Girl with DMD due to copy number gain of exons 3 to 12 in dystrophin gene and DiGeorge Syndrome due to 22q11.2 deletion

Craiu Dana [1,2], Butoianu Niculina [1,2], Alexandra Bastian[2,3], Sabina Zurac[3], Mihaela Amelia Dobrescu[3], Alexandru Caramizaru[5], Plaiasu Vasilica[6], Alexandru Iosza[4], Teodora Barbari[1], Andra Stinea[1]

1.Pediatric Neurology Clinic Alexandru Obregia Hospital Bucharest 2.Carol Davila University of Medicine, Department of Neurosciences, Discipline of Pediatric Neurology 3.Colentina University Hospital, Bucharest 4.Spitalul Clinic de Urgenta pentru 5.Copii "Marie S. Curie" Bucuresti 6. Disciplina de Genetica Medicala, UMF Craiova 7. INSMC Alessandrescu-Rusescu

INTRODUCTION

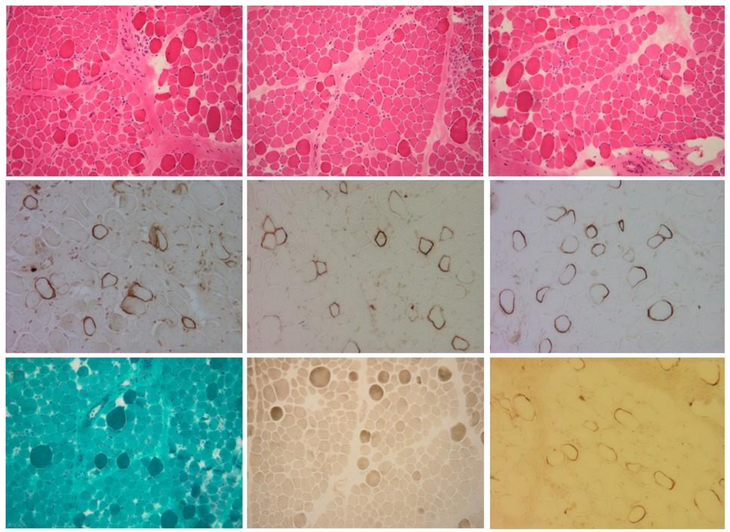
This is a report of a girl with two different genetic disorders, Duchenne muscular dystrophy (DMD) and DiGeorge syndrome. The aim of this study is to discuss the cause of manifest DMD in a female and to underline phenotypic particularities.

MATERIALS AND METHODS

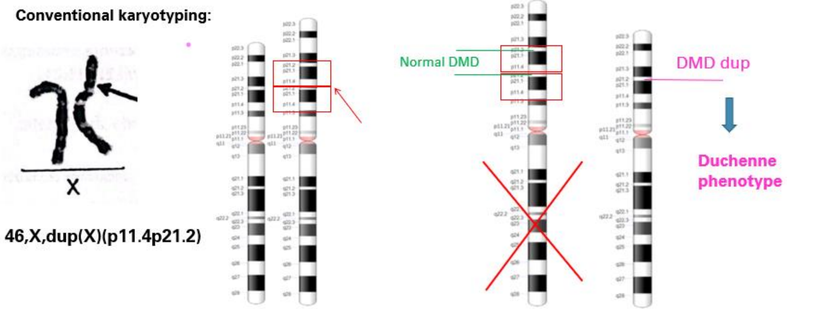
Patient's history and clinical course, neurological findings, biochemical tests including CK levels were performed. Genetic testing included first a 371 genes neuromuscular panel. A conventional karyotyping and a molecular karyotyping were also performed. Both parents were tested for DMD and karyotype. Muscle biopsy from quadriceps muscle wasfollowed by biochemical, histochemical and immunocytochemical studies.

RESULTS

A 1 year 8 months old girl from healthy parents, born after pregnancy with polyhydramnios, hypotonia and postnatal tube feeding, presented with cranio-facial abnormalities (broad flat face, epicanthic eye-folds, hypertelorism, small mouth, prominent upper lip, low-implanted helix-folded ears, short broad-root nose, bifid uvula). She had delayed milestones achievement – sits without support at 8 months, takes several steps without support at 1.8 years old. She has difficulties moving from sitting to standing, calves pseudohypertrophy, nasal speech, recurrent infections. She had creatine-kinase levels of 27.000 to 17.000 U/L. No cardiac, renal anomlies were detected.



Histochemical and immunocytochemical studies of the muscle biopsy showed a dystrophic process of moderate intensity, dystrophin (dys 1, dys2, dys 3) absent in the majority of fibers and overexpression of utrophin.



Genetic testing found a de novo copy number gain in DMD gene, exons 3-12, in frame mutation. Molecular karyotyping found, besides the DMD mutation, a deletion in TBX1 gene responsible for DiGeorge syndrome. Conventional karyotyping found a second, larger duplication on X chromosome (p11.4 p21.2). Both parents had normal karyotypes.

CONCLUSION

1. Our hypothesis for the current phenotype is that the two different duplication are on different X Chromosomes. The large duplication determined the preferential inactivation of that XC, and the XC with DMD mutation remained active. The inactivation skewing rate is currently being determined. 2.DMD and DiGeorge syndrome association was not described in the literature. 3.This association will lead to challenging management.

REFERENCES

1. Symptomatic dystrophinopathies in female children. Natashia Seemann a, Kathy Selby c, Laura McAdam d, Doug Biggar d, Hanna Kolski e,Sharan Goobie a, Grace Yoon f, Craig Campbell a,b,⇑,on behalf of the Canadian Pediatric Neuromuscular Group. 2. Van den Veyver IB. Skewed X inactivation in X-linked disorders. Semin Reprod Med. 2001 Jun;19(2):183-91. doi: 10.1055/s-2001-15398. PMID: 11480916.

dcraiu@yahoo.com; www.bolirare-obregia.ro