Case report

Genetic and Clinical Complexity in Jacobsen Syndrome: A Case of 11q23.3-q25 Deletion with Trigonocephaly and MYBPC3 Mutation

ABSTRACT

Jacobsen syndrome (JS), also known as 11q deletion disorder, is a rare chromosomal condition characterized by a wide range of congenital anomalies, developmental delays, and hematological abnormalities. This report presents the case of a 9-month-old female child with trigonocephaly, mild developmental delay, hypotonia, and ocular tracking issues. Initial examinations revealed a small atrial septal defect (ASD), a depressed and broad nasal bridge, epicanthic folds, low-set ears, overfolded helices, a smooth philtrum, and a high palate. Genetic testing, including clinical exome sequencing and chromosomal microarray analysis, identified a pathogenic heterozygous copy number deletion in the 11q23.3-q25 region, confirming the diagnosis of Jacobsen syndrome. The MRI of the brain revealed trigonocephaly, hypertelorism, and T2 prolongation of unmyelinated white matter, consistent with the syndrome's typical presentation. Additionally, pathogenic variants were identified in the MYBPC3 and SYNE1 genes, contributing to the clinical complexity. The diagnosis underscores the importance of early genetic evaluation in children with congenital anomalies and developmental delays. Comprehensive management involving genetic counseling, regular monitoring, and supportive therapies is essential to address the diverse needs of patients with Jacobsen syndrome. This case highlights the necessity for continued research and awareness to enhance understanding, treatment, and long-term outcomes for individuals affected by this rare chromosomal disorder.

Keywords: Jacobsen Syndrome, trigonocephaly, 11q deletion, hypertelorism, developmental delay

1. INTRODUCTION

In 1973, Petrea Jacobsen reported the first case of a patient with dysmorphic features, developmental delay, and congenital heart disease (atrial and ventricular septal defects) linked to an 11q deletion inherited from the father. Since then, more than 200 similar cases have been documented. **6**

Jacobsen syndrome is a multi-congenital anomaly/mental retardation (MCA/MR) contiguous gene syndrome resulting from the partial deletion of the long arm of chromosome 11. It is estimated to occur in 1 out of every 100,000 births, with a female-to-male ratio of 2:1. The most common clinical features include pre- and postnatal physical growth retardation, psychomotor delay, and distinctive facial dysmorphisms, such as skull deformities, hypertelorism, ptosis, coloboma, down-slanting palpebral fissures, epicanthal folds, a broad nasal bridge, a short nose, a V-shaped mouth, and small, low-set, posteriorly rotated ears. Abnormal platelet function, thrombocytopenia, or pancytopenia are typically present at birth.**5**
Jacobsen syndrome (JS) is usually not inherited, but an individual with the condition can transmit the deletion to their offspring. According to published data, JS is linked to attention deficit-hyperactivity disorder (ADHD) and a higher prevalence of autism spectrum disorders. About a quarter of children with JS do not survive past infancy, with congenital heart diseases

being the leading cause of death, followed by hematological disorders. Survivors require long-term specialized care, and the oldest known patient with JS is approximately 50 years old. **8**

2. PRESENTATION OF CASE

Here is a 9 month old female child presented with trigonocephaly with metopic ridging at birth, mild developmental delay, hypotonia, eye tracking issue, ? hearing impairment, ?small ASD in the first ECHO scan, AF-admitting 1 finger nevus flammeus, depressed and broad nasal bridge, epicanthic folds, low set ears, overfolded helices, smooth philtrum, high palate, sacral dimple, mild lower length discrepancy, increased tone and jerky pursuits.

MRI of the brain showed T2/FLAIR hypo-intensities with cysts in the frontal region, simplified gyration (? mild polymicrogyria) only P1L1 is myelinated and T1 hypointense-corresponding hyperintensities.

