The Turkish Journal of Pediatrics 1998; 40: 139-143

DIPLOID – TRIPLOID AND TETRAPLOID MOSAICISM IN A CHILD WITH CRYPTOGENIC CIRRHOSIS AND MEMBRANOUS GLOMERULONEPHRITIS: A CAUSAL RELATIONSHIP OR COINCIDENTAL ASSOCIATION?*

*Rezan Topaloğlu MD**, Dilek Aktaş MD***, Ayşın Bakkaloğlu MD*****
*Sevim Balcı MD****, Deniz Doğru MD*****, Ramazan Öztürk MD******

SUMMARY: Topaloğlu R, Aktaş D, Bakkaloğlu A, Balcı S, Doğru D, Öztürk R. (Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Diploid-triploid and tetraploid mosaicism in a child with cryptogenic cirrhosis and membranous glomerulonephritis: a causal relationship or coincidental association? Turk J Pediatr 1998; 40: 139-143.

We present a seven-year-old boy with cryptogenic cirrhosis, membranous glomerulonephritis, mild mental retardation and mild dysmorphic changes. Chromosomal analysis showed diploid, triploid and tetraploid mosaicism which was detected both by cytogenetic study and flow cytometric analysis of nuclear DNA content. Complete tetraploidy and triploidy, usually lethal, are rare chromosomal disorders. This is the first reported case of diploid-triploid-tetraploid mosaicism with cryptogenic cirrhosis and membranous glomerulonephritis. *Key words: triploidy, tetraploidy, mosaicism, cryptogenic cirrhosis, membranous glomerulonephritis.*

Tetraploidy and triploidy are relatively common chromosomal disorders in spontaneously aborted fetuses[1-3]. Only a few dysmorphic infants have been described with complete and mosaic tetraploidy. In complete triploidy, the longest postnatal survival is five months[4-6]. Prolonged survival has only been reported with diploid-triploid mixoploid cases[7,8]. Dysmorphic findings and multiple congenital anomalies are common[7,8]. We present a seven-year-old boy who had diploid-triploid-tetraploid mosaicism without severe dysmorphic findings but with cryptogenic cirrhosis and membranous glomerulonephritis (MGN).

Case Report

A seven-year-old boy was referred to our hospital with hepatomegaly which was found on routine physical examination. He was born following a full-term pregnancy, as the fourth child of a 33-year-old mother and 38-year-old father. Parents were

* From the Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara.

** Associate Professor of Pediatrics, Hacettepe University Faculty of Medicine.

*** Fellow in Genetics, Hacettepe University Faculty of Medicine.

**** Professor of Pediatrics, Hacettepe University Faculty of Medicine.

***** Research Assistant in Pediatrics, Hacettepe University Faculty of Medicine.

first degree cousins. There was no family history of spontaneous abortions, congenital malformations, mental retardation, cirrhosis or nephrotic syndrome.

On admission, his blood pressure was 150-100 mmHg. He had flat occiput, short palpebral fissures, low set ears, bilateral simian lines, short thumbs and grade III/VI systolic ejection murmur on the left parasternal area (Figs. 1, 2). His liver was palpable 4 cm under the costal margin in the mildclavicular line and 5 cm under xiphoid, with moderate ascites, and a 3+ pedal edema was present.

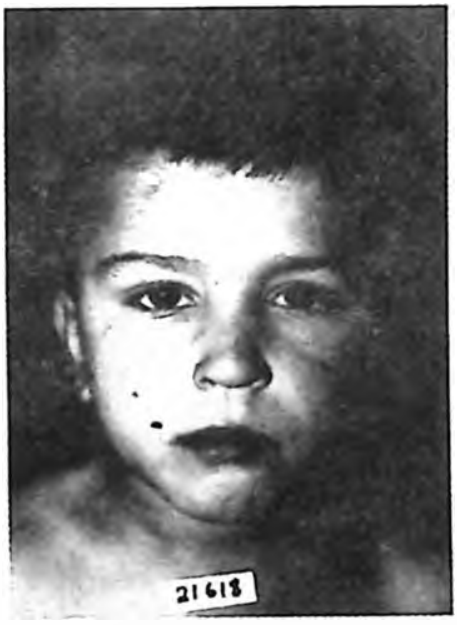

Fig. 1: Note the short palpebral fissures and low set ears of the patient.

