Received: 26 February 2018 | Revised: 18 July 2018 | Accepted: 26 July 2018

DOI: 10.1002/ajmg.a.40518

WILEY AMERICAN JOURNAL OF medical genetics PART A

RESEARCH ARTICLE

Otolaryngological features in a cohort of patients affected with 22q11.2 deletion syndrome: A monocentric survey

Fiorentino Grasso[1] | Emilia Cirillo[1] | Giuseppe Quaremba[2] | Vincenzo Graziano[2] | Vera Gallo[1] | Letizia Cruoglio[3] | Carmine Botta[4] | Claudio Pignata[1] | Sergio Motta[3]

[1]Department of Translational Medical Sciences, Pediatric section, Federico II University, Naples, Italy

[2]Department of Advanced Biomedical Sciences, Federico II University, Naples, Italy

[3]Department of Neurosciences, Reproductive and Odontostomatological Sciences, Federico II University, Naples, Italy

[4]Department of Morphologic and Functional Diagnostics, Radiotherapy and Legal Medicine, Federico II University, Naples, Italy

Correspondence
Claudio Pignata, Professor of Pediatrics, Department of Translational Medical Sciences, Pediatric section, Federico II University, via S. Pansini 5–80131, Naples, Italy.
Email: pignata@unina.it

Otorhinolaryngologic manifestations are common in 22q11.2 deletion syndrome (22q11.2DS), but poorly described. This study aimed to better define the ear-nose-throat (ENT) phenotype of 22q11.2DS patients, in the attempt to best detect subjects requiring subspecialist intervention. We enrolled 25 patients affected with 22q11.2DS. Anatomic and functional ENT findings were investigated using clinical, laboratory, and instrumental data. Immunophenotype and frequency of infections were evaluated. Univariate and multivariate analyses were performed. ENT anomalies were found in 88% of patients, and in 20% congenital palate defects required surgery. *Adenoid or palatine tonsil hypertrophy* was noted in 80% and 48%. Forty-eight percent of subjects had rhinolalia/phonia, severe in half of these. We also found nasal regurgitation or laryngeal penetration/aspiration in 20% and 16%, respectively. Instrumental exams revealed a mild conductive *hearing loss* in 32% (bilateral in most cases), tympanometric anomalies in 28%, and swallowing abnormalities in 16%. Statistical univariate analysis showed a direct association between rhinolalia/phonia and episodes of laryngeal aspiration (p = .016) and between tympanometric anomalies and increased adenoid volume (p = .044). No association between episodes of food aspiration and palatal anomalies was found. Moreover, no statistically significant association was observed between the number of airway infections and the ENT findings. This study contributes to better define the ENT phenotype in patients with 22q11.2DS, helpful to prevent potential complications. Furthermore, the identification of a subcategory of patients may allow the early adoption of specific speech therapy programs to improve the clinical outcome of 22q11.2DS patients.

KEYWORDS

22q11.2 deletion syndrome, DiGeorge syndrome, ENT phenotype

1 | INTRODUCTION

Chromosome 22q11.2 deletion syndrome (22q11.2DS) occurs in approximately 1:4,000 live births (Devriendt, Fryns, Mortier, van Thienen, & Keymolen, 1998; Tezenas Du Montcel, Mendizabai, Ayme, Levy, & Philip, 1996). The phenotype of this syndrome is complex and the clinical expression is highly variable. Major clinical features include conotruncal cardiac defects, neonatal hypocalcemia due to hypoparathyroidism; immunodeficiency due to thymic a/hypoplasia, recurrent respiratory infections, facial anomalies, intellectual disability, and speech delay. Renal, skeletal, and gastrointestinal anomalies may also be observed (Aloj et al., 2012; Cirillo et al., 2015; Giardino et al., 2014; Kobrynski & Sullivan, 2007; McDonald-McGinn et al., 1999; McDonald-McGinn & Sullivan, 2011; McDonald-McGinn et al., 2001). Psychiatric or autoimmune disorders may also be part of the clinical phenotype, in particular in older subjects (Bassett et al., 2005). The 22q11.2DS also includes ear-nose-throat (ENT) manifestations, whose variable expressivity has been poorly characterized so far.

Palatal abnormalities have been reported in more than half of the subjects, and the most common of these is velopharyngeal incompetence (VPI). The pathogenesis of this condition is multifactorial, being

Fiorentino Grasso, Emilia Cirillo, Claudio Pignata, and Sergio Motta contributed equally to this study.

linked to anatomical anomalies, and/or to functional alterations. Some patients exhibit submucosal cleft palate or bifid uvula, whereas overt cleft palate and cleft lip/palate are less common. Furthermore, most 22q11DS patients have speech or language difficulties related to velopharyngeal and palatal defects, which may present as hypernasal speech or increased nasal resonance (Ford, Sulprizio, & Rasgon, 2000; McDonald-McGinn et al., 1997). Bilateral conductive hearing loss is frequently reported, especially in subjects with recurrent acute bacterial or secretory otitis media. It is hypothesized that the anatomical and functional defects of palate and of Eustachian tube, in association with the immune deficiency, may contribute to the conductive loss. Only 15% of the patients have sensorineural hearing loss (Bassett et al., 2005; Digilio et al., 1999; Ryan et al., 1997; Verheij et al., 2017).