Clinical exome sequencing done elsewhere revealed a pathogenic variant in the MYBPC3 gene [c.33372C>A , p.Cys1124 Ter] and a variant of uncertain significance in the “SYNE1” gene [c.17938GA . p.Glu598Lys] and a likely pathogenic copy number deletion in the chromosome 11.Karyoseq with Karyotyping done elsewhere showed pathogenic CNV deletion (Chr 11: 120943729-135008516) (GRCh 37).

Whole exome sequencing done at NIMAHNS also revealed the same chromosome “11q23.3q25” copy number loss. She is suspected to be suffering from chromosome 11q, terminal deletion syndrome.

Chromosomal Microarray was done: Results were found to be positive – Pathogenic copy number loss relevant to the phenotype described in the subject was identified.

Table 1. Chromosomal Microarray

Type	Chromosome region	Size	Genomic coordinates	Zygosity	Classification
Copy no. Loss	11q23.3-11q25	14.07 Mb	Arr [GRCh 37] 11q23.3-11q25 (120864922-134944006X1)	Heterozygous	Pathogenic

Report Summary – A heterozygous copy number loss. In 11q23.3-q25 region spanning the genomic coordinates chr11:120864922-134944006 was identified. Similar sized copy no. loss overlapping this region have been reported in DECIPHER associated with similar phenotypes. This region comprises of 156 genes including HEPACAM. The leukoencephalopathy phenotype is secondary to haploinsufficiency of the HEPACAM gene (MLC2) which is reported in literature. The same copy number loss was also observed in exome sequencing of the same proband. In addition, the clinical phenotype of the proband matches to that of the proband. In view of all the current evidence , this deletion is considered to be pathogenic.

Final Interpretation – In view of the presence of a heterozygous pathogenic deletion in 11q23.3-q25 along with the matching clinical phenotype, the diagnosis of “11q23.3-q25 deletion syndrome” is confirmed in the proband.

