Patterns of cardiac and extracardiac anomalies in adults with tetralogy of Fallot

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Abstract

Background—Tetralogy of Fallot (TOF) is a complex congenital heart disease with clinical and genetic heterogeneity. Of the few known causes, 22q11.2 deletion syndrome (22q11DS) is the most common. We sought to define other clinical subgroups by focusing on cardiac and extracardiac features.

Methods—We prospectively screened a cohort of adults with TOF using an established protocol by which subjects were categorized as “syndromic” if they had at least 2 of 3 features: dysmorphic facies, learning difficulties, or voice abnormalities. We then compared the prevalence of cardiac and extracardiac features between subjects in the syndromic group ($n = 56$) and 112 age- and gender-matched subjects who did not meet our syndromic criteria.

Results—The syndromic group was more likely than the nonsyndromic group to have pulmonary atresia and/or major aortopulmonary collateral arteries (25% vs 13%, $P = .04$). There was a trend toward a higher prevalence of one or more major congenital extracardiac anomalies, primarily involving the musculoskeletal and genitourinary systems (25% vs 13%, $P = .06$). Later-onset conditions, including neuropsychiatric disorders (32% vs 17%, $P = .03$), thyroid disorders (20% vs 4%, $P = .001$), and hearing deficits (20% vs 0, $P < .001$), were more common in the syndromic group. The syndromic group tested ($n = 50$) had neither 22q11.2 deletions nor karyotypic anomalies.

Conclusion—Similar to 22q11DS, adults with TOF meeting screening criteria for a possible genetic syndrome are enriched for more severe cardiac disease and late-onset extracardiac features. Increased awareness of this subgroup with a multisystem condition may be helpful for identifying individuals for referral to medical genetics and optimizing management.

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Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart disease (CHD), comprising approximately 10% of all CHDs.¹ Known genetic defects currently account for only a minority of cases. The most common underlying genetic anomaly in patients with TOF is 22q11.2 deletion syndrome (22q11DS), occurring in 10% to 16% of cases.^{2,3} Down syndrome (trisomy 21) is the second most common genetic abnormality, found in 3% to 8% of patients with TOF.⁴ Other identified genetic anomalies associated with TOF are rare and include mutations in *NKX2.5*,⁵ *JAG1* (found in Alagille syndrome),⁶ and *FOG27* genes, as well as trisomy 138 and CHARGE syndrome.⁹ In most cases, the genetic basis of TOF is unknown; and among these patients, there is substantial phenotypic variability.

In a previous prospective study, we established that a brief clinical screening protocol successfully identified adults with 22q11DS.¹⁰ The objective of the current study was to determine if individuals with TOF who met 2 to 3 of these screening criteria but without 22q11DS or other known syndromes have a different overall clinical picture (ie, with respect to features not included in the original screening criteria) to those who did not meet these criteria. We hypothesized that subjects who met the previously defined screening criteria (syndromic group)¹⁰ would have a higher prevalence of congenital cardiovascular anomalies, congenital extracardiac anomalies, and late-onset conditions compared with a group of age- and gender-matched subjects who did not meet the screening criteria (non-syndromic group). We used subjects with 22q11DS as a reference group.

Methods

This study was approved by the institutional ethics boards. Adults (18 years old) with TOF seen at the Toronto Congenital Cardiac Centre for Adults (Toronto, Canada) and who had undergone prospective clinical screening for features suggesting a genetic syndrome, particularly 22q11DS,¹⁰ between 1998 and 2008 ($n = 447$, mean age 39 ± 13 years, 239 men [53%]) comprised the sample population. Individuals with major genetic anomalies such as Down syndrome were not included in the initial screening study. Of these 447 subjects, 395 (88%) had TOF and the remainder ($n = 52$, 12%) had TOF-pulmonary atresia.

