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ORIGINAL ARTICLE

Gastrointestinal involvement in patients affected with 22q11.2 deletion syndrome

GIULIANA GIARDINO, EMILIA CIRILLO, FILOMENA MAIO, VERA GALLO,
TIZIANA ESPOSITO, ROBERTA NADDEI, FIORENTINO GRASSO & CLAUDIO PIGNATA

Department of Translational Medical Sciences, “Federico II” University, Naples, Italy

Abstract

Objective. Enteropathy is a very common feature in patients with primary immunodeficiencies. In patients with Del22 gastrointestinal (GI) alterations, including feeding disorders and congenital abnormalities have been often reported, mostly in the first year of life. **Material and methods.** Aim of this monocentric study is to better define the GI involvement in a cohort of 26 patients affected with Del22 syndrome. Anamnestic information was retrospectively collected for each patient. Weight and height parameters at the time of the screening were recorded. Plasma levels of hemoglobin, iron, ferritin, albumin, total protein, calcium, phosphorus, transaminase levels, antigliadin (AGA) IgA and IgG, and antitissue transglutaminase (anti-TGase) titers were measured. **Results.** A GI involvement was identified in the 58% of patients. The prominent problems were abdominal pain, vomiting, gastroesophageal reflux and chronic constipation. Weight deficiency, short stature and failure to thrive were reported in 54, 42, and 30% of the patients, respectively. The evidence of sideropenic anemia, in keeping with hypoproteinemia, impaired acid steatocrit or cellobiose/mannitol test suggested an abnormal intestinal permeability. In this cohort, a high prevalence of AGA IgA and IgG positivity was observed. Celiac disease (CD) was suspected in three patients, and in one of them confirmed by histology. In this patient, a long-lasting gluten-free diet failed to restore the intestinal architecture. **Conclusions.** In conclusion, GI involvement is a very common feature in Del22 patients. A better characterization of GI involvement would be very useful to improve the management of these patients.

Key Words: Celiac disease, Del22 syndrome, malabsorption

Introduction

Chromosome 22q11 deletion (Del22) is the most common chromosomal deletion syndrome with an estimated incidence of 1:4,000 live births [1]. The most common clinical features of the syndrome are cardiac malformations, speech delay, facial dysmorphisms, and immunodeficiency [2]. Other manifestations include neuropsychiatric, gastrointestinal (GI) and otolaryngological disorders.

GI alterations, including feeding disorders [3,4] and congenital abnormalities [5], are often reported in patients with Del22 and other athymic disorders [6,7]. The commonest disorders are gastroesophageal reflux disease (GERD), esophagitis, and chronic

constipation. Feeding disorders, mostly due to dysmotility in the pharyngoesophageal area, are characterized by difficulties in coordinating the suction/deglutition/breathing reflex and result in slow feeding and episodes of regurgitation [3,4]. The GI congenital abnormalities include esophageal atresia, jejunal atresia, umbilical hernia, diaphragmatic herniation, intestinal malrotation, congenital megacolon, anorectal malformations (atresia, anterior displacement), and dental anomalies, such as delayed formation and eruption of permanent teeth and enamel hypoplasia [5]. However, a systematic and well-detailed clinical and laboratory characterization of the GI alterations in Del22 syndrome is missing. Aim of this monocentric study is to better define the

GI involvement in a cohort of patients affected with Del22.

Methods

Twenty-six patients affected by Del22 syndrome in follow-up at our Department were enrolled into the study. The clinical diagnosis of Del22 syndrome was confirmed by fluorescent *in situ* hybridization (FISH). For each patient, anamnestic information, paying a special attention to chronic diarrhea, nausea and vomiting, abdominal pain, GERD, esophagitis, chronic constipation and feeding difficulties were retrospectively collected. Weight and height parameters at the time of the screening were recorded and plotted on standard percentile growth charts and the closest percentile for age was recorded. As previously reported [8], the finding of weight below the 3rd percentile was correlated with the presence of congenital heart defect, cleft palate, and feeding difficulties. The finding of short stature (height below the 3rd percentile) was correlated with the presence of congenital heart defect and cleft palate. Statistical analysis was performed through a two tailed Fishers exact test using the statistical software GraphPad.