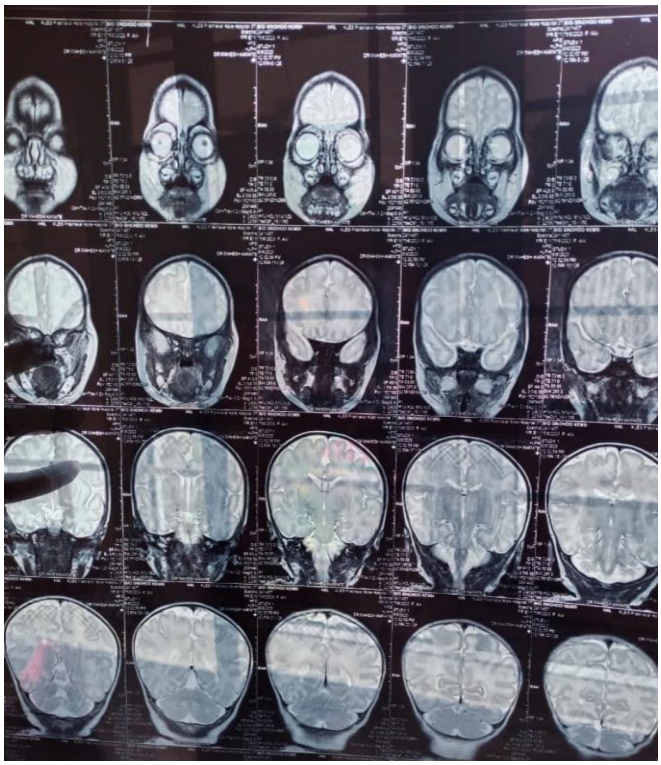

Fig 1- MRI outcome

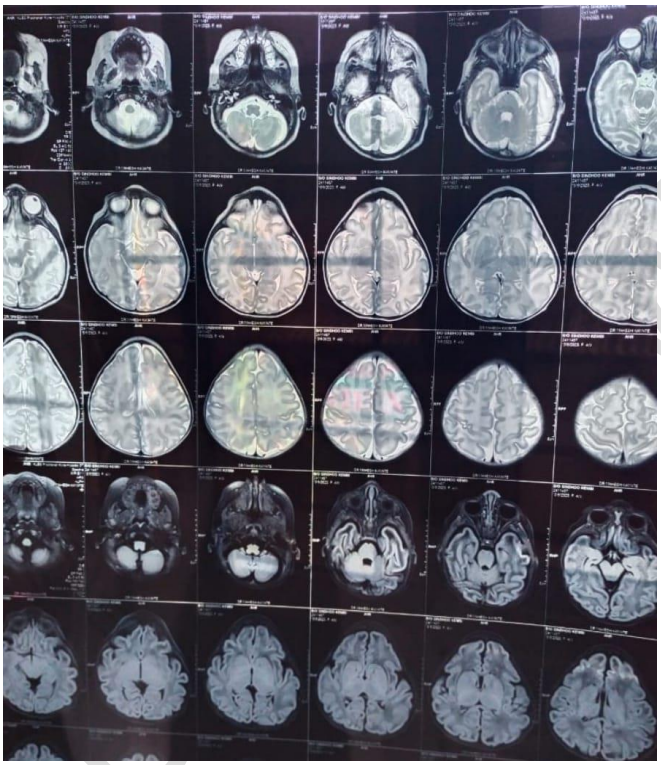

Fig 2- MRI outcome

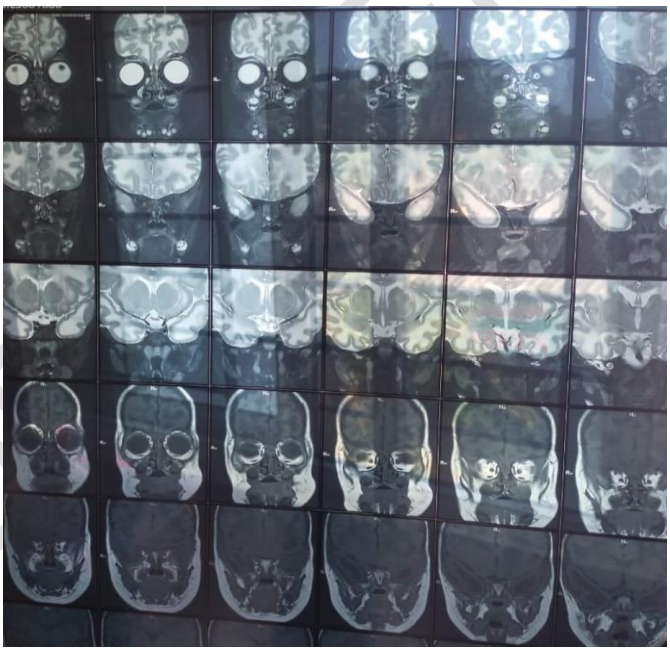

Figure no 3: MRI suggesting craniosynostosis (trigonocephaly) due to early fusion of the metopic suture

The above figures suggest Craniosynostosis (trigonocephaly) due to early fusion of the metopic suture as described

3. DISCUSSION

We documented a case of 9 month old female child who was born with trigonocephaly, slight developmental delay, hypotonia, and a difficulty with her eyes tracking. According to the ECHO scan, there was a tiny Atrial

septal defect (ASD); a depressed and broad nasal bridge, overfolded helices, low set ears, a smooth philtrum, a high palate with enhanced tone, and jerky pursuits .There was also a pink patch on the child's finger. The baby had underwent a clinical exome sequencing, which revealed a pathogenic mutation in the MYBPC3 gene, a gene that instructs making cardiac myosin binding protein C found in the heart muscle cells, and a variant in the SYNE1 gene, gene that coordinates the movement (the cerebellum) and a pathogenic copy deletion in the chromosome 11 q. Trigonocephaly is usually common in patients with Jacobsen syndrome, which is associated with large head size and skull abnormality giving forehead a pointed appearance. The patient had under-went chromosomal microarray analysis, and the findings indicated a heterozygous copy number loss in the 11q23.3q25 region. The MRI of the brain showed evidence of triangular-shaped frontal cranium due to relative fusion of metopic suture suggestive of trigonocephaly resulting in hypertelorism. There is also seen a T2 prolongation of the unmyelinated white matter. Persistent cavum septum pellucidum was noted.

