Polycystic ovary syndrome: A new phenotype in mosaic variegated aneuploidy syndrome?

Syndrome des ovaires polykystiques : un nouveau phénomène du syndrome d’anéuploïdie en mosaïque ?

1. Clinical report

A 27-year-old woman with a history of short stature in infancy and oligomenorrhea presented with secondary amenorrhea. She was the product of a third pregnancy of non-consanguineous parents. She had no cognitive impairment. She had her menarche at the age of 12 years, since then she reported chronic menstrual irregularities. She has had secondary amenorrhea since twelve months. Physical examination showed a short neck without microcephaly, short stature with a height of 1.22 meters and a short proximal limb segments (Fig. 1). Her weight was 45 kg and body mass index 30 kg/m², with a waist circumference of 80 cm. Systolic blood pressure was 90 mmHg and diastolic blood pressure was 60 mmHg. She had a facial dysmorphia: temporal bossing, triangular face, hypertelorism and micrognathia. She had male pattern with a frontal baldness without hirsutism or other signs of virilism (Fig. 2). Skeletal abnormalities were knee varus, short fingers and toes, broad first toe and a wide sandal gap between the first and the second toes (Figs. 3 and 4).

Ibtissam Oueslati, Lilia Kraoua, Karima Khiari, Ridha Mrad

Néjib Ben Abdallah

a Unité d’endocrinologie, service de médecine interne A, hôpital Charles-Nicolle, faculté de médecine de Tunis, université de Tunis El Manar, boulevard du 9-Avril, Bab souika, 1006 Tunis, Tunisia

b Service des maladies congénitales et héréditaires, hôpital Charles-Nicolle, faculté de médecine de Tunis, université de Tunis El Manar, Tunis, Tunisia

* Corresponding author.

E-mail address: medibitis@yahoo.fr (I. Oueslati)

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Fig. 1. Patient’s morphotype: short stature short proximal limb segments.

Fig. 2. Facial dysmorphia: short neck, temporal bossing, micrognathia.

Fig. 3. Feet skeletal abnormalities: broad first toe and a widely sandal gap.
The pituitary hormone tests revealed normal baseline gonadotropin level. The progesterone withdrawal test was positive. The insulin tolerance test showed an insufficient GH response (5.3 ng/mL). IGF1 level was normal for age. Thyroid and adrenal hormones were normal. Testosterone level was moderately elevated (Table 1). The metabolic tests showed hypercholesterolemia, low HDL cholesterol and a type 2 diabetic status (Table 2). The pelvic ultrasonography revealed normal ovary volume: 6.7 mL on the right, 8.4 mL on the left and multiple follicles in both ovaries. Pituitary MRI revealed a hypoplastic anterior pituitary gland and a Rathke’s cleft cyst (Figs. 5 and 6).

The initial peripheral blood chromosome study showed multiple and diverse aneuploidy in 20% of mitotic cells. The second showed aneuploidy in 30% of mitosis (Fig. 7).

The screening for neoplasia was negative; full blood count was normal. Radiographs showed a normal bone squeueleton, they did not show evidence for ovarian tumor. Abdominal pelvic ultrasound did not show evidence for ovarian tumor.

During 2 years follow-up, amenorrhea persisted but bleeding occurred whenever progestative therapy was used.

2. Discussion

Our case is the first report of metabolic syndrome and secondary amenorrhea in mosaic variegated aneuploidy syndrome (MVA). It is a very rare condition characterized by constitutional mosaic aneuploidies, non-specific phenotype including microcephaly, mild malformations, growth and mental retardation, and an increased risk of malignancy [1,2]. Dysmorphic
Facial features in MVA syndrome are low-set ears, micrognathia, epicanthic folds, occipital prominence, broad nasal bridge, triangular face, frontal bossing and hypertelorism. Other neurological and eye abnormalities, skeletal hand and foot abnormalities and dermatological anomalies have also been described [3].

The diagnosis of MVA syndrome is based on the increased rate of variable aneuploidies in observed cells. The proportion of aneuploid cells in individuals with MVA is variable, but is usually more than 10% and substantially greater than in normal individuals [4]. The phenotype was mild in our patient, including craniofacial dysmorphic feature and growth retardation, genetic study showed predominantly nonosomies with multiple trisomy in blood lymphocyte. The oligomenorrhea lets us discuss different diagnosis. The direct relationship between hypoplastic pituitary and secondary hypogonadism was less plausible as the lack of gonadotropin has not been described in MVA syndrome before and the progesterone withdrawal test was positive in our patient. Hormonal deficiencies have not been described in previous reports of MVA, although a few cases suggested this possibility [5]. Short stature is not specific of MVA syndrome; it can be related to GH deficiency as reported in some rare cases or to skeletal abnormalities [6]. Pituitary tests in our patient demonstrated a modest GH secretory response to stimulation and a normal IGF1 level, suggesting a partial GH deficiency. Oligomenorrhea in our patient may be related to the high testosterone level that is strongly suggesting a polycystic ovary syndrome (PCOS). However, the antral follicular count and follicular size were not mentioned in suprapubic pelvic ultrasound. So transvaginal ultrasound criteria for PCOS were missed. Short stature, high testosterone and amenorrhea can be also observed in congenital adrenal hyperplasia. Unfortunately, 17OH-progesterone level could not be measured in our patient. Therefore 21-hydroxylase deficiency is not ruled out. Plagia et al. previously described a case of MVA syndrome in a girl who had primary amenorrhea with normal secondary characteristics in addition to mental retardation, microcephaly and short stature. Variegated aneuploidy related to premature centromere division was found [7]. Our patient had also metabolic syndrome as she had obesity, low HDL cholesterol and diabetes mellitus. Metabolic abnormalities have not been described previously in MVA syndrome. These metabolic disorders could be related to the PCOS. One case of obesity with MVA syndrome has been published [8].

