CASE REPORT

RJME Romanian Journal of Morphology & Embryology http://www.rjme.ro/

A unique case of recurrent fetal cystic hygroma: first fetus with an inherited heteromorphism of chromosome 1 (1qh+) and the second fetus with 69XXX triploidy

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Abstract

The authors report a unique recurrent septated cystic hygroma (CH), on two successive pregnancies, at five years interval. The chromosome analysis of the first fetus showed an increase in length of heterochromatin on the long arm of chromosome 1 – 1qh+, a chromosomal polymorphism inherited from mother, 46XX,1qh+,14ps+,21ps+. The karyotype of the second CH, with more severe ultrasound (US) imaging, showed a 69XXX triploidy. The patient took no risk and underwent each time a termination of pregnancy (TOP). The first karyotype is generally considered "normal", although there are few reports linking 1qh+ with low fertility, but this was not the case, the patient having, from a previous marriage, a healthy boy and two TOPs. So, this "particular", but "healthy" karyotype was not a cause for the first CH. The second karyotype highlights a possible causality between the 69XXX triploidy, usually associated with partial hydatidiform mole, and a more severe septated CH in the last fetus. Neither the CHs' appearance nor their recurrence seemed to be family linked, as the two CHs had distinct genetic profiles. We recommend that, once CH is diagnosed, a careful US examination is compulsory for the determination of subcutaneous edema, ascites, pleural and pericardial effusions and cardiac or renal abnormalities; an early genetic work-up is mandatory, by chorionic villus sampling or amniocentesis. However, a "healthy" karyotype does not exclude a severe form, as in our first case of CH. Due to the very poor outcome of fetuses with CH, the patient must be thoroughly informed about the short and the long-term fetal prognosis.

Keywords: cystic hygroma, karyotype, heterochromatin, inherited polymorphism, triploidy.

Introduction

Cystic hygromas (CHs) are cystic congenital malformations of the lymphatic system, more frequently situated posteriorly to the neck [1, 2], but they can occur in many other sites [3]. The outcome of the CH is very poor, often progresses to *hydrops fetalis* (HF) and cause fetal death [4]. This disease frequently associates chromosomal abnormalities, Turner's syndrome being the most common [2, 4]. CHs are not, usually, inherited, although some studies showed familial recurrence, with "normal" karyotypes and raised the hypothesis of an autosomal recessive transmission of the disease [5–7]. Recurrence of CHs with different karyotypes is rarely observed, only few cases being presented until now [8, 9].

Aim

Here, we report an extremely rare case of recurrent CH with HF, revealing unique karyotypes of the fetuses. A brief review of the literature is also presented.

Case presentation

A 27-year-old woman gravida 3 and para 1 arrived for a routine visit at around seven weeks of amenorrhea. Ultrasound (US) scan showed a gestational sac (18 mm, corresponding to six weeks and four days of amenorrhea), with an embryo having cardiac activity [heart rate (HR) 163 beats per minute (bpm)]. The history, the clinical examination and the laboratory tests revealed no

abnormalities. She had, with her first husband, a 4-year-old boy and, thereafter, two terminations of pregnancy (TOPs) on her request. The pregnancy presented here was the first obtained with the second, actual, husband.

She was advised to come back between 11 and 14 weeks of pregnancy for a first trimester screening.

The patient returned five weeks later, when US examination revealed a fetus with a crown-rump length (CRL) of 5.09 cm, corresponding to 11 weeks and six days of amenorrhea. The fetus presented a large septated thin-wall sac, situated predominately on the neck, mainly on the left side, with a nuchal translucency (NT) of 5.06 mm (Figure 1, A–C). The embryo also showed subcutaneous edema, especially on the anterior body wall, with a maximal thickness of 1.1 mm (Figure 1D), without any other effusions.