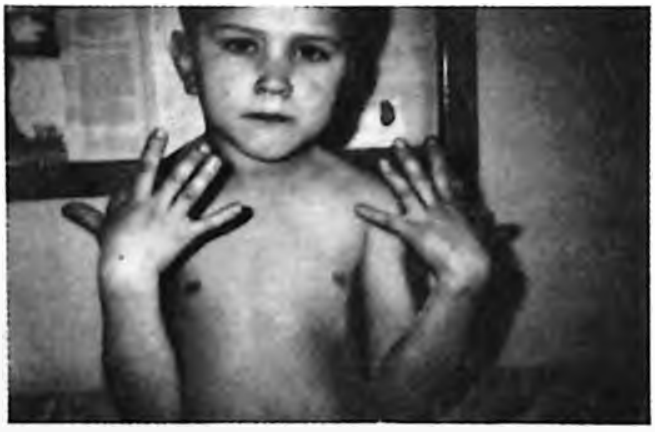

Fig. 2: Note the short thumbs of the patient.

Laboratory findings were as follows: 4+ proteinuria (150 mg/m^2/hour), microscopic hematuria with no pyuria, creatinine clearance 76 ml/min/1.73m^2, total serum protein 5.7 g/dl, serum albumin 2.2 g/dl, alanine aminotransferase (ALT) 55 IU/L, aspartate aminotransferase (AST) 87 IU/L and alkaline phosphatase 247 IU/L. An

abdominal ultrasonography study revealed parenchymal disease of liver and kidney. The following laboratory examinations were normal: serum ceruloplasmin, serum copper, sweat chloride test, serum and urinary amino acids, alpha-1-antitrypsin, antistreptolysin O titer, C-reactive protein, serum complements (C3, C4), circulating immune complex, serum immunoglobulins, cryoglobulins, antinuclear antibodies (ANA), anti-doublestranded deoxyribonucleic acid (anti-ds DNA) and myeloperoxidase-antineutrophil cytoplasmic antibodies (MPO-ANCA). His hepatitis markers (HBs, Anti HBs, HCV Ab, anti HAV) were negative and remained negative during the two year follow-up period.

His liver biopsy was reported as cirrihosis. A needle kidney biopsy was performed and found to be membranous glomerulonephritis (MGN) stage III.

Urine analysis, serum proteins and transaminases were normal in parents and siblings.

Cytogenetic studies

Peripheral venous blood samples were obtained and lymphocyte cultures were set up. For chromosome preparation the standard technique was followed. Slides were stained for Giemsa-banding and QM-banding. In these studies, 58 percent of the cells showed a normal male karyotype (46, XY), 7 percent were triploid (69, XXY) and 35 percent were tetraploid (92, XXXY) (Figs. 3-5). The karyotypes of parents

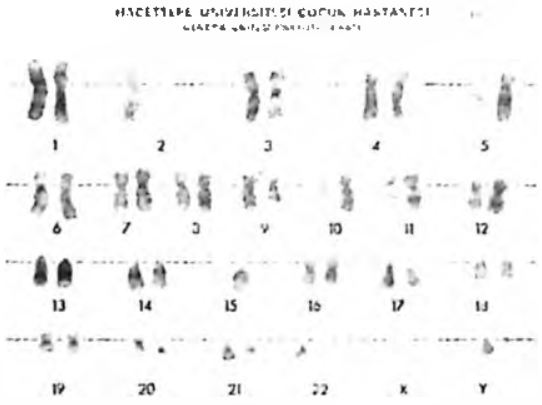

Fig. 3: A normal male karyotype (46, XY) presented in 58% of cells.

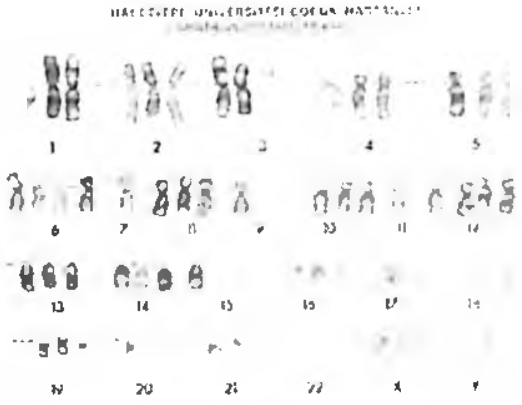

Fig. 4: A triploid karyotype (69, XXY) presented in 7% of cells.

Fig. 5: A tetraploid karyotype (92, XXXY) presented in 35% of cells.

and all three siblings were normal. DNA content in peripheral blood lymphocytes of the index patient was studied with flow cytometer, and was found to be increased to a value of 2.8 percent (normal 1%), which is compatible with mosaicism.

Discussion

Triploidy and tetraploidy frequently cause early spontaneous abortions[1,2]. Triploidy associated with molar changes of the placenta is one of the major causes for loss of triploid pregnancies. A few cases of the full triploidy without placental hydatidiform changes have survived the neonatal period but died during infancy. Prolonged postnatal survival has only been noted with diploid-triploid mixoploidy with severe dysmorphic changes[1]. Complete tetraploidy and tetraploid mosaicism appeared to be very rare (1.1%).

