Case Report

JACOBSEN SYNDROME IN A FILIPINO CHILD

Dr. Ebner Bon G. Maceda[1,2], Dr. Leniza De Castro-Hamoy[1,2]

Author's Affiliation:
1- Section of Clinical Genetics, Department of Pediatrics, Philippine General Hospital, University of the Philippines Manila
2- Institute of Human Genetics, National Institutes of Health, University of the Philippines Manila

Correspondence:
Ebner Bon G. Maceda, MD Address: Section of Clinical Genetics, Department of Pediatrics, Philippine General Hospital, Taft Avenue, Ermita, Manila 1000 Contact #: +639335796683 Email address: egmaceda@up.edu.ph

Received on: 22-Jul-19

Accepted for Publication: 31-Dec-19

ABSTRACT:

Background: Jacobsen syndrome (JS) is a chromosomal abnormality syndrome, which is caused by the partial deletion of the long arm of chromosome 11. This can be detected by standard karyotyping.

Aims: This case aims to emphasize the value of a basic karyotype in establishing a cytogenetic diagnosis in the management of patients with multiple congenital anomalies.

Case Description: We are presented with a 22 month old boy with the characteristic features of JS which include: characteristic facial features, developmental delay, congenital heart disease and neonatal thrombocytopenia. Cytogenetic diagnosis of 11q deletion allowed us to evaluate the medical problems associated with the syndrome.

Conclusion: Cytogenetic confirmation was obtained by the presence of deletion on chromosome 11q23 in this case. Given the syndrome's multi-systemic involvement, a multidisciplinary approach is necessary. This is the first reported case of Jacobsen syndrome in the Philippines.

Keywords: deletion 11q, hypertelorism, trigonocephaly, thrombocytopenia

INTRODUCTION

Jacobsen syndrome is a contiguous gene syndrome due to partial deletion of chromosome 11q. It was first described in 1973 by Dr. Petrea Jacobsen, a Danish geneticist. Worldwide, there are more than 200 reported cases with an estimated prevalence of 1 in 100,000 births. It is described by the presence of characteristics facial features which trigonocephaly, hypertelorism, downslanted palpebral fissures, broad nasal ridge, small posteriorly-rotated ears. Clinical problems associated with this syndrome which cause morbidity and mortality include congenital heart disease, intellectual disability, autism, immunodeficiency, and a congenital dysmegakaryopoietic state termed Paris-Trousseau syndrome.[1,2]

We present the clinical features of a Filipino child with Jacobsen syndrome and elaborate the management of this condition. This case emphasizes the value of a basic karyotype in establishing a cytogenetic diagnosis in the management of patients with multiple congenital anomalies.

CASE

A male from the second pregnancy of a healthy non-consanguineous couple of Filipino descent was born preterm at 33 weeks of gestation to a 28 year old mother via cesarean section secondary due to arrest in cervical dilatation. The patient was admitted at the neonatal intensive care unit for a month, was treated for neonatal sepsis and was noted to have thrombocytopenia. He was breastfed per demand for a year. Developmental assessment using the Batelle Developmental Inventory 2nd Edition showed significant delays in expressive and receptive communication, gross and fine motor, self-care, adult interaction, attention and memory, and perception and concepts.

On physical examination, the patient was severely stunted and wasted. Head circumference was below-1 standard deviation. Facial features included trigonocephaly, prominent metopic ridge, prominent forehead, open anterior fontanel, hyperteloric, sparse eyebrows, epicanthal fold, depressed nasal bridge, high insertion of the collumella, flat philtrum, and thin upper lip (Figure 1). He had a grade 2/6 systolic murmur at the left upper sternal border, bilateral single transverse palmar crease, and bilateral fifth digit clinodactyly.

Echocardiography showed a discrete mild coarctation of the aorta, patent foramen ovale and mild pulmonary stenosis with no chamber enlargement. He was then maintained on furosemide. He had normal otoacoustic emission test results. Chromosomal analysis (Figure 2) of the patient showed 46, XY, del (11) (q23).

DISCUSSION

Jacobsen syndrome is a rare chromosomal abnormality syndrome with an estimated prevalence of around 1 in 100,000 live births. It has never been reported yet in the Philippine literature. It is defined molecularly as any interstitial or terminal deletion in chromosome 11q. It is a gene-rich region with around 342 genes. This includes genes which are implicated to cause the most significant morbidity and mortality, namely congenital heart disease, Paris-Trousseau bleeding disorder, and psychomotor developmental delay.[1]

Congenital heart disease, which is a significant cause of mortality, is present in 56 % of patients with JS. The most frequent heart defects in JS include ventricular septal defect and left heart obstructive malformations like coarctation of the aorta, which is present in our patient. A rare and severe condition called hypoplastic left heart syndrome is present in 5% of JS patients. Some of the implicated genes include *ETS-1* gene and *JAM3* gene located in the 8 Mb cardiac critical region of 11q. [1,2]

Thrombocytopenia/platelet dysfunction or the Paris-Trousseau bleeding disorder is a highly penetrant feature of JS affecting at least 88.5 % of patients. These features may be misdiagnosed as signs of sepsis; hence, careful evaluation is necessary to make the correct assessment. Our patient presented with the same features, hence, subsequent evaluation and follow-up with hematology service was done. Parents were advised about the associated risk of bleeding associated in this syndrome. Based on recent studies, *FLI1* gene located in chromosome 11q24.3 is involved in platelet production and is the most likely the implicated gene for the thrombocytopenia in this syndrome.[2,3,4]

