Surgical and Radiologic Anatomy (2019) 41:601–605
https://doi.org/10.1007/s00276-018-2137-7

ANATOMIC VARIATIONS

Multiple muscular abnormalities in a fetal cadaver with CHARGE syndrome

Orhan Beger[1] · Turan Koç[1] · Burhan Beger[2] · Hakan Özalp[3] · Vural Hamzaoğlu[3] · Yusuf Vayisoğlu[4] · Derya Ümit Talas[4] · Zeliha Kurtoğlu Olgunus[1]

Received: 31 July 2018 / Accepted: 16 November 2018 / Published online: 21 November 2018

Abstract

The CHARGE syndrome characterized by coloboma, heart defects, atresia of the choanae, retarded growth, genitourinary hypoplasia, and ear anomalies is one of the rare syndromes. Although certain clinical issues (scapular winging, sloping shoulder, Sprengel's deformity, kyphosis and scoliosis) which could be related to abnormalities in musculoskeletal structures of the neck and shoulder have been identified in CHARGE syndrome, data on details of muscle anomalies seem to be quite limited in the literature. In this case report, bilateral multiple muscular abnormalities (agenesis of the trapezius, presence of the rhombo-atloid muscle, and presence of the bipartite rhomboid minor with superficial and deep parts) was presented in a fetus cadaver with atypical CHARGE syndrome to attract the attention of clinicians for definitive diagnoses and surgical reconstruction of the shoulders deformity such as scapular winging and Sprengel's deformity. By considering the previous studies, we propose that the absence of the trapezius, as well as the other muscle abnormalities around the neck and shoulder, should be revised as being a component of CHARGE syndrome.

Keywords CHARGE syndrome · Rhomboid minor · Rhombo-atloid muscle · Semicircular canals · Trapezius muscle

Introduction

A group of certain congenital anomalies (C—Coloboma; H—Heart disease; A—Atresia of the choanae; R—Retardation of the growth and development; G—Genital Hypoplasia or genitourinary anomalies; E—Ear anomalies and/or deafness), identified by Hittner et al. [7]) and Hall [6] was coined as the acronym "CHARGE" association by Pagon et al. [10]. Pagon et al. [10] also notified that minor anomalies such as cleft palate, cleft lip, omphalocele, swallowing difficulty, hypopituitarism, facial asymmetry, facial palsy, micrognathia and tracheoesophageal fistula may be accompanied with CHARGE association. With the belief that it may be a single pathogenetic basis, CHARGE association was defined as CHARGE syndrome by Blake et al. [4]. After a short time, Vissers et al. [14] declared that the cause of CHARGE syndrome was the mutations in the chromodomain helicase DNA-binding protein 7 gene (CHD7). By the time, many anomalies such as scapular winging, sloping shoulder, Sprengel's deformity, kyphosis, syndactyly, camptodactyly, scoliosis, osteoporosis, and vesicoureteric reflux have been reported to accompany CHD7-related disease [5, 8, 9]. However, the data on muscular abnormalities seem to be quite limited in patients with this phenotype [9].

In this case report, to identify the cause of scapular winging, sloping shoulder, Sprengel's deformity, kyphosis and scoliosis in CHARGE syndrome more precisely, we present multiple muscle abnormalities in the shoulder and neck region of the fetal cadaver with this phenotype.

✉ Orhan Beger
obeger@gmail.com

[1] Department of Anatomy, Mersin University Faculty of Medicine, Ciftlikkoy Campus, 33343 Mersin, Turkey

[2] Department of Pediatric Surgery, Van Yüzüncü Yıl University Faculty of Medicine, Van, Turkey

[3] Department of Neurosurgery, Mersin University Faculty of Medicine, Mersin, Turkey

[4] Department of Otorhinolaryngology, Mersin University Faculty of Medicine, Mersin, Turkey

Case report

During dissections in 10% formalin fixed 26-week-old male human fetus at Department Anatomy laboratory, Medicine Faculty, Mersin University, hypoplastic semicircular canals, left cochlear nerve absence, cleft lip and cleft palate anomalies were identified (Figs. 1, 2). Multiple muscle abnormalities were encountered in the shoulder and neck region of the fetal cadaver: 1—bilateral absence of the trapezius, 2—bilateral bipartite rhomboid minor with superficial and deep parts, and 3—bilateral presence of the rhombo-atloid muscle. The latter variant muscle originated from the transverse process of the atlas, passed deep to the levator scapulae superiorly and superficial to the splenius cervicis inferiorly. After passing deep to both parts of rhomboid minor, the variant muscle was attached to spinous process of T2–4 on both sides (Fig. 3). Morphometric data of the rhomboid major, rhomboid minor, and levator scapulae of our case was compared with the values calculated using regression formula of Beger et al. [2]. All measurements were found smaller than normal fetus (Table 1).

