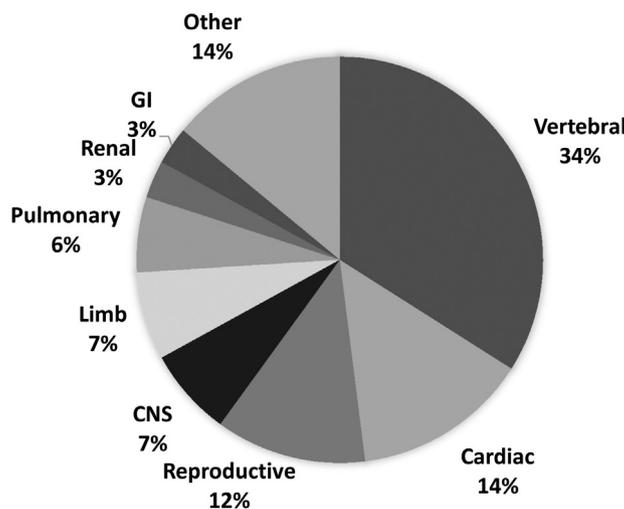


Fig. 2. Distribution of extracraniofacial anomalies among the different tracts.

one extracraniofacial anomaly (25.4%), and this group was included for further analysis (Fig. 1). Table 1 gives an overview of the basic characteristics of the patients in this cohort.

Extracraniofacial anomalies

A total of 95 extracraniofacial anomalies were found in this patient group (n = 61). The mean age at the time of diagnosing the extracraniofacial anomaly was 2.4 years.

Thirty-five patients were diagnosed with only one extracraniofacial anomaly.

The distribution of the findings in the different tracts among the 95 extracraniofacial anomalies can be found in Fig. 2. Vertebral and cardiac anomalies were most prevalent, with prevalence rates of 34% and 14%, respectively. Anomalies of the gastrointestinal and renal tracts were least prevalent, both at 3%.

In total, 32 vertebral anomalies were found in 27 patients, of whom 17 were male and 10 were female (Table 2). The

mean age at which the vertebral anomalies were diagnosed was 5.0 ± 6.5 years. Scoliosis was most frequently seen (n = 14), followed by pectus excavatum (n = 10). Two patients suffered from both scoliosis and pectus excavatum. Spina bifida and pectus carinatum were each diagnosed in two patients. No data on the therapy given was documented in the medical records.

A total of 13 cardiac anomalies were detected in nine patients, five male and four female (Table 3). The mean age at which the cardiac anomalies were diagnosed was 8 months ± 1.5 years. Four patients had a patent ductus arteriosus at birth, one of whom needed ligation therapy; three closed spontaneously. One patient presented with a ventricular septal defect (VSD) and an atrial septal defect (ASD); the VSD was closed surgically (age unknown) and the ASD was thought to be of no clinical significance. One patient presented with an ASD and ventricular septal hypertrophy at birth; no symptoms or treatment were documented. One patient had a grade 2/6 high-pitched systolic ejection murmur, and an echocardiogram showed a small VSD, which closed spontaneously at the age of 8 months. One patient had a patent foramen ovale at the age of 8 months, which closed spontaneously at the age of 1.5 years. One patient suffered from a cardiorespiratory arrest immediately after birth and died after resuscitation. This patient's echocardiogram showed a 2-mm patent ductus arteriosus with a left to right shunt. It was unclear whether this was the cause of death or not.

Congenital anomalies in the reproductive system occurred in nine patients, all of whom were male. In total, 11 anomalies were diagnosed (Table 4). The mean age at diagnosis in this subgroup was 6 ± 8 months. Three patients suffered from phimosis. Two patients had hypospadias,

Table 2. Vertebral anomalies.

Vertebral anomalies	Number (%)
Scoliosis	14 (43.8%)
Pectus excavatum	10 (31.3%)
Spina bifida occulta	2 (6.3%)
Pectus carinatum	2 (6.3%)
Hypoplastic rib	1 (3.1%)
Sacralization of the left L5 vertebral body	1 (3.1%)
Tietze syndrome	1 (3.1%)
Occipital plagiocephaly	1 (3.1%)
Total	32

Table 3. Cardiac anomalies.

Cardiac	Number
Patent ductus arteriosus	4 (30.8%)
Ventricular septal defect (VSD)	3 (23.1%)
Atrial septal defect (ASD)	2 (15.4%)
Ventricular septal hypertrophy	1 (7.7%)
Cardiomegaly	1 (7.7%)
Bicuspid aortic valve	1 (7.7%)
Patent foramen ovale	1 (7.7%)
Total	13

Table 4. Anomalies of the reproductive system.