Plasma hemoglobin, iron, ferritin, albumin, total protein, calcium, phosphorus, and transaminase levels were measured. Stool samples were collected for the measurement of fecal calprotectin, as a marker of bowel inflammation, and for the acid steatocrit estimation, as a marker of small-intestine lipid malabsorption. The cellobiose/mannitol test, performed by standard procedure, was used to investigate intestinal permeability. Results were expressed as the ratio (cellobiose/mannitol) of the 5 h urinary recovery of the two probe molecules. The test was considered impaired when cellobiose/mannitol ratio was >0.023 . To rule out GI infections, parasitological test and stool cultures were conducted.

All patients were receiving a gluten-containing diet. Enzyme-linked immunosorbent assay (ELISA) was used to measure antigliadin (AGA) IgA and IgG, and antitissue transglutaminase (anti-TGase) titers. IgA and IgG AGA titers were considered negative when <45 U/mL, and positive when >55 U/mL. IgA and IgG anti-TGase titers were considered negative when <1 U/mL, borderline when 1–6.9 U/mL and positive when >7 U/mL. The indirect immunofluorescence technique on commercially available fixed sections of monkey small intestine was used for endomysial antibody (EMA) determination. IgA levels were evaluated in each patient in order to exclude a selective IgA deficiency. According to the ESPGHAN criteria, esophagogastroduodenoscopy (EGDS) was proposed when anti-TGase antibodies were positive, but with a

title <10 times the upper normal value; in children younger than 2 years, EGDS was proposed when AGA titers were positive even though in the absence of anti-TGase antibodies. EGDS was performed upon written informed parental consent.

Results

Patients affected with Del22 syndrome had a mean age of 7.6 years (age range 0.6–20.7 years). Male to female ratio was 1.4:1. Four cases carried an inherited deletion, while in 22 cases the deletion was *de novo*. Table I shows the main clinical and demographic features of the patients enrolled into the study. In 15/26 patients (58%) clinical records revealed the presence of signs or symptoms of a GI involvement. Mean age at the onset of GI symptoms was 1.7 years (age range 0–7 years). Abdominal pain was reported in 9/15 patients, vomiting in 8/15, chronic constipation in 7/15, GERD in 6/15, feeding disorders in 4/15, failure to thrive in 4/15, epigastric pain in 3/15, and diarrhea in 4/15 (Table II). Two patients had congenital abnormalities, such as gastrectasia or anorectal malformation. All patients showed two or more symptoms.

Weight deficiency (<3 rd centile) was found in 14/26 (54%) patients, short stature (<3 rd centile) in 11/26 (42%) and failure to thrive (weight/height ratio <3 rd centile) in 8/26 (30%). Congenital heart defect was present in 13 of the 14 (93%) patients with weight below the 3rd percentile and in 9 of the 12 (75%) patients with the weight within the normal range (p 0.30). Cleft palate was present in 1 of 14 (7%) patients with weight below the 3rd percentile and in 2 of 12 (16%) patients with weight within the normal range (p 0.58). Feeding difficulties were referred in 1 of 14 (7%) patients with weight below the 3rd percentile and in 1 of 12 (8%) of those with weight above the 3rd percentile (p 1.00). Congenital heart defect was present in 11 of 11 (100%) patients with height below the 3rd percentile and in 11 of 15 (73%) patients with height above the 3rd percentile (p 0.11).

Hematological and biochemical tests revealed hypoproteinemia in 5/26 patients. In 3/5 cases, hypoproteinemia was associated with GI symptoms, including diarrhea in two cases and feeding difficulties in one case. Sideropenic anemia was observed in 14/26 patients, while one additional patient had hypsideremia and hypoferritinemia without anemia. In 5/14 patients, sideropenic anemia was not associated with an overt GI manifestation.

