FIRST CASE OF KAGAMI-OGATA SYNDROME IN A MALAYSIAN PATIENT

Fatimah Azman, Teh Keng Hwang, Nor Khatijah Mohd Aris, Siti Zaharah Farah Dura, Noor Shahizan Ajmi, Roziana Ariffin Genetic Laboratory, Pathology Department, Women and Children's Hospital Kuala Lumpur

(This article has not been published)

INTRODUCTION

The Kagami-Ogata syndrome (KOS) is a rare genetic imprinting disorder involving genes within the imprinted region of chromosome 14q32. The mechanisms responsible causing this disorder are paternal uniparental disomy 14 (upd(14)pat), epimutations (hypermethylations) and microdeletions affecting the IG-DMR and/or the MEG3-DMR of maternal origin. In the latter case, 50% recurrence risk may apply. Maternal deletion of 14q32 imprinted region accounted for 20% of cases with 50% survival rate. Phenotypes are similar irrespective of the underlying cause resulting in characteristic facies with full cheeks, protruding philtrum, and increased coat-hanger angle to the ribs constituting pathognomonic features. Other clinical manifestations that may be present are abdominal wall defects, placentomegaly and polyhydramnios.

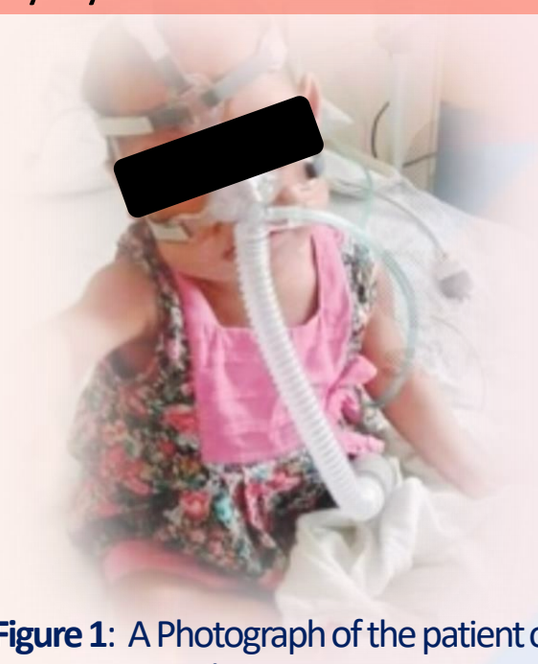

Figure 1: A Photograph of the patient on ventilation support.

BACKGROUND

This is a case of a 2-year-old Malay girl with frontal bossing, isolated thoracic dysplasia, laryngomalacia, shortened right humerus, patent foramen ovale and patent ductus arteriosus.

METHODS

The chromosomes were prepared by conventional cytogenetic analysis employing peripheral blood leucocytes microculture method and subjected to GTG banding. Genomic DNA was extracted from peripheral blood leucocytes using automated DNA extraction instrument, Prepito® and then subjected to microarray analysis using Agilent CGH microarray ISCA 4x180K.