Reproductive system	Number
Phimosis	3 (27.3%)
Hypospadias	2 (18.2%)
Undescended testicle	2 (18.2%)
Hydrocele testis right side	1 (9.1%)
Testis asymmetry	1 (9.1%)
Absent testicle	1 (9.1%)
Micropenis	1 (9.1%)
Total	11

which required meatoplasty and circumcision in both cases. Two patients had a unilateral undescended testicle, of which one was corrected with orchidopexy at the age of 2 months. One patient was born with unilateral hydrocele. One patient was born with underdeveloped external genitalia, with a hypoplastic penis and scrotum, undescended testes, and phimosis. No information on the treatment given was found.

Seven central nervous system anomalies were described in seven different patients, of whom six were male and one was female. The patients were diagnosed at a mean age of 6 ± 11 months. Two sacral dimples were seen at birth.

One patient was diagnosed with a syrinx in the spine. One patient was born with hydrocephalus, resulting in motor and sensory difficulties early in life.

There were seven types of limb anomaly that occurred in six different patients, two male and four female. The deformities were diagnosed at birth. The anomalies included pes planus, toe syndactyly, absent and hypoplastic thumbs, fusion between carpal bones, and undefined hand deformity. The treatment given consisted of pollicization in the case of absent thumbs and extension/abduction splinting.

Six pulmonary anomalies in six patients were found, of whom two were

male and four were female. Pulmonary anomalies were detected at a mean age of 1.7 ± 1.5 years. Three patients suffered from (laryngo)tracheomalacia. One patient was diagnosed with bronchomalacia and one patient had a tracheal stenosis. One laryngeal anomaly was documented, without a specific description or radiographic imaging.

Three renal anomalies in two different patients were found. One patient was male and one was female. The mean age of these patients at the time of diagnosis was 2.3 ± 0.6 years. One patient suffered from congenital bilateral hydronephrosis in combination with a non-functioning left kidney. Prenatal ultrasound of another patient showed a renal duplex system. No specific treatment was given.

Three patients, one male and two female, suffered from gastrointestinal anomalies at birth, including pyloric stenosis and oesophageal atresia. One patient with oesophageal atresia was treated with a jejunostomy at the age of 11 months.

Anomalies categorized as 'other' consisted of bilateral inguinal hernia, unilateral inguinal hernia, congenital haemangioma, unilateral absence of the parotid gland, pharyngeal hypoplasia, hiatal hernia, and missing olfactory bulb.

Twenty-six patients were diagnosed with two or more extracraniofacial anomalies. One patient was diagnosed with four anomalies in two tracts. Six patients were diagnosed with three extracraniofacial anomalies in one or two tracts, i.e. two and four patients, respectively. Eighteen patients were diagnosed with two anomalies in one or two tracts, i.e. seven and 11 patients, respectively. Three patients had a vertebral anomaly as well as an anomaly in the reproductive system. Two patients suffered from a central nervous system anomaly in combination with a limb anomaly. No other specific combinations were seen.

Hayashi classification

Clinical pictures of 196 patients in this cohort were available and 65 patients had preoperative radiographic imaging. With these images it was possible to classify 60

Table 5. Overview of the distribution of patients graded with the Hayashi classification.

Number of extracraniofacial anomalies	Hayashi classification			Total
	Grade 1 (% of total)	Grade 2 (% of total)	Grade 3 (% of total)	
0	22 (78)	16 (70)	2 (22)	40
1	4 (14)	4 (17)	3 (33)	11
2	1 (4)	3 (13)	4 (44)	8
3	1 (4)	0	0	1
<i>n</i> (% of total)	28 (47)	23 (38)	9 (15)	60

patients using the Hayashi classification. Of these 60 classified patients, 20 were diagnosed with extracraniofacial anomalies and 40 did not have any extracraniofacial anomalies.

In the group with extracraniofacial anomalies, six patients were classified as grade 1, seven as grade 2, and seven as grade 3. The mean Hayashi score in this group was 10.0 ± 4.3 . The group of 40 patients who were classified according to the Hayashi classification but had no extracraniofacial anomalies had a mean score of 8.1 ± 3.3 . The distribution of patients among the different grades is shown in Table 5. Patients with extracraniofacial anomalies were significantly more often classified as Hayashi grade 3 than patients without extracraniofacial anomalies (Pearson $\chi^2 = 9.873$ (2), $P = 0.007$) (Table 5).

Discussion

The aim of this study was to investigate the prevalence of extracraniofacial anomalies in patients with TCS. By merging the data of four craniofacial units, it was possible to present a large cohort ($N = 248$) of patients diagnosed with TCS.

The prevalence of extracraniofacial anomalies in this cohort was 25.4%. This is significantly higher than the 0.001–2% described in the general live born population.²⁷

In the study population, vertebral anomalies were most prevalent, followed by cardiac, reproductive system, central nervous system, and limb anomalies. The coexistence of facial and vertebral and spine anomalies can partly be explained by the embryological origin of these structures. From weeks 3 to 8 in utero, the paraxial mesoderm differentiates into somites, part of which later develop into the vertebrae.²⁸ At the same time, neural crest cells migrate into the pharyngeal arches, which later form the skeletal components of the face.²⁹ If genetic changes occur during this embryonic period, both developmental processes are prone to be affected. The presence of facial anomalies in combination with spine anomalies has been observed in other craniofacial conditions.^{28,30,31} The prevalence (11.3%) found in the present patient cohort corresponds with the results of previous studies, and the results might be explained by the embryogenic origin and default migration of both the paraxial mesoderm and neural crest cells. Hence, it is plausible that this combination may also apply to TCS.