IgA and IgG AGA titers were positive in the 41 and 47% of the patients, respectively. Anti-TGase IgA titers were positive in 4.5% of the patients, borderline in 32% of the patients, and negative in

Table I. Clinical and demographic features of patients.

Pz	Age (years)	Sex	Transmission	Clinical features
1	6.2	M	AD	cardiac anomalies, mental retardation
2	14.0	M	<i>de novo</i>	hypoparathyroidism, recurrent candidiasis
3	16.7	M	AD	cardiac anomalies, mental retardation
4	10.2	M	AD	cardiac anomalies, mental retardation
5	6.0	M	<i>de novo</i>	cardiac anomalies, mental retardation, neonatal tetanus, URTI
6	12.5	M	<i>de novo</i>	cardiac anomalies, mental retardation
7	11.5	F	<i>de novo</i>	cardiac anomalies, mental retardation, hypoparathyroidism, URTI, subdural hygroma
8	7.5	F	<i>de novo</i>	cardiac anomalies, mental retardation, URTI, febrile seizures, pulmonary atelectasis
9	12.5	F	<i>de novo</i>	cardiac anomalies
10	9.0	F	<i>de novo</i>	cardiac anomalies
11	20.7	F	<i>de novo</i>	cardiac anomalies, hypoparathyroidism, psoriatic arthritis, hepatitis C
12	4.5	F	<i>de novo</i>	cardiac anomalies, mental retardation
13	1.2	F	<i>de novo</i>	cardiac anomalies, gastrectasia, recurrent oral candidiasis
14	7.0	M	<i>de novo</i>	cardiac anomalies, mental retardation, autoimmune thyroiditis
15	3.5	F	AD	cardiac anomalies
16	4.5	F	<i>de novo</i>	cardiac anomalies, recurrent oral candidiasis, URTI
17	3.5	M	<i>de novo</i>	cardiac anomalies, mental retardation, neonatal tetanus, seizures
18	3.2	M	<i>de novo</i>	mental retardation, palatal defect
19	7.7	M	<i>de novo</i>	mental retardation
20	10.5	M	<i>de novo</i>	cardiac anomalies, mental retardation, thrombocytopenia, myopia, cryptorchidism, inguinal hernia, velopharyngeal synechia
21	4.5	M	<i>de novo</i>	cardiac anomalies, febrile seizures, recurrent bronchospasm, inguinoscrotal hernia
22	10.5	F	<i>de novo</i>	mental retardation, palatal defect, hypocalcemia, seizures
23	6.5	M	<i>de novo</i>	cardiac anomalies, mental retardation, hexodactily, hypoacusia, cryptorchidism, URTI, febrile seizures
24	0.7	F	<i>de novo</i>	cardiac anomalies, IgA deficiency
25	2.0	M	<i>de novo</i>	cardiac anomalies, palatal defect, URTI
26	0.6	M	<i>de novo</i>	cardiac anomalies, inguinal hernia, skeletal malformations

Abbreviations: AD = autosomal dominant; URTI = upper respiratory tract infection.

63.5%. Anti-TGase IgG titers were positive in 8% of the patients and negative in 92%. None of the patients had EMA. Celiac disease (CD) was suspected on the basis of serological tests in one patient, who showed persistently elevated anti-TGase IgA, and in two patients younger than 24 months, who had positive IgA and IgG AGA titers. The three patients with a positive serology had GI signs suggestive of CD (chronic diarrhea, abdominal pain, and failure to thrive), and only one patient had sideropenic anemia. As mentioned earlier, EGDS was performed when indicated, but one patient who refused the procedure. In two patients, aged 10 and 14 months, respectively, the intestinal histological examination revealed a villous atrophy consistent with a diagnosis of CD in one patient and a normal architecture in the second one. In the patient with villous atrophy, a moderate-to-severe villous atrophy persisted after a 7-year gluten-free diet. Thereafter, a liberalized diet did not impair the growth (weight to height ratio at the 50th percentile).