RESULTS

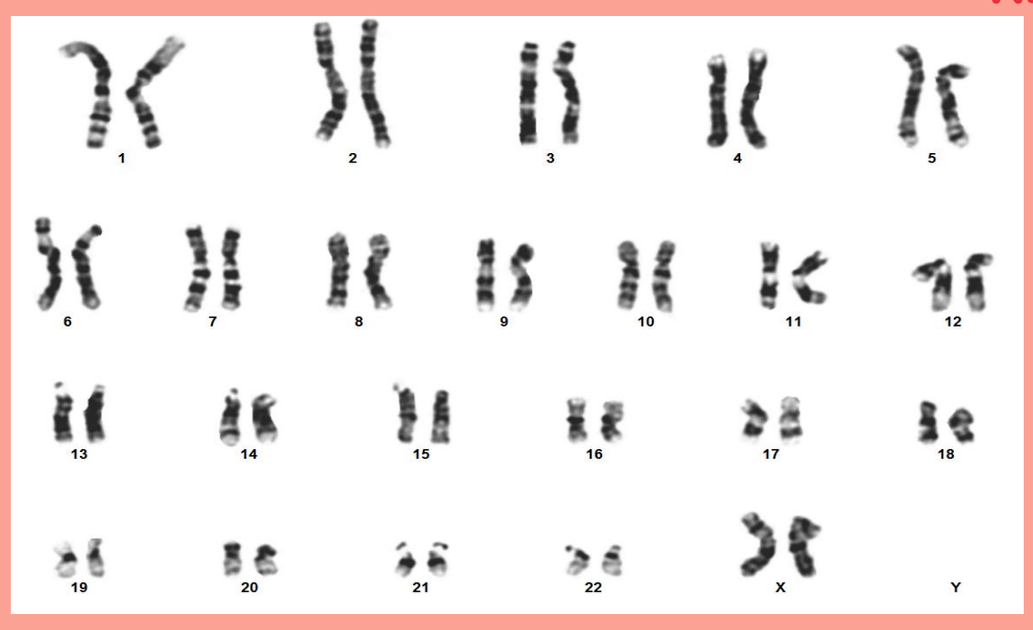

Figure 2: Cytogenetic analysis showing 46,XX karyotype pattern.

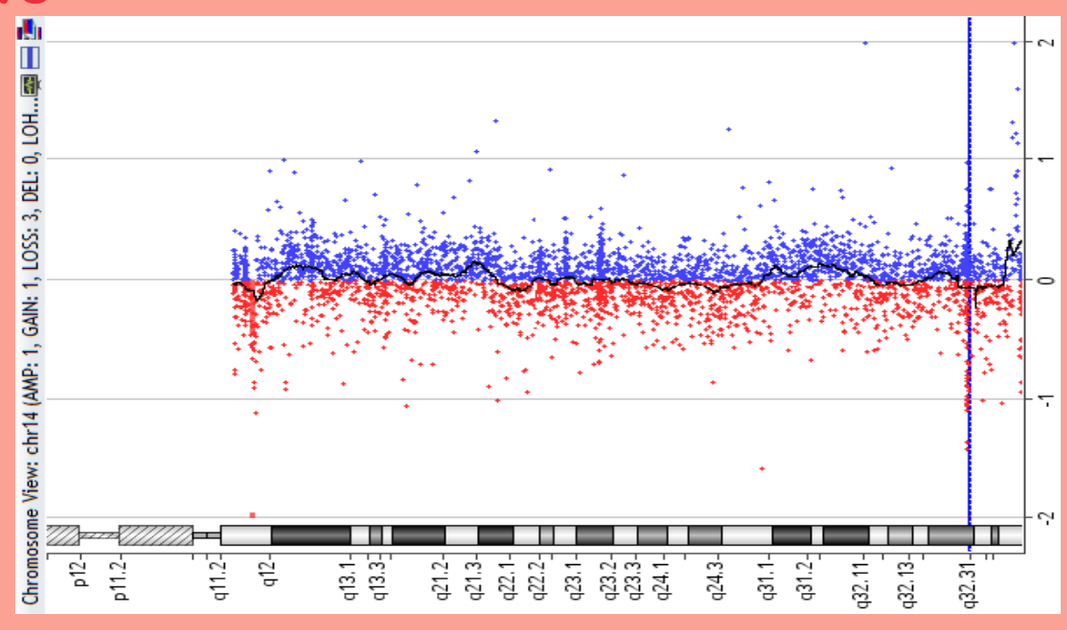

Figure 3: Microarray analysis carried out revealed a female profile with a loss of 28 probes at 14q32.2 to 14q32.31 with the size of 131Kb. This deletion interval involves 6 OMIM genes: MEG3, RTL1, MIR431, MIR433, MIR127, MIR136.