Subjects were categorized into 3 groups: syndromic, non-syndromic, and 22q11DS. Subjects were classified as syndromic if they had at least 2 of the 3 features comprising criteria previously established to identify adults with 22q11DS: an overall impression of dysmorphic facial features, cognitive impairment (eg, self-reported childhood learning difficulties), and speech problems (predominantly hypernasal speech).¹⁰ Subjects with 22q11DS who met the syndromic criteria and had a confirmed 22q11.2 deletion ($n = 39$) were used as a reference group.^{10,11} Of the initial 447 subjects, 15% ($n = 66$) were classified as syndromic, 9% ($n = 39$) had 22q11DS, and the remainder ($n = 342$) formed the total nonsyndromic group, not meeting syndromic criteria on clinical genetic screening. Excluded from the syndromic group were 5 subjects with other known genetic syndromes (CHARGE, Kartagener, Klippel-Feil, Klinefelter, and distichiasis-lymphedema syndromes) and 5 patients with a history of stroke and acquired speech and/or learning difficulties. Subjects in the remaining syndromic group ($n = 56$) were matched by age (within 5 years) and gender in a 1:2 ratio with subjects who did not meet the syndromic criteria. The matched nonsyndromic comparison group thus comprised 112 of 342 available subjects. Most ($n = 50$, 89%) of the subjects in the

syndromic group had clinical genetic testing to rule out 22q11DS and other major genetic anomalies. The majority of subjects in the nonsyndromic group were not tested for 22q11.2 deletions or other major genetic anomalies because they did not meet syndromic criteria during clinical screening and thus were not likely to have major chromosomal abnormalities.¹⁰

In addition to the prospectively collected screening data, comprehensive chart reviews using records from the adult hospital (Toronto General Hospital, Toronto, Canada) and the local referring pediatric hospital (Hospital for Sick Children, Toronto, Canada) provided lifetime information on cardiac and extracardiac features. Congenital cardiovascular abnormalities other than TOF were recorded (eg, atrial septal defect). With respect to congenital extracardiac anomalies, we chose to focus on major anomalies because these have the potential to affect the functioning of the affected individual.¹² Based on previous definitions, these included anomalies involving the following systems: central nervous system (eg, spina bifida), gastrointestinal (eg, esophageal atresia), renal (eg, renal agenesis), genital (eg, bicornuate uterus), musculoskeletal (eg, club foot), and ear deformities requiring surgery (eg, absent left ear lobe).^{12,13} Minor congenital anomalies (eg, syndactyly) were not included. *Short stature* (<third percentile) was defined as adult height at last follow up of <150 cm and <161 cm for female and male subjects, respectively (<http://www.cdc.gov/nchs/about/major/nhanes/growthcharts/datafiles.htm>).

We also recorded late-onset extracardiac conditions (including thyroid disorders, disorders of calcium metabolism, and neuropsychiatric disorders) commonly found in 22q11DS and other genetic syndromes.^{11,13} Neuropsychiatric disorders included seizures, attention-deficit disorder/attention-deficit hyperactivity disorder (ADD/ADHD), schizophrenia, and anxiety and/or depression. Treatments for these conditions were also recorded. Other late-onset conditions common in the general population and/or infrequent in this sample were not recorded (ie, gastroesophageal reflux, diabetes, urinary tract infections, and asthma).

Subjects with clinical genetic testing had standard karyotype and fluorescence in situ hybridization (FISH) testing for 22q11.2 deletions using a TUPLE 1 (Vysis) or N25 (ONCOR) probe.^{10,11,14}

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Statistical analysis

The statistical analysis was performed using SPSS software (version 16; SPSS, Inc, Chicago, IL). Continuous data are presented as mean $\pm$ SD. Differences between groups (ie, syndromic and nonsyndromic groups) were determined using χ^2 , Fisher exact, Kruskal-Wallis, or Student *t* tests as appropriate. A *P* value < .05 (2-tailed) was considered statistically significant.

Results

Table I presents the characteristics of the 3 TOF groups ($n = 207$, 106 men [51%], mean age 36 ± 10 years). Most subjects had intracardiac repair of TOF (nonsyndromic 98% vs syndromic 91% vs 22q11DS 92%, $P = .08$). The mean age at intracardiac repair was similar in the nonsyndromic and syndromic groups (6 ± 3 vs 6 ± 3 , $P = .58$). In the syndromic group, 62% (35/56) met 2 and 38% (21/56) met 3 of the predefined clinical screening criteria.¹⁰ Results for all subjects in the syndromic and nonsyndromic groups who underwent genetic testing were negative. There were no significant differences between the syndromic and nonsyndromic groups in regard to family history of CHD. The 22q11DS reference group was younger ($P = .007$) and had a higher proportion of subjects with a family history of CHD ($P = .02$) compared with the main study groups.