Acid steatocrit estimation was impaired in 6 of the 18 patients evaluated. Fecal calprotectin was impaired in 8 of the 22 patients evaluated. The cellobiose/mannitol test, performed in 14/26 patients, was

impaired in four patients. These assays were impaired contemporarily in three patients (P3, P8, and P21), who had GI clinical signs. In the overall group with altered intestinal permeability, five patients had GI clinical signs. By contrast, six of the eight patients, who had increased calprotectin levels, had GI signs.

In 12/26 patients, at least two further autoantibodies, not directly associated with the intestine, were detected (Table III).

Discussion

Patients with primary immunodeficiencies are prone to develop enteropathy with different pathogenetic mechanisms. In patients with Del22, mostly in the first year of life, GI alterations, including feeding disorders [3,4] and congenital abnormalities [5] have been already reported [8].

In this study, a GI involvement was identified in the 58% of patients affected with Del22. The most frequent clinical problems were abdominal pain, vomiting, GERD, and chronic constipation. In our cohort, weight deficiency, short stature, and failure to thrive were reported in 54, 42, and in 30% of the patients, respectively. In keeping with what previously

Table II. Clinical and laboratory GI evaluation in Del22 patients.

Pz	GI signs and symptoms	Age at onset	P/A <3rd pc	TP (g/dl)	Alb (g/dl)	Iron (µg/dl)	FT (ng/ml)	Hb (g/dl)	Ca (mg/dl)	P (mg/dl)	AST (UI/l)	ALT (UI/l)
1	-	-	+	6.6	4.5	15.0	44.0	11.0	9.3	4.5	21.0	17.0
2	-	-	-	7.8	4.9	51.0	23.0	11.4	8.7	5.1	18.0	16.0
3	+	1.3	+	5.4	3.2	14.0	19.0	12.1	8.4	4.3	22.0	19.0
	(diarrhea, vomiting, failure to thrive, abdominal pain)											
4	+	1.8	-	7.0	4.4	54.0	44.0	12.6	8.6	4.5	24.0	16.0
	(CMPI, chronic constipation, abdominal pain)											
5	+	0.2	-	5.6	3.7	15.0	7.0	10.1	9.2	4.1	52.0	21.0
	(diarrhea, GERD)											
6	+	1.7	+	7.0	3.6	15.0	8.0	10.1	9.3	4.3	75.0	59.0
	(nausea, vomiting)											
7	-	-	-	5.9	3.7	13.0	5.0	9.6	7.2	5.0	21.0	17.0
8	+	7.0	-	6.6	4.2	14.0	5.0	9.2	9.0	5.5	23.0	20.0
	(epigastric pain, abdominal pain, chronic constipation)											
9	+	1.2	-	7.0	4.7	77.0	13.0	11.7	9.0	3.0	26.0	21.0
	(chronic constipation, dyspepsia, epigastric pain, vomiting, abdominal pain)											
10	+	2.0	-	7.6	4.4	14.0	9.0	10.3	9.3	4.9	24.0	17.0
	(epigastric pain, abdominal pain)											
11	-	-	-	7.7	4.5	15.0	7.0	10.8	7.5	3.6	25.0	19.0
12	+	1.2	+	7.4	4.6	15.0	10.0	9.3	10.3	7.6	21.0	17.0
	(nausea, vomiting, diarrhea, failure to thrive, abdominal pain)											
13	+	0.5	+	5.8	2.4	59.0	13.0	11.4	9.7	6.2	23.0	19.0
	(feeding difficulties, gastrectasia)											
14	+	3.0	-	7.0	4.3	14.0	7.0	10.0	9.1	4.4	22.0	17.0
	(failure to thrive, vomiting, GERD, chronic constipation, anorectal malformation)											
15	+	0.5	+	6.3	4.4	14.0	7.0	9.9	9.2	5.3	31.0	22.0
	(chronic constipation, vomiting, GERD, feeding difficulties)											
16	+	2.2	-	6.9	4.2	32.0	15.0	11.1	9.0	5.1	22.0	18.0
	(vomiting, failure to thrive, diarrhea, abdominal pain, GERD)											
17	-	-	-	6.5	4.3	60.0	17.0	12.0	9.6	5.4	26.0	22.0
18	-	-	-	6.7	4.4	12.0	11.0	9.9	9.5	5.2	29.0	15.0
19	-	-	+	7.3	4.6	100.0	26.0	12.0	9.0	5.2	24.0	11.0
20	-	-	-	7.4	4.8	108.0	35.0	13.0	9.0	4.1	22.0	16.0
21	+	3.0	-	6.9	4.4	15.0	11.0	10.7	9.5	5.3	31.0	12.0
	(abdominal pain, vomiting, chronic constipation, GERD)											
22	-	-	-	7.5	4.2	60.0	20.0	11.6	8.7	4.2	23.0	17.0
23	-	-	+	6.9	4.5	15.0	18.0	10.8	9.5	4.4	24.0	21.0
24	-	-	-	5.4	4.4	15.0	5.0	9.5	10.1	5.6	55.0	23.0
25	+	0.1	-	6.8	4.1	58.0	53.0	11.5	9.6	5.5	32.0	19.0
	(GERD, feeding difficulties)											
26	+	0.1	-	6.1	4.5	63.0	7.0	9.3	10.5	6.8	31.0	15.0
	(chronic constipation, abdominal pain, feeding difficulties)											