Discussion

CHARGE syndrome occurring at 1 in 8500 or 10,000 live births is one of the rare syndromes characterized by ocular coloboma, heart defects, choanal atresia, growth deficiency, genitourinary hypoplasia, ear anomalies, brainstem dysfunctions, and mental retardation [5–8, 10]. This syndrome is thought to be a consequence of mutations in the CHD7 gene [14], but approximately 25–30% of the clinical

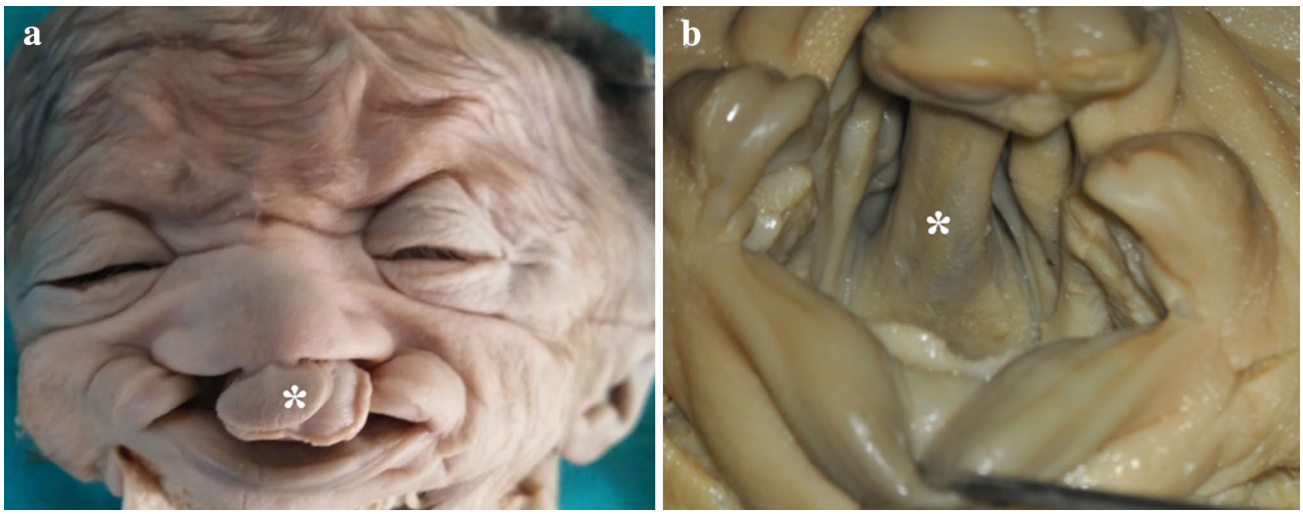

Fig. 1 The asterisks show **a** the cleft lip and **b** cleft palate on the fetal cadaver

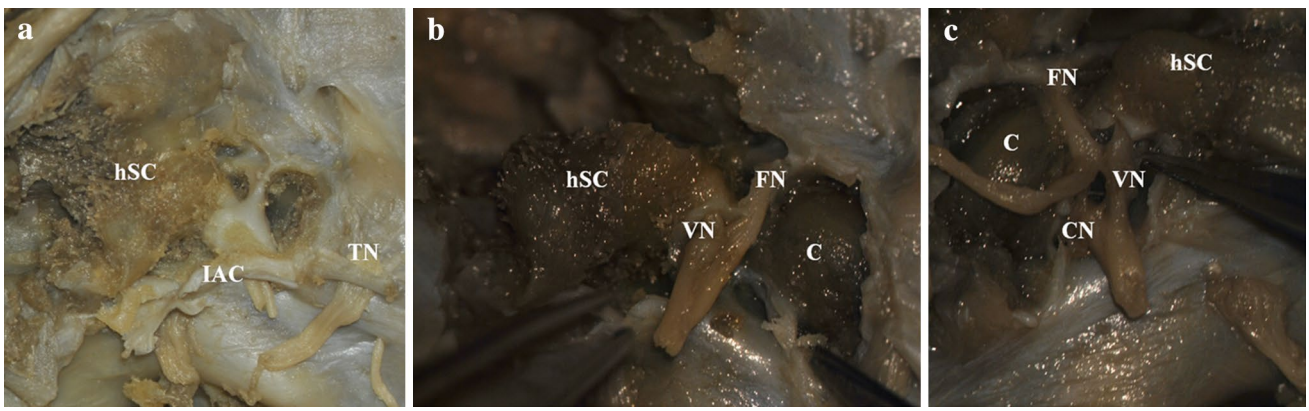

Fig. 2 The photographs show **a** the hypoplastic semicircular canals (hSC), **b** the cochlear nerve absence in the left side, **c** the cochlear nerve presence in the right side. *TN* trigeminal nerve, *VN* vestibular nerve, *FN* facial nerve, *CN* cochlear nerve, *IAC* internal acoustic canal, *C* cochlea