As expected, given the screening criteria that emphasized hypernasality,¹⁰ the prevalence of subjects with overt and submucous cleft palate was significantly greater in the syndromic than the nonsyndromic group ($n = 6$, 11% vs 0, $P = .001$). There was a trend for proportionately more subjects with short stature in the syndromic compared with the nonsyndromic group ($n = 8$, 14% vs $n = 7$, 6%; $P = .09$). Of the 15 subjects in the syndromic and nonsyndromic groups with short stature, 6 (40%) had scoliosis.

Congenital anomalies and later-onset features

Table II presents the prevalence of additional congenital cardiovascular anomalies in the 3 TOF subgroups. The overall prevalence of individuals with auxiliary cardiovascular anomalies was lowest in the nonsyndromic group (62%), followed by the syndromic group (70%) and the 22q11DS reference group (85%). Of the individual anomalies studied, the only significant difference between the syndromic and nonsyndromic groups was a higher proportion of subjects with pulmonary atresia and/or major aortopulmonary collateral arteries (MAPCAs) in the syndromic group ($P = .04$). There was a trend toward a higher prevalence of atrial septal defect ($P = .08$) and right aortic arch ($P = .09$) in the syndromic group. The increased prevalence of these cardiac lesions was similar in the syndromic and the 22q11DS groups.

Overall, the prevalence of one or more congenital extracardiac anomalies in TOF subjects in the syndromic and nonsyndromic groups was 17% (29/168). There was a trend toward a higher prevalence of one or more major extracardiac anomalies in the syndromic group compared with the nonsyndromic group ($n = 14$, 25% vs $n = 15$, 13%; $P = .06$). The proportion of subjects with 2 or more of these anomalies was small: 7% ($n = 4$) in the syndromic and 2% ($n = 2$) in the nonsyndromic group. The respective proportions for the 22q11DS group were 36% ($n = 14$) and 5% ($n = 2$) for 1 and 2 or more of these anomalies. Genitourinary and musculoskeletal anomalies were the most common of the major extracardiac congenital anomalies studied; but numbers were small, and there were no significant differences between the syndromic and nonsyndromic groups (Table III). When the syndromic and nonsyndromic groups were combined, subjects with these congenital extracardiac anomalies were more common in the 28 subjects with pulmonary atresia and/or MAPCAs compared with the 140 without these cardiac features ($n = 9$, 32% vs $n = 20$, 14%;

$P = .02$), with musculoskeletal anomalies predominating in the former group, present in 7 (78%) subjects.

Several of the later-onset extracardiac conditions studied showed significantly greater prevalence in the syndromic compared with the nonsyndromic group (Table IV). Findings were not restricted to disorders of childhood (ADD/ADHD, first onset of seizure activity, recurrent otitis media, and in some cases hearing deficits) but included adult-onset conditions such as thyroid dysfunction (only 1 syndromic subject had congenital hypothyroidism), schizophrenia, and anxiety/depression. The significantly higher prevalence of neuropsychiatric disorders in the syndromic group appeared to be related to ADD/ADHD, schizophrenia, and/or seizures (Table IV). Fourteen of the 15 subjects in the syndromic group and 2 of the 19 subjects in the nonsyndromic group who had one or more of these neuropsychiatric conditions were individuals with learning difficulties. Although the prevalence of anxiety and/or depression was similar between the 2 main study groups, a greater proportion of subjects reported anxiolytic medication use in the syndromic than in the nonsyndromic group ($n = 5, 9\%$ vs $n = 1, 1\%$; $P = .02$).

The significantly higher prevalence of endocrine disorders in the syndromic group was mainly related to thyroid dysfunction (Table IV). Sixteen (70%) of the 23 subjects in the overall sample with hypothyroidism were female. The high prevalence of hypocalcemia in the 22q11DS group was likely related to our routine practice to check ionized calcium levels in this group of patients.¹¹ In addition, 2 subjects in this 22q11DS reference group had hypogonadotropic hypogonadism.