Psychomotor developmental delay, ranging from mild to severe, is present in about 97% of patients with JS, our patient included. The degree of intellectual disability was correlated with the deletion size as showed in previous studies. A number of genes were implicated, such as *B3GAT1*, *BSX*, *NRGN*, *FEZ1* and *RICS*.[2]

Other associated malformations in Jacobsen syndrome include kidney malformation, digestive tract anomalies, central nervous system anomalies, reproductive abnormalities, and skeletal malformations. Hearing problems, although not common in JS, should still be investigated.[5]

Management approach of patients with this condition is multi-disciplinary. Complete evaluation for JS patients include clinical assessment by a general pediatrician, baseline evaluation and echocardiogram by a pediatric cardiologist, baseline evaluation by a neurologist, abdominal ultrasound, ophthalmologic examination, complete

blood count, platelet counts, platelet function studies, bleeding time, endocrinologic evaluation and immunologic assessment.[2,6]

Ideally, parental karyotypes should be obtained to know if it is a de novo deletion or from a parental balanced translocation. This will have implications in genetic counseling since a de novo deletion will almost have a negligible risk for recurrence while that from a balanced translocation from a parent will have a higher risk.[2]

CONCLUSION

In summary, we described a case of Jacobsen syndrome with characteristic facial features, congenital heart disease, thrombocytopenia and developmental delay. Cytogenetic confirmation was obtained by the presence of deletion on chromosome11q23. Given the syndrome's multi-systemic involvement, a multidisciplinary approach is necessary.

CONSENT

Written informed consent was obtained from the parents of the patient for publication of this case report and the accompanying images.

ACKNOWLEDGEMENT

The authors would to like to extend their gratitude to the Cytogenetics Laboratory of the Institute of Human Genetics, National Institutes of Health, Manila, Philippines for providing a photo of the chromosomal analysis of the patient.

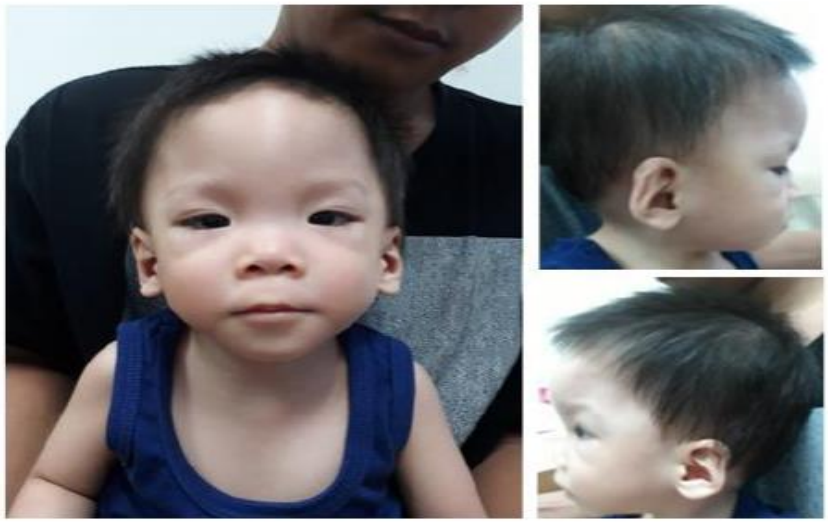

Figure 1. Characteristic facial features of Jacobsen syndrome such as trigonocephaly, prominent metopic ridge, prominent forehead, hypertelorism, sparse eyebrows, epicanthal fold, depressed nasal bridge, high insertion of the collumella, flat philtrum, and thin upper lip

REFERENCES

1. Favier R, Akshoomoff N, Mattson S, Grossfeld P. 2015. Jacobsen Syndrome: Advances in our Knowledge of phenotype and genotype. *Am J Med Genet Part C Semin Med Genet* 169C:239-250
2. Favier R, Jondeau K, Boutard P, Grossfeld P, Reinert P, Jones C, Bertoni F, Cramer EM. Paris-Trousseau syndrome: clinical, hematological, molecular data of ten new cases. *Thromb Haemost* 2003; 90:893-7
3. Kato T, Mizuno S, Kurosawa K, Suzuki S, Niimi T, Natsume N. Jacobsen syndrome associated with cleft lip: A patient report and review. *J Oral Maxillofac Surg Med Pathol* (2014)
4. Krishnamurti L, Neglia JP, Berry SA, Lohr J, Hirsch B, White JG. Paris-Trousseau Syndrome Platelets in a Child With Jacobsen's Syndrome. *American Journal of Hematology* 66:295-299 (2001)
5. Losos M, Kahwash BM, Conces M, Thompson J, Kumar R, Kahwash SB. Jacobsen/Paris-Trousseau SyndromeL Report of a Case with Emphasis on Platelet's Light Microscopic and Ultrastructure Findings. *Open Journal of Pathology*, 2016,6, 8-13
6. Nalbantoğlu B, Donma MM, Nişli K, Paketçi C, Karasu E, Özdilek B, Mintaş NE. Jacobsen syndrome without thrombocytopenia: a case report and review of literature. *The Turkish Journal of Pediatrics* 2013; 55: 203-205