Abnormalities of the oropharyngeal and/or crico-esophageal swallowing phases are further features of 22q11.2DS children and can be responsible for dysphagia, leading to failure to thrive, and aspiration-based infections (LaMantia et al., 2016; Ryan et al., 1997).

The purpose of this study is to describe in detail the ENT phenotype of 22q11.2DS patients, in the attempt to identify functional implications of the anatomical alterations and their possible role in determining susceptibility to infections, and to highlight the otolaryngological anomalies that best identify patients to be referred for a subspecialty intervention.

2 | MATERIALS AND METHODS

We conducted a prospective study at a single Italian tertiary reference Center for Immunodeficiencies. Patients enrolled into the study were diagnosed as affected with 22q11.2DS by molecular analysis, and had an age greater than 3 years. Historical, clinical, laboratory, and instrumental data were collected for every subject. Informed consent was obtained from all patients or guardians.

Oropharingoscopy was used to define the palatine tonsils volume according to Brodsky's modified classification (Brodsky, 1989), and to establish the characteristics of the palate and its morphofunctional abnormalities (Finkelstein, Hauben, Talmi, Nachmani, & Zohar, 1992). The videonasopharyngoscopic examination was performed by flexible endoscope. When a reduced collaboration limited the execution of this exam, the data were integrated with oropharyngoscopic static and dynamic findings for the classification of any morphofunctional palatal anomalies and with videofluoroscopic findings for the classification of the adenoids volume, according to the Cassano modified classification (Cassano, Gelardi, Cassano, Fiorella, & Fiorella, 2003). The classification of nasal air emission was based on the perceptual relief of air emission during the articulation of plosive, fricative, and affricate phonemes (Kummer, 2016) integrated with the evaluation of Glatzel mirror test and of the acoustic timbre variation produced by the examiner's occlusion of nostrils during the verbal articulation. A vocal record of standard words/phrases in Italian with fricative, affricate, and plosive consonants was collected in all patients. The record was obtained through the Voice Analysis module of the digital program Daisy 3.6.13 (Biomedica Amplifon, Italy). This examination aimed to grading the articulatory alterations according to Massari modified classification (Motta & Cesari, 1996).

A videofluoroscopic study of swallowing was performed in all patients. The examination also included the evaluation of the adenoid volume, in those cases where nasopharyngoscopy was not possible. Routine audiometric and tympanometric exams were performed by standard procedures.

A phoniatrist was dedicated to the classification of objective findings including palatal abnormalities, otoscopic findings, tonsils, and adenoids volume, the latter in conjunction with the radiologist who conducted the videofluoroscopic examination. The recorded voice samples were analyzed by three experienced speech specialists independently for the grading of rhinolalia/rhinophonia.

The obtained data were classified by a semi-quantitative scale in which the increasing score indicated a progressively more severe clinical, morphological, and/or functional condition.

The immunophenotype (lymphocyte cells count, lymphocyte subset cells count, serum levels of immunoglobulin, isohemagglutinins, and antigen-specific antibodies following immunization) was evaluated in every subject.

The infections of the last 24 months were detected in all patients, considering those diagnosed at our Center and by the primary care physician, according to guidelines; we included infections of the ENT district (otitis, pharyngitis, and sinusitis) and of the lower respiratory tract. None of the patients underwent prophylactic antibiotic therapy or immunoglobulin replacement therapy.

As for the statistical analysis, in a first step, we examined the association between each pair of variables. Associations between continuous variables were examined by using Spearman rank correlation test or Pearson correlation test. The level at which results were defined as being statistically significant was set at a p value of less than .05. In a second step, we performed a hypothesis-free multivariate analysis, using factor analysis. This method divides total data variability into key components to explain the largest amount of variability in the data. Factors contributing to the same component are considered to be associated with each other. A scree plot was used to select the appropriate number of components for evaluation. The size of each variable's contribution to each factor can be determined by the factor loading size. A loading of 0.7 or greater indicates that a variable was associated with that component. A varimax rotation was used to enable a clearer interpretation of the results. Variables showing distribution to be highly skewed were analyzed on the log scale. The calculations were performed using IBM SPSS Statistics, v.20.0 software (IBM Corp. Armonk, NY).

3 | RESULTS

Our cohort of patients, as illustrated in Table 1, included 25 subjects (16 males); of these, 9 subjects are aged between 4 and 8 years, 10 between 9 and 13 years, 6 between 14 and 21 years. No patient was affected by Complete DiGeorge syndrome (ESID Diagnostic criteria) and approximately 76% of the subjects had a cardiac conotruncal defect.

