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Meier-Gorlin syndrome caused by *ORC1* mutation associated with chromosomal breakage — coincidental finding or new feature of known syndrome?

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Introduction

Meier-Gorlin syndrome (MGS) is a genetically heterogeneous primordial dwarfism syndrome. It was first described in 1959, and since then only a few tens cases have been reported; however, no association with chromosomal breakage has been described, until now. Meier-Gorlin syndrome belongs to the disease group called "primordial dwarfism" due to severe prenatal and postnatal growth retardation. In addition to absent or hypoplastic patellae and microtia, many other symptoms may accompany this syndrome, such as respiratory disorders, feeding problems, craniofacial anomalies (microcephaly with usually normal intellect, maxillary and mandibular hypoplasia, full lips, prominent nose), skeletal abnormalities (joints dislocation, slender ribs and long bones, hooked clavicles, clinodactyly, delayed bone age), genitourinary abnormalities, and rarely neurological abnormalities (delayed psycho-motor development, deafness, congenital labyrinthine anomalies).

Case report

A seven-year-old girl, born small for gestational age (2100 g, 39 cm) in the 39th gestational week, was examined because of delayed growth. In physical examination, proportional short stature (99.6 cm, –5.02 SD), microcephaly (43.3 cm, –5.9 SD), micrognathia, prominent nose, small low-set ears, valgosity of knees, and absent patellae on both sides were present (Fig. 1). Luxation of hip and knees joints was found just after the birth. In her family history, two cousins of her mother had Nijmegen breakage syndrome; however, neither her mother nor her maternal grandfather were carriers of *NBS* mutation. The parents of our patient were in a non-consanguineous relationship. In the course of investigations, celiac disease was not confirmed by enterobiopsy, ultrasound revealed normal abdominal organs, but larger thyroid gland with multiple microcysts up to 3 mm and in laboratory findings, subclinical hypothyroidism, hypovitaminosis D, and normal immunologic profile were found (Tab. I). Magnetic resonance imaging of the brain was without pathological findings, and her IQ was 91. Genetic analysis revealed normal karyotype (46,XX) with higher count of spontaneous chromosomal breakage (8%), while mutations in the *NBS* and *ATM* gene (typical for Nijmegen breakage

Publisher's note: The picture has been blackened due to the withdrawal of consent for publication by the patient's parents

Figure 1. *A girl with Meier-Gorlin syndrome and chromosomal instability: (**A**) proportional short stature, valgosity of the knees, (**B**) prominent nose, micrognathia, and (**C**) small low-set ears*

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Table I. *Selected laboratory parameters*

Parameter [units]	Concentration (evaluation)
Glucose [mmol/L]	4.4 (OK)
Creatinine [μmol/L]	52 (OK)
Cholesterol [mmol/L]	4.48 (↑)
Aspartate transaminase [μkat/L]	0.15 (OK)
Alanine transaminase [μkat/L]	0.32 (OK)
CRP [mg/L]	0.4 (OK)
IgG [g/L]	10.76 (OK)
IgA [g/L]	0.908 (OK)
IgM [g/L]	0.518 (OK)
Leucocytes [.10^9/L]	5.00 (OK)
Haemoglobin [g/L]	128 (OK)
Platelets [.10^9/L]	284 (OK)
TSH [mIU/L]	7.01 (↑)
Free T4 [pmol/L]	11.4 (OK)
Vitamin D [ng/mL]	21.6 (↓)
IGF-1 [ng/mL]	180(OK)
IGFBP-3 [ng/mL]	2600
Thyroid peroxidase and thyroglobulin antibodies	Negative
Tissue transglutaminase and endomysial antibodies	Negative
Chromosome breaks (%)	8 (↑)

CRP — C-reactive protein; Ig — immunoglobulin; TSH — thyroid-stimulating hormone; IGF-1 — insulin-like growth factor 1; IGFBP-3 — insulin-like growth factor-binding protein 3

syndrome and ataxia-telangiectasia, respectively) were not confirmed. Homozygous mutation p.Phe89Ser (c.266T>A) in *ORC1* (origin recognition complex) gene (1p32) was found by whole genome sequencing that referred to Meier-Gorlin syndrome type 1. The patient has been advised to avoid X-rays and other radiation, and the treatment with levothyroxine and vitamin D was started. She has been closely followed and until now (10 years old) no neoplasm or any signs of lymphoproliferation have appeared.

Discussion

Mutations in several genes (*ORC1, ORC4, ORC6, CDT1, CDC6*) have been identified as causing various types of MGS; all of them belong to the pre-replication complex necessary for initialisation of DNA replication, cell-cycle progression, and growth. Pre-replication complex is formed by the loading of the ORC1–6 proteins onto chromatin during M and early G1 phases of the cell cycle. Further proteins (including CDT1 and CDC6) are recruited, and the complex loads the multimeric MCM helicase (minichromosomal maintenance protein complex) to complete licencing of the origin. The partial loss-of-function mutations in MGS patients probably leads to reduced MCM helicase loading and reduced origin licensing capacity [1].

A possible link between DNA instability and mutation in the *ORC1* gene is not completely clear. Maintenance of genome stability is a complex process crucial for proper cell function and tumour suppression. Chromosome instability can result from many endogenous factors (errors in DNA replication, DNA repair processes, post-transcriptional modifications of RNA, or posttranslational modifications of histone or non-histone proteins) or exogenous factors (ultraviolet light, radiation, chemical mutagens, and oxidants). The *ORC1* gene seems to have an important function in normal growth and development because, according to published genotype–phenotype studies, individuals with *ORC1* mutations have significantly shorter stature and smaller head circumferences than individuals with mutations of other genes [1]. The *ORC1* gene probably also has another unique function, the loss of which induces instability in the chromosome, as was found in *Saccharomyces cerevisiae* [2]. Centrosomes are multifunctional regulators of genome stability [3], and human *ORC1* has been found to be required for controlling centriole and centrosome number and for maintenance of higher order chromatin structure [4]. Similarly, mutation in the *ORC4* gene leads to locus-specific chromosome breakage and a ribosomal RNA deficiency in yeast [5].

Despite the fact that the exact mechanism of an association between chromosomal breaks and MGS is not clear, an indicated connection is essential for further management of individuals carrying *ORC1* mutation. Firstly, patients with MGS or at least with *ORC1* mutation should have examined also the possible presence of chromosomal breaks; and secondly, MGS patients with increased occurrence of chromosomal breaks should be closely followed for possible tumour genesis. A question remains, if MGS or at least mutations in *ORC1* gene should be classified as one of the chromosomal breakage syndromes.

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