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Congenital respiratory tract disorders in 22q11.2 deletion syndrome

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ABSTRACT

Objective: Respiratory tract disorders have been reported in patients with 22q11.2 deletion syndrome, however infrequently. This study describes the respiratory tract disorders encountered in a cohort of 278 patients with 22q11.2 deletion syndrome.

Methods: We conducted a retrospective, cross-sectional, study at a single tertiary referral center. We identified the patients with 22q11.2 deletion syndrome and with an upper and/or lower respiratory tract disorder at our otorhinolaryngologic department. The different disorders were described.

Results: Out of 278 patients referred to the otorhinolaryngologic department, we identified 14 patients with a laryngeal and/or tracheal disorder. Nine patients had more than one congenital disorder in this anatomical area. Disorders included a choanal stenosis (n = 1), laryngeal web (n = 5), laryngeal cleft (n = 2), subglottic stenosis (n = 3), pharyngo-, laryngo-, tracheo- and/or bronchomalacia (n = 11) and tracheal stenosis (n = 1).

Conclusion: Different types of respiratory tract disorders can be present in patients with 22q11.2 deletion syndrome. Clinicians should be aware of this clinical association for timely and accurate diagnosis and treatment. In addition, the diagnosis 22q11.2 deletion syndrome should be considered in patients presenting with a congenital respiratory tract disorder.

1. Introduction

22q11.2 deletion syndrome (22q11DS) is caused by a deletion on the long arm of chromosome 22 and characterized by many different disorders, such as dysmorphic facial features, congenital cardiac anomalies (~75%), immunodeficiency (~75%), palatal abnormalities (70–100%), including velopharyngeal insufficiency (~30–90%), endocrine abnormalities, including hypocalcaemia (50–65%) and psychiatric problems, including schizophrenia (25%) [1–3]. Respiratory tract disorders are also described, however less frequently. These occur in different forms and include subglottic stenosis, laryngeal web, laryngeal cleft, laryngo-, tracheo and/or bronchomalacia [4–15]. Although rarely reported, respiratory tract disorders have important clinical implications and can even be fatal [16]. Attentiveness to these disorders in children with 22q11DS is essential, as they should be detected early and treated to avoid severe complications.

The objectives of this study were: 1. to describe the respiratory tract disorders, present in patients with 22q11DS who presented for clinical follow-up at our otorhinolaryngology department, and 2. to give an overview of reported respiratory tract disorders in patients with 22q11DS in the literature.

2. Methods

We conducted a retrospective, cross-sectional, study at a single tertiary referral center. We reviewed medical files of all patients diagnosed with 22q11DS and assessed by our otorhinolaryngology department from 1993 through April 2017. Since 2007, patients with 22q11DS have been universally referred to our institution's multidisciplinary 22q11DS team. As part of this referral, assessment by otorhinolaryngology is standard care, and does not depend on symptoms. The diagnosis 22q11DS was confirmed with fluorescence in situ hybridization or multiplex ligation-dependent probe amplification. We identified all patients with a respiratory tract disorder including pharyngeal-, laryngeal-, tracheal- and bronchial disorders. The Medical Ethics Review Committee deemed this study exempt from review due to its retrospective design.

Data including the presence of prematurity (born < 37 weeks of gestation), history of velopharyngeal insufficiency and history of congenital cardiac diseases were collected. Clinical presentation of a

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Table 1
Demographic characteristics.

	Patients (n = 14)
Median follow-up time between first DLB and last clinic visit in months (range) (n = 9)[a]	14 (0–71)
Male:female	3:11
Number of patients with DLB (%)	11 (79)
Median age in months at (first) DLB (range) (n = 9)[a]	7 (0–35)
Prematurity (%)	6 (43)
Velopharyngeal insufficiency (%) (n = 9)[b]	6 (67)
Congenital cardiac disease (%)	8 (57)

Abbreviation: direct laryngoscopy and bronchoscopy (DLB).
Legend: [a] In two patients the exact date at DLB was not reported (patient 6 and 14). [b] Nine patients were of appropriate age for speech assessment.

respiratory tract disorder comprising presence of stridor, dyspnea, a history of recurrent respiratory tract infections, feeding difficulties (including insufficient intake or swallowing dysfunction), signs of aspiration (including recurrent respiratory tract infections) or voice abnormalities were described.