The patients have been investigated about a number of anatomical and functional otolaryngological features, as detailed in Table 2. Twenty percent of the subjects had congenital palatal abnormalities

TABLE 1 Main descriptive data of the cohort of 22q11.2DS patients

No. of patients	25
Age (years) (Median [range])	10.0 (4–21)
Male (%)	64
Complete DiGeorge syndrome (%)	0
ENT anomalies (%)	88
ENT surgery (%)	20
Speech therapy (%)	60
Congenital cardiac defects (%)	76
Hypoparathyroidism (%)	12

requiring surgery, including submucous cleft palate, cleft velum, and cleft palate.

Overall, palatal abnormalities affected 21 of the 25 patients (84%): more than half of them (56%) had occult submucous cleft palate, while 20% of the subjects had a hypomobile palate, and 8% had an immobile palate. The otological exam showed normal tympanic membranes in 16 of the 25 patients (64%), bilateral retracted tympanic membrane in 8 of 25 (32%), and bilateral tympanic effusion in 1 subject (3.8%). As for the palatine tonsils volume, 13 of the 25 patients (52%) had tonsils not exceeding the pillars, 10 patients (40%) had tonsils up to 50% of the space between loggia and median line, and 2 patients (8%) had tonsils up to 75%. Moreover, 5 of the 25 patients (20%) had adenoids occupying up to 25% of the nasopharynx, 15 (60%) had adenoids occupying up to 50% and 5 (20%) had adenoids occupying up to 75% of the nasopharynx. As for the presence of rhinolalia/rhinophonia, 13 subjects (52%) had normal articulation, 7 (28%) had some typical slight articulatory defects with mild/moderate open rhinophonia (hypernasality), and 5 (20%) had constant articulatory defects with moderate/severe open rhinophonia. About the study of nasal air emission, audible inconsistent nasal emission in 7 cases (28%) and audible consistent nasal emission in 6 out of 25 cases (24%) was highlighted. Episodes of laryngeal aspiration/penetration were reported in 4 out of 25 subjects (16%), while episodes of nasal regurgitation in 7 patients (28% of the cases). Concerning the presence of food consistency restrictions, we found restriction in 1 food consistency (solid) in 5 of 25 subjects (20%), and in 2 or 3 consistencies in 2 (8%). Finally, about respiratory pattern in our patients, 5 out of 25 subjects (20%) were mouth breathers, and 8 out of 25 (32%) were mixed breathers.

Instrumental investigations were carried out to better characterize the patients. Bilateral type B tympanogram was found in 5 out of 25 subjects (20%), unilateral type B in 1 (4%), bilateral type C in 1 (4%), and bilateral type A tympanogram in the remaining 18 patients (72%). Audiometry revealed mild bilateral conductive hearing loss (25–40 dB) in 7 patients (28%), mild unilateral conductive hearing loss (25–40 dB) in 1 (4%), bilateral normoacusia in 17 patients (68%). Videofluoroscopy was normal in 21 patients (84%); the exam showed hypopharyngeal residues after swallowing in 2 cases (8%), and nasal regurgitation with or without hypopharyngeal residues after swallowing in other 2 cases (8%).

Statistical analysis to identify an association between the anatomical, functional as well as instrumental alterations of otolaryngologic phenotype is illustrated in Tables 3 and 4. As illustrated in Table 3,

TABLE 2 Frequency of ENT features in the cohort of patients

	n	%
Previous surgery		
No surgery	20	80
Submucous cleft palate	2	8
Cleft velum	2	8
Cleft palate	1	4
Palatal classification		
No anatomical and functional anomalies	4	16
Minimal anomalies (occult submucous cleft)	14	56
Minor anomalies with palatal hypomotility	5	20
Major anomalies with absent motility	2	8
Nasal air emission		
No air emission on pressure sensitive sounds	12	48
Audible inconsistent nasal emission	7	28
Audible consistent nasal emission	6	24
Inaudible nasal emission	0	0
Rhinolalia/rhinophonia classification		
Normal articulation without appreciable alterations of resonance	13	52
Some typical slight articulatory defects with mild/moderate open rhinophonia	7	28
Typical and consistent articulatory defects with moderate/severe open rhinophonia	5	20
Palatine tonsils volume		
Tonsils not exceeding the pillars (0%)	13	52
Tonsils up to 50% of the space between loggia and median line	10	40
Tonsils up to 75%	2	8
Tonsils up to 100%	0	0
Adenoids volume		
Adenoids occupying up to 25% of the nasopharynx	5	20
Adenoids occupying up to 50%	15	60
Adenoids occupying up to 75%	5	20
Subtotal or total obstruction of nasopharynx	0	0
Otoscopic findings		
Normal tympanic membrane on both sides	16	64
Bilateral retracted tympanic membrane	8	32
Bilateral tympanic effusion	1	4
Tympanogram		
Type A bilaterally	18	72
Type C bilaterally	1	4
Type A on one side and type B on the other	1	4
Type B bilaterally	5	20
Hearing		
Normal hearing (<25 dB)	17	68
Mild monolateral conductive hypoacusia (25–40 dB)	1	4
Mild bilateral conductive hypoacusia (25–40 dB)	7	28