The increased proportion of subjects with hearing deficits in the syndromic group compared with the nonsyndromic group appeared to be at least partly accounted for by a history of recurrent otitis media (Table IV). Myringotomy tube procedures were documented in 41% (17/41) of subjects with a history of otitis media. Of the 21 subjects with hearing deficits, 3 in the syndromic and 1 in the 22q11DS group had a documented congenital cause (1 with congenital deafness and 3 with congenital ear deformities requiring surgery).

When we reanalyzed the data after excluding the 6 subjects from the syndromic group who have not yet had genetic testing, along with the corresponding 12 age- and gender-matched subjects from the nonsyndromic group, the results showed little change. Compared with the nonsyndromic group, the syndromic group's higher prevalence of subjects with seizures ($n = 8, 16\%$ vs $n = 6, 6\%$; $P = .047$), schizophrenia ($n = 2, 4\%$ vs 0% ; $P = .04$), gastrointestinal anomalies ($n = 2, 4\%$ vs 0% ; $P = .04$), and ear deformities ($n = 2, 4\%$ vs 0% ; $P = .04$) reached significance, whereas pulmonary atresia and/or MAPCAs ($n = 12, 24\%$ vs $n = 12, 12\%$; $P = .059$) were at a trend level.

Discussion

The results from this study demonstrate that, in addition to those with 22q11DS and major chromosomal anomalies, in a substantial proportion of subjects, TOF represents a multisystem disorder. A priori, we selected a group of subjects who, after systematic clinical genetic screening, met criteria suggesting that they may have a more complex developmental

and multisystem condition.¹⁰ We found evidence that this was the case. In this syndromic group, there was a higher prevalence of individuals with more severe cardiac disease and later-onset neuropsychiatric and endocrine disorders. Notably, none of these features overlapped with those used in the initial designation of the syndromic group¹⁰; and several would not be identifiable in infancy. These findings are novel and have potential implications for clinical management.

We found that, similar to the 22q11DS group, 1 in 4 subjects in the syndromic group had complex cardiac disease (MAPCAs and/or pulmonary atresia), features that can be associated with worse outcomes.¹⁵ Others have found that individuals with genetic changes such as 22q11.2 deletions¹⁶ may have more complex cardiac lesions. The higher prevalence of extracardiac anomalies in subjects with pulmonary atresia and/or MAPCAs compared with those without these features may suggest pleiotropic expression, with changes in genes involved in very early development, like the TBX1 transcription factor of 22q11DS.

The overall prevalence of individuals with one or more major congenital extracardiac anomalies in our study sample, excluding the 22q11DS group, was 17%, broadly consistent with several previous reports of TOF^{17–20} and substantially higher than general population expectations.²¹ However, most of these studies^{17,18,20} would have been performed before detection of 22q11.2 deletions was possible. This may have been why we did not replicate previous reports of elevated prevalence of gastrointestinal anomalies.^{18,20} The most common anomalies we encountered involved the genitourinary and musculoskeletal systems, consistent with some previous reports.^{18,19}

A novel finding of our study is the high prevalence of several late-onset conditions in the syndromic group, comparable to that in 22q11DS and greater than that reported in the general population for seizures (4%–10%), ADD (5%), schizophrenia (1%), and thyroid dysfunction (1%–5%).^{22–25} The etiology of thyroid dysfunction in our sample is unknown, with possibilities including common autoimmune abnormalities or faulty neural crest–derived thyroid glandular cells.^{26,27} Almost all subjects in the syndromic and nonsyndromic groups had reparative cardiac surgery, performed at a similar age (ie, at a similar era) in both groups. Although multifactorial in nature, the high prevalence of neuropsychiatric conditions in the syndromic group is not likely related to cardiac surgery alone.²⁸ Patients with TOF secondary to Down syndrome and 22q11DS have previously been shown to have worse neurodevelopmental outcomes than those without genetic syndromes, suggesting that genetic factors, not simply environmental factors related to open heart surgery, are important.²⁹ As in 22q11DS and other large, rare copy number variations (CNVs), there was some overlap between learning difficulties and neuropsychiatric disorders such as ADD/ADHD, seizures, and schizophrenia in the TOF syndromic group studied.³⁰

The syndromic group identified represents an initial step toward delineating more homogenous populations with TOF that could help identify those enriched for specific genetic causes of this disease. To date, the most prevalent causes of TOF involve changes in gene dosage associated with structural genomic anomalies.^{2–4} More recent research suggests that rare, large, highly penetrant CNVs other than 22q11.2 deletions may play a

role in the etiology of TOF.^{30–34} We would predict that this group would be enriched for such CNVs. In addition to DNA sequence mutations, there may be CNVs with lower penetrance that contribute to risk for TOF in the syndromic or nonsyndromic groups, or both.^{30,31} Delineating the genetic causes of TOF will be important not only for understanding the disease mechanism but also potentially for clinical management.