4. CONCLUSION

Jacobsen disease, also known as 11q deletion disorder, is a rare chromosomal condition with a spectrum of clinical manifestations. This case highlights the importance of early diagnosis and comprehensive management to improve the quality of life for affected individuals. Our patient presented with characteristic features such as developmental delays, congenital anomalies, and hematological abnormalities. The multidisciplinary approach involving genetic counseling, regular monitoring, and supportive therapies proved crucial in addressing the diverse needs of the patient. Continued research and awareness are essential to enhance understanding and treatment of Jacobson disease, ultimately paving the way for better prognostic outcomes.

CONSENT

As per international standards, parental written consent has been collected and preserved by the author (s).

ETHICAL APPROVAL

As per international standards or university standards written ethical approval has been collected and preserved by the author(s).

REFERENCES

- Mattina T, Perrotta CS, Grossfeld P. Jacobsen syndrome. Orphanet journal of rare diseases. 2009 Dec;4:1-0.
- Ichimiya Y, Wada Y, Kunishima S, Tsukamoto K, Kosaki R, Sago H, Ishiguro A, Ito Y. 11q23 deletion syndrome (Jacobsen syndrome) with severe bleeding: a case report. Journal of Medical Case Reports. 2018 Dec;12:1-4.
- Favier R, Akshoomoff N, Mattson S, Grossfeld P. Jacobsen syndrome: advances in our knowledge of phenotype and genotype. InAmerican Journal of Medical Genetics Part C: Seminars in Medical Genetics 2015 Sep (Vol. 169, No. 3, pp. 239-250).
- Blazina Š, Ihan A, Lovrečić L, Hovnik T. 11q terminal deletion and combined immunodeficiency (Jacobsen syndrome): Case report and literature review on immunodeficiency in Jacobsen syndrome. American Journal of Medical Genetics Part A. 2016 Dec;170(12):3237-40.
- Dalm VA, Driessen GJ, Barendregt BH, van Hagen PM, van der Burg M. The 11q terminal deletion disorder Jacobsen syndrome is a syndromic primary immunodeficiency. Journal of clinical immunology. 2015 Nov;35:761-8.
- Jones C, Slljepcevic P, Marsh S, Baker E, Langdon WY, Richards RI, Tunnacliffe A. Physical linkage of the fragile site FRA11B and a Jacobsen syndrome chromosome deletion breakpoint in 11q23. 3. Human molecular genetics. 1994 Dec 1;3(12):2123-30.

- Böhm D, Hoffmann K, Laccone F, Wilken B, Dechent P, Frahm J, Bartels I, Bohlander SK. Association of Jacobsen syndrome and bipolar affective disorder in a patient with a de novo 11q terminal deletion. American Journal of Medical Genetics Part A. 2006 Feb 15;140(4):378-82.
- Noh JH, Park IS, Lee HK, Kim YC. A Case of Jacobsen Syndrome. Journal of the Korean Society of Neonatology. 2002 Nov 1;9(2):211-4.
- Gadzicki D, Baumer A, Wey E, Happel CM, Rudolph C, Tönnies H, Neitzel H, Steinemann D, Welte K, Klein C, Schlegelberger B. Jacobsen syndrome and Beckwith-Wiedemann syndrome caused by a parental pericentric inversion inv (11)(p15q24). Annals of Human Genetics. 2006 Nov;70(6):958-64.