(*Continues*)

TABLE 2 (Continued)

	n	%
Moderate conductive hypoacusia (40–60 dB)	0	0
Episodes of laryngeal aspiration/penetration		
No current or previous disorder	21	84
Previous episodic disorders	3	12
Previous and current episodic disorders	1	4
Episodes of nasal regurgitation		
No current or previous disorder	18	72
Previous episodic disorders	4	8
Previous and current episodic disorders	3	12
Swallowing anomalies		
No abnormalities	21	84
Hypopharyngeal residues after swallowing	2	8
Nasal regurgitation with or without hypopharyngeal residues	2	8
Respiratory pattern		
Nasal	12	48
Mixed	8	32
Oral	5	20
Food restrictions		
No restrictions	18	72
In 1 consistency	5	20
In 2 or 3 consistencies	2	8

Abbreviation: n, absolute number of patients per feature.

a significant association between the severity of palatal anomalies requiring surgery and the degree of rhinolalia/phonia (p = .017), as well as between the severity of palatal anomalies requiring surgery and nasal air emission (p = .012) was found. As expected, a correlation was also found when palatal abnormalities degree was compared with the degree of rhinolalia/phonia (p < .0005) and with nasal air emission (p < .0005). Rhinolalia/phonia grading also correlated with the presence of episodes suggesting laryngeal aspiration/penetration (p = 0.016) and with severity of food restriction (p = .001). There was also a correlation between episodes of nasal regurgitation and of laryngeal aspiration/penetration (p = .009). In addition, food restrictions were significantly associated with nasal air emission (p = .007), with nasal regurgitation episodes (p < .0005), with the presence of episodes of laryngeal penetration/aspiration (p < .0005), and with mouth breathing pattern (p = 0.019). As illustrated in Table 4, the tympanometric pattern correlated, as expected, with the abnormal otoscopic findings (p = .022) and with the adenoid volume (p = .044); there was also an association with mouth respiratory pattern (p = .023). Similarly, the more severe audiometric anomalies the more profound abnormal respiratory pattern (p = .003) was noted. Eventually, the abnormal transit of the bolus, detected at videofluoroscopy, correlated with episodes of laryngeal aspiration/penetration (p = .016), with a linear progression.

TABLE 3 Univariate analysis. Relationships between anatomic and functional variables in our cohort of subjects

	Rhinolalia/phonia grading	Nasal air emission	Episodes of nasal regurgitation
Surgery			
Spearman's rho	0.472	0.494	0.117
p value	**.017**	**.012**	.578
Minor palatal abnormalities			
Spearman's rho	0.754	0.746	0.288
p value	**.000**	**.000**	.163
Episodes of laryngeal P/A			
Spearman's rho	0.476	0.328	0.511
p value	**.016**	.110	**.009**
Food restrictions			
Spearman's rho	0.604	0.522	0.680
p value	**.001**	**.007**	**.000**

Abbreviation: P/A, penetration/aspiration.

We also studied the immunophenotype in our cohort of subjects. Lymphopenia affected 4 of 25 patients (16%). Nine of the 25 patients (36%) had a reduced number of CD4+ cells compared to normal range for age. Eleven out of 25 (44%) and 4 out of 25 (16%) patients had a reduced number of CD8+ or CD19+ cells, respectively. About serum levels of immunoglobulin of our 25 patients, 1 (4%) had a reduced serum concentration of IgA, 8 (32%) had reduced levels of IgM, and 1 (4%) patient had reduced concentration of IgG compared to normal range for age. All subjects produced isohemagglutinins and antigen-specific antibodies following immunization.

The mean ($\pm SD$) of the number of respiratory infections in the patients group during the last 24 months was 2.77 $\pm$ 2.96; six of

TABLE 4 Univariate analysis. Relationships between instrumental ENT variables and anatomic-functional ENT variables in our cohort of subjects

	Otoscopic anomalies	Adenoid volume	Respiratory pattern	Episodes of laryngeal P/A
Tympanometric anomalies				
Spearman's rho	0.457	0.407	0.453	−0.020
p value	**.022**	**.044**	**.023**	.925
Audiometric alteration				
Spearman's rho	0.382	0.280	0.571	0.204
p value	.059	.176	**.003**	.327
Videofluoroscopic pattern				
Spearman's rho	0.073	0.000	0.078	0.475
p value	.728	1.000	.709	**.016**

Abbreviation: P/A, penetration/aspiration.