Clinical implications

The high prevalence of congenital extracardiac anomalies and later-onset conditions in adults with TOF should alert physicians to the potential multisystem nature of this disorder. An awareness of these phenotypes is important in the clinical setting; the common association of certain extracardiac anomalies with TOF provides patterns helpful for diagnosis, allowing for early detection and treatment.^{11,35} Because certain extracardiac conditions are present from birth, some are detectable in childhood, and others develop later, it is important to maintain vigilance for new-onset conditions, particularly in adulthood. Multidisciplinary management with the endocrinologist, orthopedic surgeon, psychiatrist, geneticist, and other specialties may be necessary. Consultation with a clinical geneticist may help identify recognizable genetic syndromes, allowing for appropriate genetic counseling and anticipatory guidance.¹⁰

Limitations

This was largely a retrospective study that relied on chart review to document features. It is routine practice (in cardiac clinics) to check for other cardiac anomalies in patients with TOF. Extracardiac conditions, however, are more likely to be underdiagnosed. To attempt to minimize this bias, we comprehensively reviewed all available adult and pediatric medical records. Nonetheless, this remains an important limitation. Furthermore, we would not have included children who did not survive to adulthood, which may have resulted in the underrepresentation of extracardiac conditions relevant to early mortality. Our study did not include investigation of the impact of pediatric postoperative complications on neurodevelopmental outcomes. However, studying adults made it possible to include late-onset conditions with developmental origins, such as neuropsychiatric and endocrine disorders. Most subjects in the syndromic group have not yet had a formal clinical genetics consultation as an adult. Many had genetic evaluation in childhood, but genetic testing at that time would have been limited. In addition, the genetic testing we performed would have missed copy number changes below the resolution of karyotype (~5–10 megabases) and FISH using standard clinical probes that detect >95% of 22q11.2 deletions.

Conclusion

Brief screening in the clinical setting can identify a syndromic group of TOF subjects, in addition to those with 22q11DS,¹⁰ who have multisystem disease involving significant congenital extracardiac features, late-onset conditions, as well as elevated prevalence of severe cardiac disease. An awareness of these multisystem phenotypic variations is important for the clinician in cardiac clinics. Extracardiac abnormalities warrant regular monitoring to take timely preventative measures and improve management. These findings may also provide a means of identifying a subset of patients enriched for certain genetic

causes of TOF that warrant referral to medical genetics. Genomewide microarrays and other specific genetic testing may delineate the underlying molecular anomalies in some, or eventually many, cases.³⁶

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Table I

Baseline characteristics

	Nonsyndromic group (n = 112)	Syndromic group (n = 56)	22q11DS reference group (n = 39)	P value (nonsyndromic vs syndromic groups)
Mean age, y	37 ± 10	37 ± 11	31 ± 10	.71
Male	56 (50%)	28 (50%)	22 (56%)	1.0
Family history of CHD	15 (13%)	6 (11%)	12 (31%)	.62
1st-degree relatives	11 (10%)	5 (9%)	8 (21%)	.85
2nd-degree relatives	6 (5%)	1 (2%)	6 (15%)	.43
Ethnicity, white (n = 203)	87/108 (81%)	48 (86%)	38 (97%)	.22
Genetic testing results available *	9 (8%)	50 (89%)	39 (100%)	<.001

* Clinical karyotype and FISH testing using probes for common 22q11.2 deletions.

