Complex conotruncal heart defect, severe bleeding disorder and 22q11 deletion: a new case of Bernard-Soulier syndrome and of 22q11 deletion syndrome?

Maria R. Iascone, Monica Sacchelli, Simona Vittorini, Sandra Giusti*

*Molecular Biology Laboratory, *Pediatric Cardiology Unit, "G. Pasquinucci" Hospital, Massa, Italy*

Key words:
Bleeding disorder; Congenital heart disease; 22q11 deletion.

A patient with a deletion in the DiGeorge/velocardiofacial chromosomal region in 22q11, underwent cardiac repair for truncus arteriosus with a separate origin of the pulmonary arteries. This patient presented with a severe coagulation disorder similar to that described in the Bernard-Soulier syndrome. Additional features included minor facial anomalies, transient hypocalcemia and renal failure. To the best of our knowledge, this is the third case of a severe bleeding disorder associated with 22q11 deletion reported in the literature.

(Ital Heart J 2001; 2 (6): 475-477)

Received January 24, 2001; revision received March 19, 2001; accepted March 27, 2001.

Address:

Dr.ssa Sandra Giusti

Cardiologia Pediatrica
IFC-CNR
Ospedale "G. Pasquinucci"
Via Aurelia Sud
54100 Massa
E-mail: sgiusti@ifc.pi.cnr.it

Introduction

The 22q11 deletion syndrome includes a wide clinical spectrum of both functional and structural anomalies, including DiGeorge/velocardiofacial syndrome, conotruncal anomaly face syndrome and some other less frequent disorders[1]. This syndrome is highly variable in severity and shows a continuous spectrum of phenotypic manifestations with considerable inter and intrafamilial variability[1].

In 1995, Budarf et al.[2] reported a patient with a 22q11 deletion, velocardiofacial syndrome and a rare bleeding disorder. These three characteristics constitute the "Bernard-Soulier syndrome". Ludlow et al.[3] showed that a recessive mutation in the promoter region of the glycoprotein (GP)Ibβ gene, which maps in the commonly deleted region in 22q11, was responsible for the etiology of Bernard-Soulier syndrome in the same patient. Kenny et al.[4], in 1999, reported a further patient with a single nucleotide deletion within the coding region of the GPIbβ gene and with a 22q11 deletion. This patient was affected by Bernard-Soulier syndrome and had subclinical features of the velocardiofacial syndrome. Both cases are heterozygous compound for the mutation in GPIbβ and for the 22q11 deletion. Recently, we have evaluated a newborn child with the 22q11 deletion who, we believe, could be affected by the Bernard-Soulier syndrome.

Case report

This patient, delivered after an uneventful pregnancy, at term and weighing 2950 g at birth was born to a 32-year-old primigravida and her healthy, non-consanguineous husband. The family history was unremarkable and there were no recordings of congenital heart defects. At 1 day of age, a heart murmur was heard and a diagnosis of truncus arteriosus was made by cross-sectional echocardiography. Subsequent angiocardiography confirmed the presence of truncus arteriosus type A3 with a separate origin of the pulmonary arteries. The right pulmonary artery arose directly from the common arterial trunk whereas the left pulmonary artery originated from the descending aorta. About 40% of patients with truncus arteriosus have the 22q11 deletion[5,6] and, in particular, the rare type A3 is more frequently associated with this haploinsufficiency[5-8]. For this reason, we included this patient in a study of the molecular characterization of 22q11 hemizygosity in conotruncal heart defects. This study is currently underway in our hospital. We used 15 consecutive simple tandem repeat polymorphic (STRP) markers that map

in the 22q11 region in order to genotype, by polymerase chain reaction, the patient and his parents and to define more precisely the size and origin of the deletion. The STRP markers used, from the centromere to the telomere, were: D22S420, D22S427, D22S1638, D22S941, D22S1648, D22S944, D22S1623, D22S264, D22S311, D22S1709, D22S306, D22S308, D22S425, D22S303, and D22S257. The methodology used to genotype the patient's and his parents' DNA was that described by Carlson et al.[9], with some modifications. We resolved the polymerase chain reaction fragments in small 12% polyacrilamide gels (about 10 cm long) which were then stained with silver nitrate. Haplotype analysis showed that the patient had a *de novo* 1.5 Mb deletion with a proximal breakpoint flanked by the marker D22S427 and a distal breakpoint between the STRP markers D22S1623 and D22S264. The deletion was paternal in origin.

After genotyping, we retrospectively revised the clinical data of the patient. His medical history included abnormal clotting at the time of correction which was performed at 14 days of age. Moderate thrombocytopenia ($96 \times 10^3/l^{-3}$) and a prolonged bleeding time (activated partial thromboplastin time 55.2 s, ratio 1.78) were present at birth. The platelet morphology and size were never recorded. The coagulation status became very abnormal soon after surgery and the patient required repeated platelet transfusions. He never regained a normal platelet count. Additional features included overfolded helices, transient hypocalcemia, and renal failure. This patient developed a sepsis 3 weeks postoperatively and subsequently died at 3 months of age before molecular analysis of the 22q11 deletion was performed and before the platelet morphology and function and the coagulation system could be investigated in detail.