Abbreviations: Alb = albumin; Ca = calcium; CMPI = cow's milk protein intolerance; FT = ferritin; GERD = gastroesophageal reflux disease; Hb = hemoglobin; P = phosphorus; Pc = percentile; TP = total protein.

Table III. Serological markers of autoimmunity.

PZ	AGA IgA (U/ml)	AGA IgG (U/ml)	Anti-TGasi IgA (U/ml)	Anti-TGasi IgG (U/ml)	EMA	ANA	Anti-dsDNA	ENA	Anti-TG	Anti-TPO	CIC C1q	CIC C3d	C3	C4
1	-	-	-	+	NA	+	+	+	-	-	+	+	+	+
				(13.1)										
2	-	NA	-	-	NA	-	-	-	-	-	+	+	+	-
3	+	+	±	+	-	+	+	-	-	-	+	+	+	+
	(1362.0)	(1771.0)	(1.3)	(8.0)										
4	+	+	-	-	-	+	+	+	+	-	+	+	+	+
	(400.0)	(400.0)												
5	+	+	±	-	-	+	+	+	-	-	+	+	+	+
	(150.0)	(125.0)	(1.7)											
6	-	-	-	-	NA	+	+	NA	-	-	+	+	+	+
7	+	+	-	-	-	+	-	+	-	-	+	+	+	+
	(384.0)	(400.0)												
8	+	+	±	-	-	+	-	-	-	-	+	+	+	+
	(196.0)	(77.0)	(2.2)											
9	+	+	±	-	-	+	+	+	-	-	+	+	+	+
	(298.0)	(400.0)	(2.8)											
10	+	-	+	-	-	-	-	NA	-	-	+	+	+	-
	(200.0)		(8.0)											
11	-	NA	-	-	NA	-	-	-	-	-	NA	-	-	-
12	+	+	-	-	-	-	-	-	-	-	+	+	-	+
	(81.0)	(400.0)												
13	-	NA	-	-	NA	-	-	-	-	-	NA	-	-	-
14	+	+	-	-	-	+	-	NA	+	+	+	+	+	+
	(320.0)	(97.0)												
15	-	-	-	-	NA	+	-	+	-	-	+	+	-	-
16	-	-	±	-	NA	+	+	+	+	-	+	+	+	+
			(2.5)											
17	-	+	-	-	-	-	-	NA	-	-	+	+	+	+
		(78.0)												
18	-	-	-	-	NA	+	-	+	-	-	+	+	+	NA
19	-	-	-	-	NA	+	-	+	-	-	+	+	+	-
20	-	-	NA	-	NA	-	-	NA	-	-	-	-	-	NA
21	NA	-	±	-	-	NA	-	-	-	-	-	-	+	+
			(1.6)											
22	-	NA	-	-	NA	-	-	NA	-	NA	+	+	+	+
23	NA	-	±	-	NA	+	-	NA	-	-	+	+	+	+
			(2.0)											
24	NA	NA	NA	NA	NA	NA	NA	NA	-	-	-	NA	NA	NA
25	-	NA	-	-	NA	-	-	-	-	-	+	+	-	-
26	-	-	-	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Abbreviations: AGAs = antigliadin antibodies; ANAs = antinuclear antibodies; anti-dsDNAs = antidouble-stranded DNA antibodies; anti-TGs = antithyroglobulin antibodies; anti-TGasis = antitransglutaminase antibodies; anti-TPOs = antithyroperoxidase antibodies; CICs = circulating immune complexes; EMAs = antiendomysium antibodies; ENAs = extractable nuclear antigen antibodies; + = positive; - = negative; ± = borderline; NA = not available.