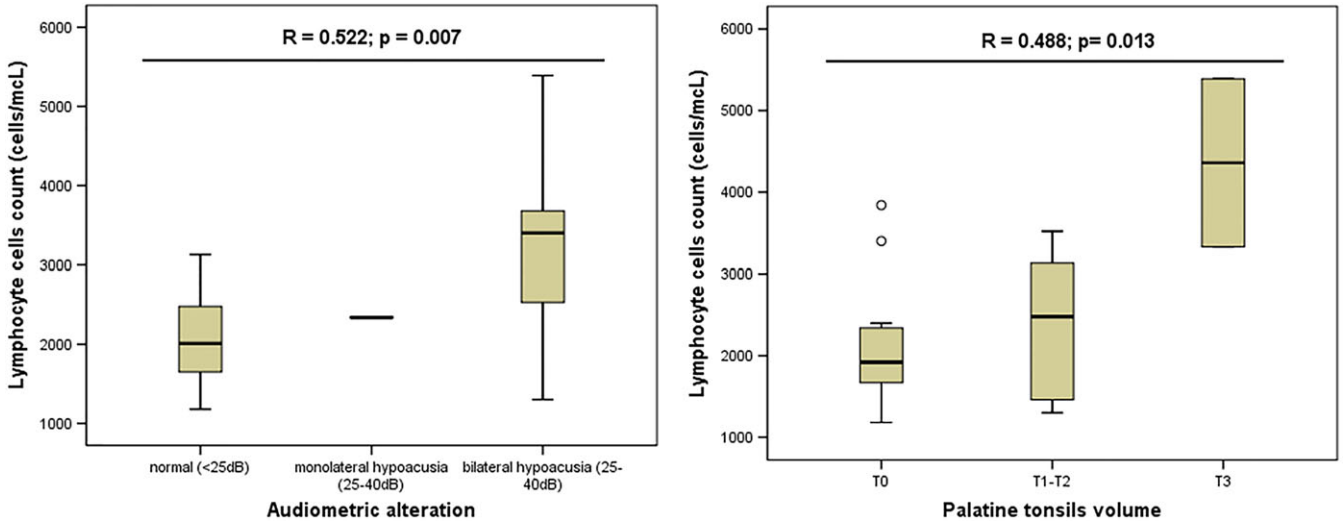


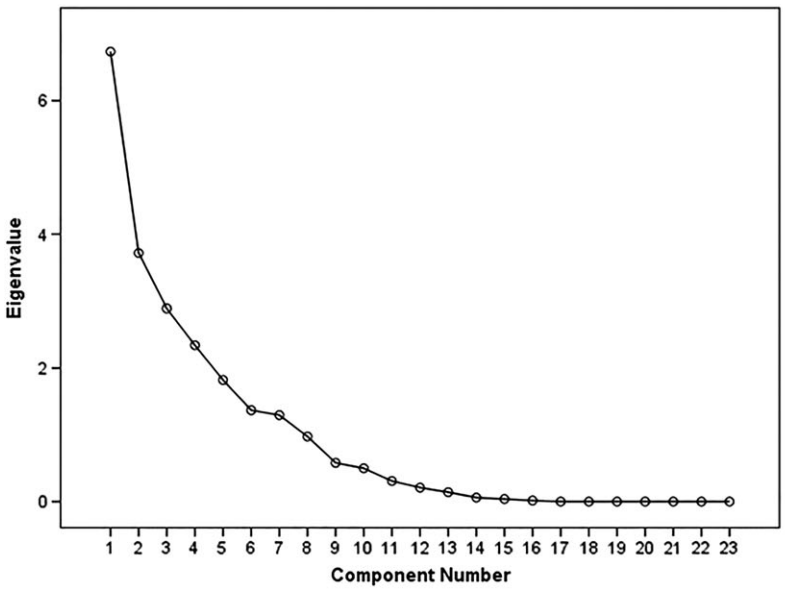
FIGURE 1 Univariate analysis. Box plots show the distribution of the variable "Lymphocyte cells count" in our cohort of patients, using like grouping variables "audiometry" and "Palatine tonsils volume". The analyses suggest positive association between "lymphocyte count" and the two variables (p = .007, p = .013, respectively) [Color figure can be viewed at wileyonlinelibrary.com]

them had a number of infections greater than 6 and only 3 of them experienced at least 1 episode of otitis during the observation period. No statistically significant association was observed between the number of infections and the ENT findings already mentioned. Moreover, there was no association between infections and immunophenotypic findings.

To find a correlation between the age of the subjects and the variables under examination, we performed a Spearman rank correlation test between age and all ENT findings and between age and the number of infections in the last 24 months. We found a significant negative correlation between age and adenoid volume (p < .005) or tonsillar volume (p = .029); no correlation between age and the other ENT findings, neither between age and the number of infections, was found.

As shown in the Figure 1, using the Pearson correlation test, we observed a direct correlation between lymphocyte cells count and the severity of audiometric alteration (p = .007) and the palatine tonsils volume (p = .013).