DISCUSSION

The absence of MEG3 gene expression is characterized by defects in skeletal muscle maturation, bone formation, placenta size and organization, and prenatal lethality. While most cases result from a chromosomal deletion that occurs as a random event during gamete formation or in embryogenesis, some individuals may inherit an unbalanced translocation from an unaffected parent whom carries a reciprocal translocation. As this patient harbours deletion of MEG3 gene, further investigations are warranted to determine the origin, whether it is a *de novo* or maternally-derived.

CONCLUSION

Identification of mutation spectrum in this patient has crucial implications for understanding of a disease and its behaviour, leading to modifications of therapeutic recommendations, prognostic predictions and genetic counselling. To the best of current knowledge, this case is the first and only KOS case diagnosed in Malaysia. Hence, this case is reported for its rarity and for case collection to correlate between genotype-phenotype of KOS in Malaysia.

PATHOGNOMONIC FEATURES

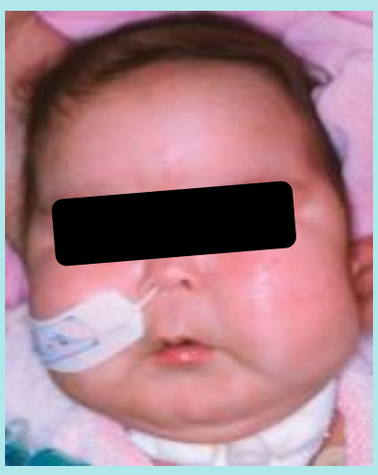

Figure 4: Facial gestalt of full cheeks and protruding philtrum.

Figure 5: Chest radiograph showing increased coat-hanger angle to the ribs.

ACKNOWLEDGEMENT

We thank all doctors and staff of Genetic Laboratory, Women and Children's Hospital Kuala Lumpur and Paediatric Department, Hospital Sultan Abdul Halim; also the patient and her family for their valuable contributions in this case report.

REFERENCES

Beygo, J., Elbracht, M., deGroot,K., Begemann, M., Kanber,D., Platzer,K.etal. Novel deletions affecting the MEG3-DMRprovide furtherevidence for a hierarchical regulation of imprinting in 14q32. Eur. J. Hum. Genet. 23, 180 –188 (2014).

Buiting, K., Kanber, D., Martín-Subero, J. I., Lieb, W., Terhal, P., Albrecht, B. et al. Clinical features of maternal uniparental disomy 14 in patients with an epimutation and a deletion of the imprinted DLK1/GTL2 gene cluster. Hum. Mutat. 29, 1141–1146 (2008).

Hoffmann, K. & Heller, R. Uniparental disomies 7 and 14. Best Pract. Res. Clin. Endocrinol. Metab. 25, 77 –100 (2011).

Kagami, M., O'Sullivan, M. J., Green, A. J., Watabe, Y., Arisaka, O., Masawa, N. et al. The IG-DMR and the MEG3-DMR at human chromosome 14q32.2: hierarchical interaction and distinct functional properties as imprinting control centers. PLoS Genet. 6, e1000992 (2010).

Ogata T.,and Kagami M. Kagami–Ogata syndrome: a clinically recognizable upd (14)pat and related disorder affecting the chromosome 14q32.2 imprinted region. Journal of Human Genetics (2016) 61, 87–94

Rocha, S. T., Edwards, C. A., Ito, M., Ogata, T. & Ferguson-Smith, A. C. Genomic imprinting at the mammalian Dlk1-Dio3 domain. Trends Genet. 24, 306 –316 (2008).

Zechner, U., Kohlschmidt, N., Rittner, G., Damatova, N., Beyer, V., Haaf, T. et al. Epimutation at human chromosome 14q32.2 in a boy with a upd(14)mat-like clinical phenotype. Clin. Genet. 75, 251 (2009)