Cardinal findings of triploidy syndrome are characterized by syndactyly of the third and fourth fingers and severe intrauterine growth retardation[9]. In our patient, both cytogenetic and flow cytometric DNA analysis revealed the diploid-triploid-tetraploid mosaicism. Some associated features have been noticed in mosaic cases. Rojanasakul et al.[10] noted tetraploidy mosaicism in two sisters with polycystic ovary syndrome. Near triploidy, near tetraploidy and near diploidy have been reported in pediatric solid tumors and in Hodgkin's disease[11]. Kidney malformations, such as horseshoe kidney, cystic dysplasia, membranoproliferative glomerulonephritis, amyloidosis and immunotactoid glomerulonephritis may be associated with chromosomal anomalies, particularly with Down syndrome[12-14]. In complete triploidy, cystic dysplastic kidneys have been noted[15].

Our patient exhibited cryptogenic cirrhosis and MGN. Glomerular morphologic abnormalities may be seen in more than 50 percent of cirrhotic livers on necropsy or biopsy. This has been the first asociation of MGN related to cryptogenic cirrhosis with diploid, triploid and tetraploid mosaicism.

Although a coincidental relation cannot be excluded, a disturbance of the mitotic process expressed in an increased frequency of polypoidy might well have temporal pathogenetic significance. The disturbance of the mitotic process could be due to an underlying gene defect which may also predispose to cryptogenic cirrhosis and related glomerulopathy.

We think more reports of similar cases are needed to clarify the nature of the association of mixoploidy with coexisting diseases.

Acknowledgement

We thank Dr. Altan Yalçıner for his help with the flow cytometric analysis of the patient.

REFERENCES

1. Graham JM Jr, Rawnsley EF, Simmons GM, et al. Triploidy: pregnancy complicatilons and clinical findings in seven cases. Prenat Diagn 1989; 9: 409-419.
2. Veenema H, Tasseron EW, Geraedts JP. Mosaic tetraploidy in a male neonate. Clin Genet 1982; 22: 295-298.
3. Kajii T, Ferrier A, Niikawa N, Takahara H, Ohama K, Avirachan S. Anatomic and chromosomal anomalies in 639 spontaneous abortuses. Hum Genet 1980; 55: 87-98.
4. Lopez Pajores I, Delicado A, Diaz de Bustamante A, et al. Tetraploidy in a liveborn infant. J Med Genet 1990; 27: 782-783.
5. Qiroz E, Orozco A, Salamanca F. Diploid-tetraploid mosaicism in a malformed boy. Clin Genet 1985; 27: 183-186.
6. Cassidy SB, Whitworth T, Sanders D, Lorber CA, Engel E. Five month extrauterine survival in a female triploid (69, XXY) child. Ann Genet 1977; 20: 277-279.
7. Graham JM Jr, Hoehn H, Lin MS, Smith DW. Diploid-triploid mixoploidy: clinical and cytogenetic aspects. Pediatrics 1981; 68: 23-28.
8. Strobel SL, Brandt JT. Abnormal hematologic features in a live-born female infant with triploidy. Arch Pathol Lab Med 1985; 109: 775-777.
9. Jones KL. Smith's Recognizable Patterns of Human Malformation. Philadelphia: WB Saunders Company; 1988: 32-33.
10. Rojanasakul A, Gustavson KH, Lithell H, Nillius SJ. Tetraploidy in two sisters with the polycystic ovary syndrome. Clin Genet 1985; 27: 167-174.
11. Ankathil R, Vijayakumar T, Pillai GR, Nair MK. Chromosomes in Hodgkin's disease-analysis of involved lymph nodes. Neoplasma 1992; 39: 245-248.
12. Takemura T, Yoshioka K, Akano N, et al. Immunotactoid glomerulopathy in a child with Down syndrome. Pediatr Nephrol 1993; 7: 86-88.
13. Gilli G, Berry AC, Chantler C. Syndromes with a renal component. In: Holliday MA, Barratt TM, Vernier RL (eds). Pediatric Nephrology (2nd ed). Baltimore: Williams and Wilkins; 1987: 384-404.
14. Gupta SK, Venkataseshan VS, Churg J. Mesangiocapillary glomerulonephritis in Down's syndrome. Am J Nephrol 1991; 11: 112-117.
15. Gilbert E, Opitz J. Renal involvement in genetic hereditary malformation syndromes. In: Hamburger J, CrosnierJ, Grünfeld JP (eds). Nephrology (1st ed). New York: John Wiley and Sons; 1979: 914.