We next performed multivariate analysis (namely factor analysis) to obtain information about the interdependency between the observed variables in our cohort of 22q11.2DS patients. As detailed in the Figure 2, we found six clusters of variables (defined as components), where a few variables are correlated one to each other. In particular, as illustrated in the Figure 2B, four of them are represented by functional and anatomical ENT features. The first ENT cluster includes variables related to swallowing disturbances, namely food restriction, episodes of nasal regurgitation, or laryngeal penetration/aspiration; the second one includes variables related to speech disturbance, such



	Component					
	1	2	3	4	5	6
CD3+ cells count	,940					
Lymphocyte cells count	,920					
CD4+ cells count	,889					
CD19+ cells count	,806					
CD8+ cells count	,792					
IgA serum level						
Food restrictions		,842				
Episodes of nasal regurgitation		,839				
Episodes of laryngeal penetration/aspiration		,774				
Videofluoroscopy						
Minor palatal abnormalities			,856			
Nasal air emission			,836			
Rhinolalia/phonia grading			,800			
Major palatal abnormalities						
IgG serum level				,928		
Total Ig serum level				,927		
Tympanometry					,820	
Hearing					,818	
Otoscopic findings						
Adenoid volume						,862
Respiratory pattern						,772
Palatine tonsils volume						
IgM serum level						

FIGURE 2 Multivariate analysis. All components with eigenvalues under 1.5 were dropped. Varimax rotation method was used. Factor loadings in multivariate analysis, including all the variables are illustrated in the right part of the figure. Factor analysis shows that within each factor there are clusters of variables, which are positively correlated one to each other

as nasal air emission, rhinolalia/phonia grading, and minor palatal abnormalities; the third and the fourth group concern otological and upper respiratory tract disturbances, being represented by tympanometric alterations and severity of conductive hearing loss or by adenoid volume, and mouth breathing pattern, respectively. Further, two clusters refer to immunological parameters.

4 | DISCUSSION

Otolaryngologic manifestations are quite common in 22q11.2DS and, in particular in subjects with a mild phenotype, can represent one of the clinical features for which the patient is referred to the physician. A better characterization of ENT abnormalities and the understanding of the relationship between these and other aspects of the clinical phenotype of the syndrome are therefore necessary. We examined at a single Center a cohort of 25 patients diagnosed as 22q11.2DS and found that 88% of the subjects had otolaryngologic anomalies. The prevalence of cleft palate requiring surgery in our cohort (including submucous cleft palate, cleft velum, and cleft palate) was 20%, while the prevalence of palatal anomalies in length and/or mobility was 28%. In addition, we observed a high prevalence of minimal palatal abnormalities, largely corresponding to cases of occult submucous cleft palate (56%). Overall, palatal anomalies affected 84% of the subjects and positively correlate with episodes of nasal regurgitation, nasal air emission, and articulatory defects. Thus far, a specific approach for the clinical management of such problems is not yet well defined.

In the present study, it was found that in 48% of the patients tonsils exceeded the pillars and in 80% adenoids occupied more than 25% of nasopharynx. Comparing these data with those reported in a healthy pediatric population (Akcay, Kara, Dagdeviren, & Zencir, 2006; Wang, Bernheim, Kaufman, & Clement, 1997), the adenoid and tonsillar size in our cohort are generally higher. This finding was unexpected, since previous studies (Ford et al., 2000; Ruotolo et al., 2006) documented a reduced volume of tonsils and adenoids in patients with 22q11.2DS, compared with the general population, it being interpreted as a potential cause of the velopharyngeal incompetence. Rhinolalia/phonia, already described as a feature of 22q11.2DS (McDonald-McGinn et al., 1999), was also found in 52% of our cohort of patients, and in 24% a severe articulation defect was documented; moreover, the severity of rhinolalia/phonia correlated with palate abnormalities, as well as with food restriction, and with episodes of laryngeal penetration/aspiration. This indicates that a videofluoroscopic swallowing study in patients with articulation defects would help manage such patients in early detecting bolus transit abnormalities. This could also pave the way to set up strategies to prevent associated complications, as ab ingestis pneumonitis. Furthermore, the early adoption of a specific speech therapy program could be helpful in improving the overall quality of life of such patients (Speyer, Baijens, Heijnen, & Zwijnenberg, 2010).

No association was observed between episodes of nasal regurgitation and palate anomalies (including major and minor abnormalities), nor between the latter and episodes of laryngeal penetration/aspiration, which are different from what is observed in patients not affected with 22q11.2DS with palate abnormalities, in whom a positive correlation was found (Walter, Nisa, & Leuchter, 2013). This finding would suggest that further factors, as dysmorphic features or muscular dysmotility, may be implicated in the pathogenesis of dysphagia and nasal regurgitation associated with 22q11.2DS.

