Microdeletion 22q11 and oesophageal atresia

Maria Cristina Digilio, Bruno Marino, Pietro Bagolan, Aldo Giannotti, Bruno Dallapiccola

Abstract

Oesophageal atresia (OA) is a congenital defect associated with additional malformations in 30-70% of the cases. In particular, OA is a component of the VACTERL association. Since some major features of the VACTERL association, including conotruncal heart defect, radial aplasia, and anal atresia, have been found in patients with microdeletion 22q11.2 (del(22q11.2)), we have screened for del(22q11.2) by fluorescent in situ hybridisation (FISH) in 15 syndromic patients with OA. Del(22q11.2) was detected in one of them, presenting with OA, tetralogy of Fallot, anal atresia, neonatal hypocalcaemia, and subtle facial anomalies resembling those of velocardiofacial syndrome. The occurrence of del(22q11.2) in our series of patients with OA is low (1/15), but this chromosomal anomaly should be included among causative factors of malformation complexes with OA. In addition, clinical variability of del(22q11.2) syndrome is further corroborated with inclusion of OA in the list of the findings associated with the deletion.

(*J Med Genet* 1999;**36**:137–139)

Keywords: microdeletion 22q11; oesophageal atresia; VACTERL association; velocardiofacial syndrome

Departments of Medical Genetics, Paediatric Cardiology, and Neonatal Surgery, Bambino Gesù Hospital, Piazza S Onofrio 4, 00165 Rome, Italy
M C Digilio
B Marino
P Bagolan
A Giannotti

Department of Human Genetics, Tor Vergata University, and Mendel-CSS Institute, Rome, Italy
B Dallapiccola

Correspondence to:
Dr Digilio.

Received 30 January 1998
Revised version accepted for publication 13 July 1998

Microdeletion 22q11.2 (del(22q11.2)) is known to be related to DiGeorge, velocardiofacial, and conotruncal anomaly face syndromes,[1 2] but the spectrum of associated anomalies is becoming wider.[3]

Oesophageal atresia (OA) is a congenital defect which can occur as an isolated malformation or in association with additional malformations in 30-70% of patients.[4–12] Specifically, OA is a component of the VACTERL association (V=vertebral defects, A=anorectal defects, C=cardiac defects, TE=oesophageal atresia with Tracheo-oEsophageal fistula, R=renal anomalies, radius aplasia, rib anomalies, L=limb defects), occurring in 20 to 67% of patients with this multiple anomaly association.[13–15] Some major clinical features of the VACTERL association have been found in patients with del(22q11.2), including conotruncal heart defect,[15] radial aplasia,[16] renal anomalies,[17] and anal atresia.[18] However, OA has never been described in patients with del(22q11.2). We have screened for del(22q11.2) by fluorescent in situ hybridisation (FISH) in order to evaluate the prevalence of the deletion in syndromic patients with OA.

Patients and methods

From January 1995 to September 1997, 15 patients with syndromic OA and normal standard chromosomes were referred to the Department of Medical Genetics of our hospital for genetic evaluation. All patients were clinically examined and checked for additional malformations by two clinical geneticists. There were eight males and seven females. Their mean age was 2.1 years (age range 0.1 to 10.8 years). Clinical features of the patients included in the study are summarised in table 1. OA type III (OA with distal tracheo-oesophageal fistula) was found in 13 patients and OA type I (OA without tracheo-oesophageal fistula) in two. Six patients had multiple anomalies that fulfilled the criteria for VACTERL association. Velocardiofacial syndrome was diagnosed in one case, CHARGE (C=coloboma, H=heart defect, A=atresia choanae, R=retarded growth, G=genital hypoplasia, E=ear anomalies) association in one, and Goldenhar syndrome in another one. For the remaining six patients, a diagnosis of a recognisable genetic condition was not reached.

FISH ANALYSIS

FISH analysis using the Sc11.1,[19] Co23,[20] and D22S75 and D22S39 (control, ONCOR) probes was performed in all patients.

Results

FISH analysis showed 22q11.2 hemizygosity in one of the 15 (6.7%) patients analysed. Del(22q11.2) was sporadic, as shown by normal FISH analysis in the unaffected parents. The deleted patient was a female neonate with OA associated with tetralogy of Fallot, anorectal malformation (rectovestibular fistula), and subtle facial anomalies resembling those of velocardiofacial syndrome (table 1). In addition, hypocalcaemia was present in the first days of life. At 7 months of age, weight was 5800 g (3rd centile), length 65 cm (10th centile), and head circumference 43 cm (10th centile). A normal thymic shadow was detected on chest *x* ray and echocardiographic study. T lymphocyte numbers were slightly below the normal range.