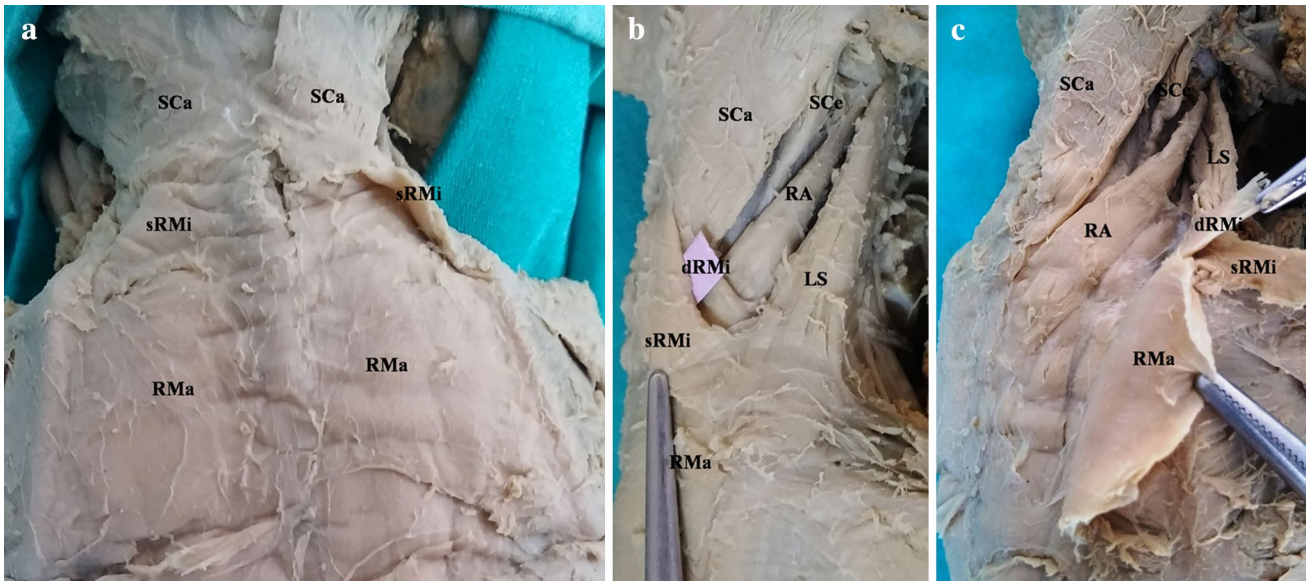

Fig. 3 The photographs show **a** the bilateral absence of the trapezius, **b** the presence of the rhombo-atloid muscle (RA) and presence of the rhomboid minor separated into superficial (sRMi) and deep (dRMi) parts, **c** the presence of RA. *SCa* splenius capitis, *SCe* splenius cervicis, *LS* levator scapulae, *RMa* rhomboid major

Table 1 Morphometric data of the muscles in our case evaluated regarding the data from regression formulas of Beger et al. [2]

Muscles	Parameters	Our case (right/left)	Calculated values [2][a]
Levator scapulae	Length of anterior margin (mm)	21.98/20.17	30.87
	Length of posterior margin (mm)	19.17/19.30	30.13
	Width (its widest level) (mm)	5.94/5.71	6.74
Rhomboid major	Length of medial margin (mm)	22.66/21.82	28.49
	Length of lateral margin (mm)	22.41/21.96	25.99
	Width of superior margin (mm)	14.25/14.15	17.28
	Width of inferior margin (mm)	16.98/17.10	21.75
Rhomboid minor (Superficial—deep part)	Length of medial margin (mm)	6.13/7.24–5.89/6.04	9.47
	Length of lateral margin (mm)	5.97/6.25–6.01/5.71	8.55
	Width of superior margin (mm)	14.72/14.51–14.22/14.31	16.82
	Width of inferior margin (mm)	15.13/15.22–14.96/14.49	17.57
Rhombo-atloid	Length of anterior margin (mm)	30.97/30.46	–
	Length of posterior margin (mm)	23.65/24.09	–
	Width (its widest level) (mm)	7.01/6.79	–