Discussion

Many of the tissues and structures involved in the 22q11 deletion syndrome derive from the pharyngeal arches of the developing embryo, where the neural crest cells migrate and participate in the formation of both the craniofacial region and the neck as well as of the outflow region of the heart. A defect of either the neural crest cells or of their migration is responsible for the main clinical findings in the 22q11 deletion syndrome. However, not all the clinical findings associated with this deletion can be attributed to a defect of the neural crest cells.

Several reports suggest that some of the anomalies associated with the 22q11 deletion occur as a result of the phenotypic manifestation of recessive mutations in additional genes which are localized in the commonly deleted region but which do not affect the neural crest cells. The Bernard-Soulier syndrome is a rare inherited disorder of platelet function due to either a quantitative or qualitative defect in the platelet GPIb-IX-V membrane receptor complex[10]. The complex is composed of four subunits, namely GPIbα, GPIbβ, GPIX, and GPV. The Bernard-Soulier syndrome is usually inherited in an autosomal recessive manner and is characterized by a prolonged bleeding time, thrombocytopenia and giant platelets[10]. Most of the mutations responsible are thought to be in the GPIbα gene[10]. The GPIbβ gene has been mapped in the chromosome 22q11 region[11], within the region commonly deleted in patients with DiGeorge/velocardiofacial syndrome. Two cases of mutations in the GPIbβ gene together with a deletion on the homologous chromosome 22q11 region have been previously described. The vast majority of patients with 22q11 deletion are obligate heterozygote carriers for GPIbβ deficiency, and therefore for Bernard-Soulier syndrome. However, this abnormality may not *per se* induce a bleeding tendency.

Our patient, presenting with truncus arteriosus, had moderate thrombocytopenia before surgical repair and developed a severe coagulopathy postoperatively. The diagnosis of Bernard-Soulier syndrome in this child is suspected on clinical grounds, and is not based on a specific molecular test. The patient showed an estimated 1.5 Mb deletion and the GPIbβ gene maps within this region. Because the loss of one GPIbβ allele alone is not sufficient to produce a bleeding disorder, it is likely that this patient had had a single mutation of the remaining GPIbβ allele.

In conclusion, attention should be given to patients with 22q11deletion because they could be at risk for excessive postoperative bleeding which is associated with an increase in morbidity and mortality. In a wider perspective, patients with a microdeletion syndrome are at an increased risk for autosomal recessive disorders. Although such cases may be relatively rare, particular care should be given to atypical patients who show features which can be ascribed to both a microdeletion syndrome and to an autosomal recessive disorder.

References

1. Burn J, Goodship J. Congenital heart disease. In: Rimoin DL, Connor JM, Pyeritz RE, eds. Emery and Rimoin's principles and practice of medical genetics. New York, NY: Churchill Livingstone, 1996: 767-828.
2. Budarf ML, Konkle BA, Ludlow LB, et al. Identification of a patient with Bernard-Soulier syndrome and a deletion in the DiGeorge/velo-cardio-facial chromosomal region 22q11.2. Hum Mol Genet 1995; 4: 763-6.
3. Ludlow LB, Schick BP, Budarf ML, et al. Identification of a mutation in a GATA binding site of the platelet glycoprotein Ibbeta promoter resulting in the Bernard-Soulier syndrome. J Biol Chem 1997; 271: 22076-80.
4. Kenny D, Morateck P, Gill JC, Montgomery RR. The critical interaction of glycoprotein (GP) Ibβ with GPIX - a genetic cause of Bernard-Soulier syndrome. Blood 1999; 93: 2968-75.

5. Goldmuntz E, Clark BJ, Mitchell LE, et al. Frequency of 22q11 deletion in patients with conotruncal defects. J Am Coll Cardiol 1998; 32: 492-8.
6. Momma K, Ando M, Matsuoka R. Truncus arteriosus communis associated with chromosome 22q11 deletion. J Am Coll Cardiol 1997; 30: 1067-71.
7. Marino B, Digilio MC, Dallapiccola B. Severe truncal valve dysplasia: association with DiGeorge syndrome? (letter) Ann Thorac Surg 1998; 66: 980.
8. Toscano A, Marino B, Digilio MC, et al. Truncus arteriosus with discontinuity of the pulmonary arteries and DiGeorge phenotype. (abstr) G Ital Cardiol 1998; 28 (Suppl 3): 7.
9. Carlson C, Sirotkin H, Pandita R, et al. Molecular definition of 22q11 deletions in 151 velo-cardio-facial syndrome patients. Am J Hum Genet 1997; 61: 620-9.
10. Konkle BA. The Bernard-Soulier syndrome. Trends Cardiovasc Med 1997; 7: 239-44.
11. Kelly MD, Essex DW, Shapiro SS, et al. Complementary DNA cloning of the alternatively expressed endothelial cell glycoprotein Ib beta (GPIb beta) and localization of the GPIb beta gene to chromosome 22. J Clin Invest 1994; 93: 2417-24.