The instrumental study of the acoustic function was performed by audiometry and timpanometry. The results appear to be substantially in line with those described in larger studies (Van Eynde et al., 2016; Verheij et al., 2017). Statistical analysis showed that abnormal timpanometric findings were directly related to the audiometric and otoscopic alterations, and with the adenoid volume, as well. These data suggest that a careful management of adenoid hypertrophy should be considered to prevent tympanometric alterations in patients with 22q11.2DS. Regarding the respiratory pattern, there was an interdependence between mouth breathing and increased adenoid volume. This observation would favor the hypothesis that adenoid hypertrophy could play a cause role in determining the respiratory pattern of patients with 22q11.2DS, whereas, previously, a significant role was attributed to the neurological status or to the narrow nasal vault (Ford et al., 2000).

Eventually, although we could not find any association between the ENT findings and the number of infections of the ENT region and of lower respiratory tract, we cannot conclusively rule out that ENT abnormalities may have a role in favoring infections due to the limited number of patients studied. In particular, only 12% of them had at least one episode of otitis during the observation time. A possible explanation is that the majority of the enrolled subjects (65%) were older than 8 years. A multicentric study, enrolling a larger cohort of patients, could be helpful in answering to this issue.

ORCID

Fiorentino Grasso http://orcid.org/0000-0002-3900-5859
Claudio Pignata http://orcid.org/0000-0003-1568-9843

REFERENCES

Akcay, A., Kara, C. O., Dagdeviren, E., & Zencir, M. (2006). Variation in tonsil size in 4- to 17-year-old schoolchildren. *The Journal of Otolaryngology*, *35*(4), 270–274.

Aloj, G., Giardino, G., Valentino, L., Maio, F., Gallo, V., Esposito T., … Pignata C. (2012). Severe combined immunodeficiences: new and old scenarios. *International Review of Immunology*, *31*, 43–65. https://doi.org/10.3109/08830185.2011.644607

Bassett, A. S., Chow, E. W., Husted, J., Weksberg, R., Caluseriu, O., Webb, G. D., & Gatzoulis, M. A. (2005). Clinical features of 78 adults with 22q11 deletion syndrome. *American Journal of Medical Genetics. Part A*, *138*(4), 307–313. https://doi.org/10.1002/ajmg.a.30984

Brodsky, L. (1989). Modern assessment of tonsils and adenoids. *Pediatric Clinics of North America*, *36*(6), 1551–1569.

Cassano, P., Gelardi, M., Cassano, M., Fiorella, M. L., & Fiorella, R. (2003). Adenoid tissue rhinopharyngeal obstruction grading based on fiberendoscopic findings: A novel approach to therapeutic management. *International Journal of Pediatric Otorhinolaryngology*, *67*(12), 1303–1309.

Cirillo, E., Giardino, G., Gallo, V., D'Assante, R., Grasso, F., Romano, R., … Pignata, C. (2015). Severe combined immunodeficiency--an update. *Annals of the New York Academy of Sciences*, *1356*, 90–106. https://doi.org/10.1111/nyas.12849

Devriendt, K., Fryns, J. P., Mortier, G., van Thienen, M. N., & Keymolen, K. (1998). The annual incidence of DiGeorge/velocardiofacial syndrome. *Journal of Medical Genetics*, *35*(9), 789–790.

Digilio, M. C., Pacifico, C., Tieri, L., Marino, B., Giannotti, A., & Dallapiccola, B. (1999). Audiological findings in patients with

microdeletion 22q11 (di George/velocardiofacial syndrome). *British Journal of Audiology*, *33*(5), 329–333.

Finkelstein, Y., Hauben, D. J., Talmi, Y. P., Nachmani, A., & Zohar, Y. (1992). Occult and overt submucous cleft palate: From peroral examination to nasendoscopy and back again. *International Journal of Pediatric Otorhinolaryngology*, *23*(1), 25–34.

Ford, L. C., Sulprizio, S. L., & Rasgon, B. M. (2000). Otolaryngological manifestations of velocardiofacial syndrome: A retrospective review of 35 patients. *Laryngoscope*, *110*(3 Pt 1), 362–367. https://doi.org/10.1097/00005537-200003000-00006

Giardino, G., Cirillo, E., Maio, F., Gallo, V., Esposito, T., Naddei, R., … Pignata, C. (2014). Gastrointestinal involvement in patients affected with 22q11.2 deletion syndrome. *Scandinavian Journal of Gastroenterology*, *49*(3), 274–279. https://doi.org/10.3109/00365521.2013.855814

Kobrynski, L. J., & Sullivan, K. E. (2007). Velocardiofacial syndrome, DiGeorge syndrome: The chromosome 22q11.2 deletion syndromes. *Lancet*, *370*(9596), 1443–1452. https://doi.org/10.1016/S0140-6736(07)61601-8

Kummer, A. W. (2016). Evaluation of speech and resonance for children with craniofacial anomalies. *Facial Plastic Surgery Clinics of North America*, *24*(4), 445–451. https://doi.org/10.1016/j.fsc.2016.06.003