[a]The values belong to Beger et al. [2] obtained from their regression formula by taking into account 26-week-old fetus

cases detected in this phenotype are reported to be lack of the CHD7 gene mutation [5, 15]. For this reason, clinical diagnosis is important in patients with CHARGE syndrome [5, 15]. Pagon et al. [10] notified that a patient must have at least four of the most common findings that make up the acronym "CHARGE" association to diagnose. Blake et al. [4] defined the findings of CHARGE syndrome as 4C criteria (Coloboma, atresia of the Choanae, Characteristic ears abnormalities, and Cranial nerve dysfunctions) and minor criteria (genital hypoplasia, development delay, cardiovascular malformations, growth deficiency, cleft lip, cleft palate, tracheoesophageal fistula, and characteristic face). The authors explained that a patient must have 4C criteria or 3 major criteria (any 3 of the 4C) and 3 minor criteria to be CHARGE syndrome [4]. Verloes [13] reconsidered the major and minor components of CHARGE syndrome and classified the findings of this phenotype to be typical (2 major and 2 minor criteria), partial (2 major and 1 minor

criteria), and atypical (2 major criteria or 1 major and 3–5 minor criteria). Wineland et al. [15] proposed changing the name of the syndrome to 3C (coloboma, choanal atresia, and semicircular canal anomaly) to focus on the most important clinical findings of CHARGE syndrome, especially semicircular canal hypoplasia.

Due to the presence of bilateral cleft palate in our case, choanal atresia was not observed. In addition, coloboma was not found in our fetal cadaver. In patients genetically identified with CHARGE syndrome, it was declared in the previous studies that the most persistent finding is semicircular canal hypoplasia [15]. In addition, classical choanal atresia and coloboma may not be seen [5, 15]. Atypical CHARGE syndrome was predicted in our fetal case in the direction of one major criterion (semicircular canal hypoplasia) and 3 minor findings (absence of the cochlear nerve, cleft palate/lip, and muscle abnormalities).

One of the muscular abnormalities of our case, bipartite rhomboid minor with superficial and deep parts has not been encountered in the literature. Additionally, a variant muscle originated from the transvers process of atlas and attached to T2–4 spinous process was detected on both sides. This variant muscle is called "rhombo-atloid" (the splenius accessory, the adjuvant splenius, the musculus singularis splenius accessory, the splenius capitis accessory, and the splenius colli accessory) [12]. This variant muscle close to medial spinal attachment of the rhomboid minor was reported to attach to the spinous processes of C6–C7, C7, T1, T1–T2, or T2–T3 [12]. In our study, the variant muscle was attached to the T2–T4 spinous processes.

Partial or complete absence of unilateral or bilateral trapezius is reported as a part of Poland's Syndrome, Prune Belly Syndrome or Eagle-Barrett Syndrome [1, 16]. O'Grady et al. [9] stated a de novo missense variant in patients with CHARGE syndrome including hypoplasia of the trapezius and sternocleidomastoid in addition to hypoplasia of the paraspinal muscles. An experimental study on zebrafish model showed that reductions in CHD7 expression lead to disorders in the organization of cranial motor nerves [11]. O'Grady et al. [9] proposed that hypoplasic trapezius and sternocleidomastoid may be associated with impaired cranial nerve organization. They suggested that the abnormalities observed in paraspinal muscles may be expressed by the abnormal migration and differentiation of muscle progenitor cells [9]. Our findings including the left cochlear nerve absence, bilateral trapezius agenesis, and presence of the rhombo-atloid muscle and bipartite rhomboid minor seems to support O'Grady et al.'s [9] interpretation. As cranial nerve dysfunctions do not explain the cause of presence of the rhombo-atloid muscle and bipartite rhomboid minor as well as previously mentioned paraspinal muscle abnormalities, we proposed that those issues could also be handled in a part of CHARGE syndrome.

Allouh et al. [1] indicated a case of complete unilateral absence of the trapezius in a cadaver with enlarged levator scapulae and rhomboid muscles. Due to being seen as the anomalies such as scapular winging in patients with CHARGE syndrome and the use of the Eden-Lange procedure in the treatment of these abnormalities [3], algebraic anatomy of the levator scapulae, rhomboid major and rhomboid minor can be important for muscle transfers or transposition. Beger et al. [2] calculated the linear functions about growth of the levator scapulae, rhomboid major and rhomboid minor lengths and widths in normal human fetuses. When the measurements belong to these muscles in our case were compared with the values calculated from the linear functions of Beger et al. [2] for the same age, all values were found smaller than the normal (Table 1).