In the study cohort, 13 cardiac anomalies were found in nine patients, which is equivalent to 3.8% of the total patient group. One study reported congenital cardiac defects in 8% of patients with the *TCOF1* gene.³² Experiments with 13-cis retinoic acid (Accutane) describe a possible association between the TCS phenotype and the presence of congenital cardiac defects.^{33–35} In these experiments, mice were given Accutane and this resulted in TCS phenotypes. Accutane is known to kill neural crest cells and to interfere with their migration.³³ Neural crest cells populate the pharyngeal arches and the developing truncus arteriosus and conus cordis. Thus, an abnormality in Accutane metabolism could affect crest cells, resulting in craniofacial anomalies and also abnormalities of the great vessels, such as tetralogy of Fallot, transposition of the great vessels, and septal defects.¹⁸

Oesophageal atresia was described in two patients in this cohort, which is higher than the general incidence of oesophageal atresia (1 in 3500 live births).²⁷ A possible association between mandibulofacial dysostosis (MFD) and oesophageal atresia has been described previously in the literature. Originally, MFD and TCS were described as different diagnoses, but today they are used as eponyms for the same craniofacial disorder.¹⁵ Gordon et al. reviewed 14 patients with MFD and oesophageal atresia and found that a mutation in the *EFTUD2* gene may be responsible for oesophageal atresia as a common additional feature of TCS.³⁶ In situ hybridization on embryonic mice using labelled *EFTUD2* probes was performed in this previous study. Strong expression of the probes was seen in the mesenchyme of the trachea and oesophagus, as well as the mandibular mesenchyme and otic vesicle. Another study described the *EFTUD2* gene as one of the genes responsible for the development of MFD.³⁷ Combining these results, it is thought that insufficiency of the *EFTUD2* gene causes the oesophageal abnormalities in combination with cranial malformations seen in MFD as well as TCS.

In this study, as many patients as possible were classified with the Hayashi classification. To classify a patient correctly, a computed tomography scan (unoperated) or panoramic radiograph of good quality and clinical photographs are required, which is the reason why not every patient could be classified; hence the absolute numbers are small. However, when observing percentages, a significant correlation was found between the severity of TCS and the presence of extracraniofacial anomalies. In addition, the mean

Hayashi score in the extracraniofacial anomalies group was found to be higher than the mean Hayashi score in the no extracraniofacial anomalies group, which is in line with our hypothesis. However, the patient numbers are small, so care must be taken when drawing conclusions. Future studies should also focus on inter-observer reliability when using this classification.

This study has several limitations including incomplete medical charts that did not provide information on whether extracraniofacial anomalies were present or not. This means that either the patient had no extracraniofacial anomaly or the physician did not discover the abnormality; hence, the prevalence of extracraniofacial anomalies reported here will be an underestimation. However, if the patient does not experience symptoms, the clinical relevance of knowledge of the anomaly is questionable.

A number of patients received (surgical) treatment in order to prevent severe complications resulting from the extracraniofacial anomaly. However, again some data were missing because patients were treated in another hospital or the reports lacked specific information about the type of treatment. Therefore, it was not possible to give a representative overview of the treatment given in the total patient group. Nevertheless, an overview with representative prevalence numbers is provided, which was the main purpose of this study.

In short, this study of a cohort of 248 patients diagnosed with TCS showed that extracraniofacial anomalies are significantly more prevalent in patients with TCS than in the general population: 25.4% vs 0.001–2%, respectively. Vertebral and cardiac anomalies were most frequently seen, but not specifically as a combination. Based on the prevalence of specific extracraniofacial anomalies in combination with their clinical relevance, it cannot be concluded that specific tests are indicated in a protocolled screening method (e.g. echocardiogram, ultrasonography, spine radiography). However, we recommend that clinicians fully examine a new TCS patient so that cardiac, vertebral, renal, reproductive system, limb, and other anomalies are recognized as soon as possible. Knowledge and awareness of the prevalence of extracraniofacial anomalies is important to improve the multidisciplinary treatment of this challenging patient group.

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None.

Competing interests

None.

Ethical approval

Ethical approval was given by the ethics committee of the Erasmus Medical Centre (Reference number: MEC-2015-539).

Patient consent

Not applicable.

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Corresponding author at: Department of Oral and Maxillofacial Surgery
Erasmus University Medical Center
Sophia Children's Hospital Rotterdam
's Gravendijkwal 230
3015 CE Rotterdam
The Netherlands
E-mail: c.caron@erasmusmc.nl