Table II

Congenital cardiovascular anomalies

	Nonsyndromic group (n = 112)	Syndromic group (n = 56)	22q11DS reference group (n = 39)	P value (nonsyndromic vs syndromic groups)
Any cardiovascular anomaly	69 (62%)	39 (70%)	33 (85%)	.31
Pulmonary atresia and/or MAPCA	14 (13%)	14 (25%)	10 (26%)	.04
Atrial septal defect	11 (10%)	11 (20%)	6 (15%)	.08
Right aortic arch	28 (25%)	21 (38%)	18 (46%)	.09
Left SVC draining into coronary sinus	5 (4%)	4 (7%)	2 (5%)	.48
Aberrant subclavian artery	9 (8%)	6 (11%)	14 (36%)	.57
Hypoplastic pulmonary artery	20 (18%)	12 (21%)	12 (31%)	.58
Other arterial anomalies *	17 (15%)	7 (13%)	6 (15%)	.64
Absent pulmonary valve	1 (1%)	1 (2%)	2 (5%)	1.00
Other venous anomalies †	8 (7%)	4 (7%)	1 (3%)	1.00

SVC, Superior vena cava.

* Arterial anomalies included anomalous origin of coronary arteries, vertebral artery anomalies, innominate artery anomalies, double aortic arch, subclavian artery anomalies, aberrant coronary artery crossing over the right ventricular outflow tract or pulmonary valve, absent left coronary artery, hemitruncus arteriosus, and bitruncus brachiocephalic arteries.

† Venous anomalies included left-sided SVC, bilateral SVC, innominate vein anomalies, hemitranssection of the right upper pulmonary vein, anomalous right superior pulmonary vein draining into the right atrium, and partial anomalous pulmonary vein drainage to the SVC.

Table III

Congenital extracardiac anomalies

	Nonsyndromic group (n = 112)	Syndromic group (n = 56)	22q11DS reference group (n = 39)	P value (nonsyndromic vs syndromic groups)
Musculoskeletal anomaly	7 (6%)	7 (13%)	6 (15%)	.17
Major musculoskeletal anomaly [*]	5 (4%)	5 (9%)	4 (10%)	.25
Scoliosis requiring surgery	2 (2%)	3 (5%)	2 (5%)	.34
Genitourinary anomaly	9 (8%)	6 (11%)	4 (10%)	.57
Renal [†]	7 (6%)	4 (7%)	3 (8%)	1.00
Genital [‡]	2 (2%)	3 (5%)	2 (5%)	.34
Gastrointestinal anomaly [§]	0	2 (4%)	3 (8%)	.11
Ear anomaly	0	2 (4%)	1 (3%)	.11
Central nervous system anomaly [¶]	1 (1%)	2 (4%)	3 (8%)	.26

^{*} Major musculoskeletal anomalies were polydactyly, bifid terminal phalanx of thumb, digitalized thumb, club foot, hemi and butterfly vertebrae, and dysplastic ribs.

[†] Renal anomalies were renal agenesis, horseshoe kidney, ectopic kidney, collecting duct anomaly, and congenital hydronephrosis.

[‡] Genital anomalies were undescended testes, hypospadias, chordee, and bicornuate uterus.

[§] Gastrointestinal anomalies included esophageal atresia, anal atresia/stenosis, pyloric stenosis, and Meckel diverticulum.

^{||} Major ear anomalies included absent left ear lobe, absent left external ear canal, and congenital lop ear deformity.

[¶] Central nervous system anomalies included spina bifida, hydrocephaly, hypoplastic pituitary gland, and diffuse cerebral and cerebellar atrophy.

Table IV

Late-onset extracardiac conditions

	Nonsyndromic group (n = 112)	Syndromic group (n = 56)	22q11DS reference group (n = 39)	<i>P</i> value (nonsyndromic vs syndromic groups)
Any neuropsychiatric disorder	19 (17%)	18 (32%)	20 (51%)	.03
Seizures	7 (6%)	8 (14%)	8 (21%)	.09
ADD/ADHD	0	6 (11%)	2 (5%)	.001
Schizophrenia	0	2 (4%)	4 (10%)	.11
Anxiety and/or depression	12 (11%)	5 (9%)	11 (28%)	.72
Any endocrine disorder	4 (4%)	12 (21%)	19 (49%)	<.001
Thyroid dysfunction	4 (4%)	11 (20%)	8 (21%)	.001
Hypocalcemia and/or hypoparathyroidism	0	1 (2%)	17 (44%)	.33
Recurrent otitis media	13 (12%)	13 (23%)	15 (38%)	.05
Hearing deficit	0	11 (20%)	10 (26%)	<.001
In the absence of otitis media	0	3 (5%)	2 (5%)	.04