LaMantia, A. S., Moody, S. A., Maynard, T. M., Karpinski, B. A., Zohn, I. E., Mendelowitz, D., … Popratiloff, A. (2016). Hard to swallow: Developmental biological insights into pediatric dysphagia. *Developmental Biology*, *409*(2), 329–342. https://doi.org/10.1016/j.ydbio.2015.09.024

McDonald-McGinn, D. M., Kirschner, R., Goldmuntz, E., Sullivan, K., Eicher, P., Gerdes, M., … Zackai, E. H. (1999). The Philadelphia story: The 22q11.2 deletion: Report on 250 patients. *Genetic Counseling*, *10*(1), 11–24.

McDonald-McGinn, D. M., LaRossa, D., Goldmuntz, E., Sullivan, K., Eicher, P., Gerdes, M., … Zackai, E. H. (1997). The 22q11.2 deletion: Screening, diagnostic workup, and outcome of results; report on 181 patients. *Genetic Testing*, *1*(2), 99–108. https://doi.org/10.1089/gte.1997.1.99

McDonald-McGinn, D. M., & Sullivan, K. E. (2011). Chromosome 22q11.2 deletion syndrome (DiGeorge syndrome/velocardiofacial syndrome). *Medicine (Baltimore)*, *90*(1), 1–18. https://doi.org/10.1097/MD.0b013e3182060469

McDonald-McGinn, D. M., Tonnesen, M. K., Laufer-Cahana, A., Finucane, B., Driscoll, D. A., Emanuel, B. S., & Zackai, E. H. (2001). Phenotype of the 22q11.2 deletion in individuals identified through an affected relative: Cast a wide FISHing net! *Genetics in Medicine*, *3*(1), 23-29. doi:10.109700125817-200101000-00006

Motta, S., & Cesari, U. (1996). Aerodynamic study of velopharyngeal insufficiency before and after logopedic treatment. *Folia Phoniatrica et Logopaedica*, *48*(1), 11–21. https://doi.org/10.1159/000266378

Ruotolo, R. A., Veitia, N. A., Corbin, A., McDonough, J., Solot, C. B., McDonald-McGinn, D., … Kirschner, R. E. (2006). Velopharyngeal anatomy in 22q11.2 deletion syndrome: A three-dimensional cephalometric analysis. *The Cleft Palate-Craniofacial Journal*, *43*(4), 446–456. https://doi.org/10.1597/04-193.1

Ryan, A. K., Goodship, J. A., Wilson, D. I., Philip, N., Levy, A., Seidel, H., et al. (1997). Spectrum of clinical features associated with interstitial chromosome 22q11 deletions: A European collaborative study. *Journal of Medical Genetics*, *34*(10), 798–804.

Speyer, R., Baijens, L., Heijnen, M., & Zwijnenberg, I. (2010). Effects of therapy in oropharyngeal dysphagia by speech and language therapists: A systematic review. *Dysphagia*, *25*(1), 40–65. https://doi.org/10.1007/s00455-009-9239-7

Tezenas Du Montcel, S., Mendizabai, H., Ayme, S., Levy, A., & Philip, N. (1996). Prevalence of 22q11 microdeletion. *Journal of Medical Genetics*, *33*(8), 719.

Van Eynde, C., Swillen, A., Lambeens, E., Verhaert, N., Desloovere, C., Luts, H., … Hens, G. (2016). Prevalence and nature of hearing loss in 22q11.2 deletion syndrome. *Journal of Speech, Language, and Hearing Research*, *59*(3), 583–589. https://doi.org/10.1044/2015_JSLHR-H-15-0098

Verheij, E., Kist, A. L., Mink van der Molen, A. B., Stegeman, I., van Zanten, G. A., Grolman, W., & Thomeer, H. G. (2017). Otologic and audiologic findings in 22q11.2 deletion syndrome. *European Archives of Oto-Rhino-Laryngology*, *274*(2), 765–771. https://doi.org/10.1007/s00405-016-4365-y

Walter, V., Nisa, L., & Leuchter, I. (2013). Acute isolated velopharyngeal insufficiency in children: Case report and systematic review of the literature. *European Archives of Oto-Rhino-Laryngology*, *270*(7), 1975–1980. https://doi.org/10.1007/s00405-012-2215-0

Wang, D. Y., Bernheim, N., Kaufman, L., & Clement, P. (1997). Assessment of adenoid size in children by fibreoptic examination. *Clinical Otolaryngology and Allied Sciences*, *22*(2), 172–177.

How to cite this article: Grasso F, Cirillo E, Quaremba G, et al. Otolaryngological features in a cohort of patients affected with 22q11.2 deletion syndrome: A monocentric survey. *Am J Med Genet Part A*. 2018;e40518. https://doi.org/10.1002/ajmg.a.40518