reported, the presence of congenital heart defect or cleft palate has no impact on the overall growth patterns. In fact, the correlation between the presence of these risk factors and low weight or short stature in our cohort of patients was not statistically significant. Contrary to what was previously reported, feeding difficulties do not seem to predispose to growth abnormalities. However, it should be noted that in our cohort of patients, only few of them had feeding difficulties, thus making difficult any statistical comparison.

In this study, we identified a high prevalence of AGA IgA and IgG positivity. Studies on Italian students, aged 11–15 years, revealed a prevalence of AGA positivity of 2% [9,10]. An elevated

prevalence of AGA positivity has already been reported in different genetic disease [11–13], such as Down syndrome [14,15] and Williams syndrome. In these patients, this finding was initially explained by an impaired intestinal permeability, which is a well-documented feature in patients with congenital immunodeficiencies as a consequence of the increased susceptibility to infections. In our cohort, the presence of sideropenic anemia in 14 patients may suggest an iron malabsorption, in keeping with hypoproteinemia, impaired acid steatocrit or cellobiose/mannitol test observed in six of them. The underlying mechanism to explain abnormal intestinal permeability in these patients is, however, distinct from the mechanism implicated in CD, in that in CD

the altered permeability is associated with permeability genes variations, which was not found in other conditions associated with AGA positivity [15,16]. Since in Del22 syndrome the number of GI infections is usually not higher than controls, other immunologic phenomena may be implicated in the increased prevalence of elevated AGA, possibly involving altered induction and/or maintenance of tolerance [15,17]. Patients affected with immunodeficiency, and, in particular, patients affected with Del22 are particularly prone to develop autoimmune disorders [18]. In our cohort, 7/9 patients with AGA positivity had at least 1 further autoantibody, not directly related to intestinal autoimmunity, even though none of them showed an overt clinical autoimmune disorder.

An increased incidence of CD has already been reported in Del22 patients [19]. The criteria to suspect a CD were present in three patients, but none of the patients had EMA. Moreover, a long-lasting gluten-free diet failed to restore the intestinal architecture, indicating a different pathogenetic mechanism for such histological alterations. Intestinal villous atrophy mimicking CD has been observed in the 31% of common variable immunodeficiency (CVID) patients with GI symptoms or anemia (12). The enteropathy of CVID patients significantly differs from typical forms of CD. In particular, the resistance to gluten-free diet is common, while steroids are effective on GI symptoms and in reducing the mucosal damage. Similar to CVID, the enteropathy associated with Del22 is nowadays poorly characterized, and its possible relationship with the well-defined pathogenetic mechanism of the enteropathy in CD is still poorly investigated.

In conclusion, GI involvement is a very common feature in Del22 patients. A better characterization of GI involvement would be very useful to improve the management of patients with Del22.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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