We described laryngeal clefts using the classification described by Benjamin and Inglis [17]. The severity of a subglottic stenosis was graded according to the Myer-Cotton classification [18]. In describing laryngeal webs, we used the Cohen's classification [19]. Other disorders, including laryngo-, tracheo- and bronchomalacia, vocal cord anomalies or other encountered abnormalities were described by location and severity.

3. Results

Out of 278 patients with 22q11DS who were assessed by our department, we identified 14 patients with a respiratory tract disorder. All 14 patients were referred to our multidisciplinary 22q11DS team. See Table 1 for demographic characteristics. Six of the nine patients who were of appropriate age for speech assessment demonstrated velopharyngeal insufficiency.

Eleven patients underwent a direct laryngoscopy and bronchoscopy (DLB) for evaluation of stridor, dysphagia, dyspnea or the evaluation prior to tracheostomy tube decannulation. There were no airway-related mortalities in our cohort (median age at last consultation was 5 years).

Table 2 provides an overview of all encountered disorders. It shows that nine patients had more than one respiratory tract disorder (patients 1, 3, 4, 8, 9, 10, 11, 13, 14). Three patients required a tracheostomy (patients 10, 13 and 14).

As shown in Table 2, there were five patients with a laryngeal web (see Table 2). One patient had a type 1 web, two patients had a type 2, one patient a type 3 web and in one patient the grade of the web was unknown. This patient also had a tracheal stenosis which necessitated a tracheostomy at age 7 days, with subsequently dilating and stenting of the trachea. Three patients required incising of the web (patients 3, 4 and 9). In addition, there were three patients with a subglottic stenosis. Two patients had a grade 1 and one patient had a grade 3 stenosis. The latter required a single stage laryngotracheal reconstruction, with anterior and posterior costal cartilage grafting (patient 4).

The laryngeal cleft present in patients 1 and 3 (see Table 2) were both a type 1 (a cleft limited to the supraglottic and interarytenoid area) and did not require surgical treatment.

Five patients suffered from an airway malacia caused by a vascular structure compressing the airway (patients 3, 7, 8, 11 and 12). These vascular structures included a arteria lusoria, right sided aortic arch and brachiocephalic artery. The arteria lusoria was in all cases divided (patients 8, 11, 12). In one patient the tracheomalacia was treated with an aortopexy (patient 8).

Table 2
Overview of different respiratory tract disorders in 14 patients.

Patient	Clinical symptoms	DLB	Age at DLB in months	Choanal stenosis	Pharyngo-malacia	Subglottic stenosis	Laryngeal web	Laryngeal cleft	Laryngomalacia	Tracheal stenosis	Tracheomalacia	Bronchomalacia
1	Dyspnea, stridor, rec RTI	+	35 and 66	–	–	+	–	+	–	–	–	–
2	High pitched voice	–		–	–	n/a	+	n/a	n/a	n/a	n/a	n/a
3	Insufficient oral intake	+	13	–	–	–	+	+	–	–	+	+
4	Insufficient oral intake, dysphagia, dyspnea, stridor	+	10	–	–	+	+	–	–	–	+	–
5	?	–		–	–	n/a	n/a	n/a	+	n/a	n/a	n/a
6	Aspiration with rec RTI	+	?	–	–	–	–	–	–	–	+	–
7	Insufficient oral intake	+	5	–	–	–	–	–	–	–	–	+
8	Aspiration with rec RTI	+	7	–	–	–	+	–	–	–	+	+
9	Dyspnea	+	5 and 20	–	–	–	+	–	+	–	–	–
10	Dyspnea	+	0 (3 weeks) and 62	–	–	+	–	–	–	–	+	+
11	Dyspnea and rec RTI	+	7	–	–	–	–	–	–	–	+	+
12	Aspiration with rec RTI	+	17	–	–	–	–	–	–	–	+	–
13	Dyspnea	–		+	+	n/a	n/a	n/a	n/a	n/a	n/a	n/a
14	Dyspnea	+	Assumingly 1 week	–	–	–	+	–	–	+	–	–

Abbreviations: direct laryngoscopy and bronchoscopy (DLB), recurrent respiratory tract infections (rec RTI).
Legend: DLB performed or disorder present: +. DLB not performed or disorder absent: -. Not assessed (when no DLB is performed): n/a.