Discussion

OA is associated with a great variety of congenital defects.[4–12] In our previously reported series of 107 patients observed between 1976 and 1986, associated anomalies were present in 47% of cases.[10]

To our knowledge, the present case is the first report of OA with del(22q11.2). The association of OA, tetralogy of Fallot, and anal atresia presented by our patient had first

Table 1 Clinical and FISH findings in patients with syndromic oesophageal atresia

Case	Sex	Age (y)	Oesophageal atresia (type)	Facial anomalies	Vertebral anomalies	Cardiac defect
1	F	0.1	III	Prominent nose, small mouth, dysmorphic ears	–	TF
2	M		III	–	+	Dextrocardia
3	M	0.1	III	–	–	–
4	F	2.9	III	Epicanthic folds, dysmorphic ears	+	TF
5	M	0.1	III	–	–	ASD, dextrocardia
6	F	0.1	III	Dysmorphic ears, preauricular pits	–	–
7	M	1	III	–	–	TF
8	M	0.2	I	Downward slanted palpebral fissures, dysmorphic ears	–	TF
9	M	0.1	III	Otodysplasia, preauricular pits	–	–
10	F	0.1	III	–	–	–
11	M	0.4	III	–	–	–
12	M	9.7	I	Hypertelorism, small mouth, everted ears	–	ASD
13	F	1	III	Epicanthic folds, flat nasal bridge	–	Congenitally corrected TGA in situs inversus
14	F	0.1	III	–	–	–
15	F	10.8	III	–	–	ASD

FISH = fluorescent in situ hybridisation, P = patient, Del22 = deletion 22q11, F = female, TF = tetralogy of Fallot, VCFS = velocardiofacial syndrome, M = male, ASD= atrial septal defect, NV = not valuable, VSD = ventricular septal defect, MCA = multiple congenital abnormalities, TGA = transposition of the great arteries

suggested the clinical diagnosis of VACTERL association, but, subsequently, the coexistence of conotruncal heart defect, neonatal hypocalcaemia, T lymphocyte defect, and facial anomalies prompted the clinical diagnosis of velocardiofacial syndrome. We believe that careful clinical examination for evident or even subtle facial dysmorphism of velocardiofacial or DiGeorge syndrome[21 22] is essential in patients with clinical features of VACTERL association, expecially those with conotruncal heart defect. Del(22q11.2) should be included among causative factors of malformation complexes with OA or other features of VACTERL association. In fact, radial aplasia, renal anomalies, and anal atresia are additional malformations found to be associated with del(22q11.2) in some cases.[16–18] Clinical variability of del(22q11.2) is further supported by the present report, and OA is added to the list of clinical findings associated with the deletion. Nevertheless, the occurrence of del(22q11.2) in our series of patients with EA is low, and accurate evaluation for specific anomalies of velocardiofacial or DiGeorge syndromes can select patients for FISH analysis.

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Table 1 continued

Anal atresia	*Radial anomalies*	*Renal/urinary anomalies*	*Ocular anomalies*	*Cleft palate*	*Choanal atresia*	*Hypo-calcaemia*	*Low T lymphocytes*	*Diagnosis*	*Del22*
+	−	−	−	−	−	+	+	VCFS	+
−	+	Hypoplastic right kidney	−	−	−	−	−	VACTERL	−
+	−	Double urethra	−	−	−	−	−	VACTERL	−
+	−	−	−	−	−	+	−	VACTERL	−
+	−	−	−	−	−	−	NV	VACTERL	−
+	−	Pyelic ectasia	−	−	−	−	NV	VACTERL	−
−	+	−	−	−	−	−	−	VACTERL	−
−	−	−	Left micro-phthalmia, coloboma	−	−	+	−	CHARGE	−
−	−	−	−	+	+	NV	NV	Goldenhar syndrome	−
−	−	−	−	−	+	−	−	MCA	−
+	−	−	−	−	+	NV	NV	MCA	−
−	−	−	−	−	−	−	−	MCA	−
−	−	−	−	−	−	−	−	MCA	−
−	−	−	−	−	+	NV	NV	MCA	−
−	−	−	−	−	−	−	−	MCA	−