Conclusion

In the literature, we did not encounter any case including the agenesis of trapezius, the presence of rhombo-atloid muscle and bipartite rhomboid minor accompanied to CHARGE syndrome. The deformities of neck, shoulder and vertebral column, i.e. scapular winging, sloping shoulder, Sprengel's deformity, kyphosis, scoliosis could require surgical reconstruction by considering local structures. However, structural details underlying these pathological conditions have not been established in the clinical cases with CHARGE syndrome adequately. We propose that the complex muscular abnormalities in the neck and shoulder region could be taken into account in patients with CHARGE syndrome. Furthermore, detailed intracranial examination is of great importance for early diagnosis of anomalies such as semicircular canal and/or cochlear nerve abnormalities to overcome any management delays, in cases with apparent external anomalies such as cleft palate/lip and sloping shoulder.

Author contributions OB: Project development, Data collection, Data analysis, Manuscript writing, Manuscript editing. TK: Project development, Data collection, Data analysis, Manuscript writing, Manuscript editing. BB: Project development, Data analysis, Manuscript editing. HÖ: Project development, Data analysis, Manuscript editing. VH: Project development, Data analysis, Manuscript editing. YV: Project development, Data analysis, Manuscript editing. DÜT: Project development, Data collection, Data analysis, Manuscript editing. ZKO: Project development, Data collection, Data analysis, Manuscript editing.

Funding None.

Compliance with ethical standards

Conflict of interest The authors have no conflict of interest or financial ties to disclose.

References

1. Allouh M, Mohamed A, Mhanni A (2004) Compete unilateral absence of trapezius muscle. MJM 8:31–33
2. Beger O, Dinç U, Beger B, Uzmansel D, Kurtoğlu Z (2018) Morphometric properties of the levator scapulae, rhomboid major, and rhomboid minor in human fetuses. Surg Radiol Anat 40(4):449–455
3. Bigliani JU, Compito CA, Duralde XA, Wolfe IN (1996) Transfer of the levator scapulae, rhomboid major, and rhomboid minor for paralysis of the trapezius. J Bone Jt Surg Am 78:1534–1540
4. Blake KD, Davenport SLH, Hall BD et al (1998) CHARGE association: an update and review for the primary pediatrician. Clin Pediatr (Phila) 37(3):159–173
5. Blake KD, Prasad C (2006) CHARGE syndrome. Orphanet J Rare Dis 7(1):34
6. Hall BD (1979) Choanal atresia and associated multiple anomalies. J Pediatr 95(3):395–398
7. Hittner HM, Hirsch NJ, Kreh GM, Rudolph AJ (1979) Colobomatous microphthalmia, heart disease, hearing loss, and mental retardation: a syndrome. J Pediatr Ophthalmol Strabismus 16(2):122–128
8. Issekutz KA, Smith IM, Prasad C, Graham JM Jr, Blake KD (2005) An epidemiological analysis of CHARGE syndrome: preliminary results from a Canadian study. Am J Med Genet A 133A(3):309–317
9. O'Grady GL, Ma A, Sival D et al (2016) Prominent scapulae mimicking an inherited myopathy expands the phenotype of CHD7-related disease. Eur J Hum Genet 24(8):1216–1219
10. Pagon RA, Graham JM Jr, Zonana J, Young SL (1981) Coloboma, congenital heart disease, and choanal atresia with multiple anomalies: CHARGE association. J Pediatr 99(2):223–227
11. Patten SA, Jacobs-McDaniels NL, Zaouter C, Drapeau P, Albertson RC, Moldovan F (2012) Role of Chd7 in Zebrafish: a model for CHARGE syndrome. PLoS One 7(2):e31650
12. Tubbs RS, Shoja MM, Loukas M (2016) Bergman's comprehensive encyclopedia of human anatomic variation. Wiley-Blackwell, Hoboken, p 279
13. Verloes A (2005) Updated diagnostic criteria for CHARGE syndrome: a proposal. Am J Med Genet A 133A(3):306–308
14. Vissers LE, van Ravenswaaij CM, Admiraal R et al (2004) Mutations in a new member of the chromodomain gene family cause CHARGE syndrome. Nat Genet 36(9):955–957
15. Wineland A, Menezes MD, Shimony JS, Shinawi MS, Hullar TE, Hirose K (2017) Prevalence of semicircular canal hypoplasia in patients with CHARGE syndrome: 3C syndrome. JAMA Otolaryngol Head Neck Surg 143(2):168–177
16. Yiyit N, Işıtmangil T, Oztürker C (2014) The abnormalities of trapezius muscle might be a component of Poland's syndrome. Med Hypotheses 83(5):533–536