Common tumors reported in MVA syndrome are Wilms tumour, rhabdomyosarcoma, leukaemia and granulosa cell tumor of the ovary [1]. MVA patient with BUB1B mutation are different regarding the risk of cancer. In fact, except leukemia, malignancy risk seems to be related to BUB1B mutation. The age of tumor diagnosis varied and ranged between nine weeks and seven years in most cases [9]. However, our patient was 27 years old and no cancer was found.

### 3. Conclusion

The phenotype of our patient was not specific. This case reported the first case of MVA syndrome that associates secondary amenorrhea and metabolic abnormalities. Additional features mimicking PCOS may occur in MVA syndrome.

### Consent statement

Informed consent was obtained from the patient for publication of the case report and accompanying images.

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**Fig. 7. Blood chromosome study.**

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Disclosure of interest

F. Chaker, M. Chihaoûi, M. Yazidi, O. Rejeb, S. Neji, H. Kraoua declare that they have no competing interest.

References


Fatma Chaker a,*, Melika Chihaoûi a, Mériem Yazidi a, Ons Rejeb b, Hedia Slimane a, Sonia Neji b, Houda Kraoua c

a Department of endocrinology and diabetes, Rabta University hospital, Faculty of medicine, University of Tunis El Manar, Tunis, Tunisia

b Department of neuroradiology, National Institute of Neurology, Faculty of medicine, University of Tunis El Manar, Tunis, Tunisia

c Department of genetics, Charles Nicolle university hospital, Faculty of medicine, University of Tunis El Manar, Tunis, Tunisia

*Corresponding author.

E-mail addresses: fatmachaker@yahoo.fr (F. Chaker), melikachihaoûi@yahoo.fr (M. Chihaoûi), mieri yazidi@gmail.com (M. Yazidi), ons.rejeb@gmail.com (O. Rejeb), hedia.slimane@nts.tn (H. Slimane), sonianeji@nts.tn (S. Neji), houdakraoua@yahoo.fr (H. Kraoua)

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Fetal hypothyroidism induced by maternal anti-TSH receptor blocking antibodies and complicated by polyhydramnios despite the absence of goiter. Treatment by intra-amniotic injections of levothyroxine

Hypothyroïdie fœtale induite par des anticorps bloquants antirécepteur de la TSH d’origine maternelle, compliquée de polyhydramnios malgré l’absence de goître. Traitement par injection intra-amniotique de levothyroxine

1. Case report

A 33-year-old young woman starting her first pregnancy had a history of hypothyroidism since her teenage years, due to an auto-immune chronic thyroiditis with a hypoplastic thyroid and high levels (200 UI/L) of TSH-receptor antibodies (TRAb) with more than 80% thyroid blocking antibody activity. She was treated with levothyroxine 150 μg/day resulting in a normal TSH (0.5 mU/L).

Given the potential fetal consequences of the maternal thyroid disease a close multidisciplinary monitoring (obstetrician, sonographist, endocrinologist) was initiated. At 16 weeks of gestation (WG), TRAb levels were 350 UI/L with 86% blocking activity, TSH 0.345 mU/L (N: 0.17–4.23 mU/L) and FT4 23 pmol/L (N: 12–22 pmol/L). The ultrasonographies at 18 and 25 WG found no abnormal morphological elements, but femoral length was at the 10th percentile. At 33 WG the mother maintained a normal TSH (0.873 mU/L) and FT4 (16.5 pmol/L). Ultrasound monitoring showed a polyhydramnios (vertical dimension of the largest pocket of amniotic fluid: 10 cm) and a delay in bone maturation: absence of femoral epiphyseal ossification, with a femoral length still at the 10th percentile while cephalic and abdominal biometrics were at the 50th percentile. There was no gestational diabetes. Fetal hypothyroidism was suspected and the case was presented at the Multidisciplinary Committee of Prenatal Diagnosis of University Hospital in Grenoble. The advice of the committee was to perform amnio-reduction for the following objectives: drainage of polyhydramnios to avoid pregnancy complications; determination of fetal karyotype; evaluation of fetal thyroid function by measurement of thyroid hormones and TRAb in the amniotic fluid; and finally injection of 200 μg levothyroxine after amniotic reduction.

The procedure was carried out at 34 WG + 4 days without difficulty allowing a drainage of 1000 mL of amniotic fluid. Amniotic TSH was elevated: 4.36 mU/L (N: 0.04–0.51 mU/L) while FT4 was undetectable (<2.4 pmol/L); TRAb were very high at 67.40 UI/L (54% of stimulating TRAb, >80% of blocking TRAb). Normal values are those published in 2007 [1].

This allowed to confirm fetal hypothyroidism linked to transplacental transfer of maternal TRAb and it was decided to carry out new intra-amniotic injections of levothyroxine weekly until childbirth, with monitoring of the treatment on amniotic hormones levels (Fig. 1). Because the first injection lead to normalization of amniotic levels of FT4 and FT3, the same dosage of levothyroxine (200 μg) was used at each injection. Successive ultrasound examinations showed no recurrence of