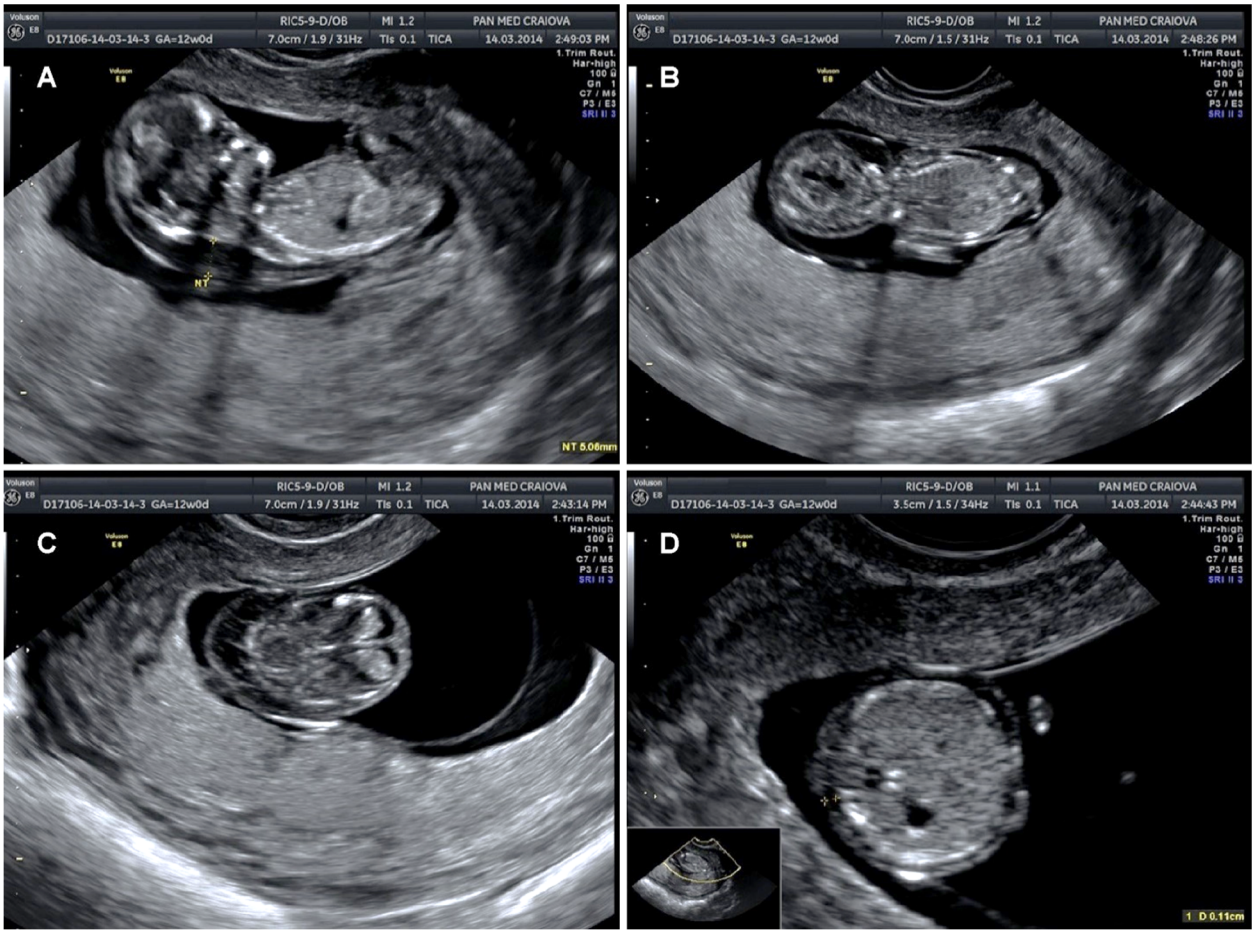

Figure 1 – ***Ultrasound images on the first fetus with cystic hygroma: (A) Sagittal view, NT 5.06 mm; (B) Frontal view – CH can be observed, predominantly developed on the left part of the neck; (C) Head, transversal section – detail of multi thin-septated CH, especially on left side; (D) Abdominal transversal section – the subcutaneous edema can be observed (1.1 mm), especially affecting the anterior wall. CH: Cystic hygroma; NT: Nuchal translucency.***

The diagnostic of CH was established and the patient was informed about the very poor fetal prognostic of this abnormality.

The patient was advised to undergo genetic investigation and she agreed for chorionic villus sampling (CVS). The karyotype was 46XX, but an increase in length of heterochromatin on the long arm of chromosome 1 (1qh+) (Figure 2, A and B) was detected in all metaphases.

Although this karyotype was considered "normal" and "safe", the patient decided for a TOP.

One month later, she returned for her own and for her husband karyotypes. The chromosome analysis from mother peripheral blood showed a heteromorphic variant of chromosome 1 (1qh+), and additionally other two chromosomal variants: an increase in length of the satellites on the short arm of chromosomes 14 and 21 – 46XX, 1qh+14ps+,21ps+ (Figure 2, A and B).

The patient, a university graduate, had no mention of such abnormality in her family or in the partner's family.

The father's karyotype was normal – 46XY.

Despite the medical counseling on the very low risk for another, future, CH, especially in cases with "normal" karyotype and without an indicative familial history, the patient decided not to have another pregnancy.

However, after five years, she returned with a new immunological positive pregnancy test, at six weeks of amenorrhea.

US examination revealed a normal gestational sac (16 mm, corresponding to six weeks and two days of amenorrhea), with an embryo having cardiac activity (171 bpm). Again, the history, clinical and laboratory investigations showed no abnormality.

At around 12 weeks of pregnancy, at the first trimester screening, the US revealed a fetus (CRL 5.82 cm, corresponding to 12 weeks and two days of amenorrhea) with a large septated CH, covering almost all back side of the fetus, mainly around the neck (NT 7.78 mm). The fetus showed, also, subcutaneous edema, especially

involving the anterior thoracic and abdominal wall (1.3 mm) (Figure 3, A–F).

The patient asked for immediately pregnancy interruption. TOP was performed by uterine aspiration.

The genetic analysis of the tissue sample from the aspirative product revealed an extremely rare aspect – a 69XXX triploidy (Figure 4).

Discussions

The incidence of the fetal CH has been reported to be around 0.6% for the fetuses between weeks 11 and 14 of pregnancy [10] and one case per 6000–16 000 live births [11, 12]. They consist in a single or multiloculated asymmetric thin-walled cavities, filled with clear or turbid fluid, more frequently situated at the neck level (>75%) [1] – especially on left side [13] and mainly in the posterior triangle [3]. Ten to twenty percent of the tumors occur in axilla [14] and, more infrequently, in mediastinum [15], groin, scrotum [16], retroperitoneum [17], abdominal viscera [3], pelvis [18] or on the chest wall [19]. There is a male predominance – from a slight general one (59%) [13, 20] to a five times ratio, for the groin [21].

CH is the result of an aberrant development of the lymphatic system, process which is complete in the first two months of pregnancy [22]. These tumors are thought to arise from the failure of the lymphatics to connect to the venous system [2]. CHs can be also the result of the abnormal budding of the lymphatic tissue or of the persistence of isolated lymphatic rests, which retain their embryonic potential, become canalized and continue to secret lymph, generating cystic structures [2, 12].

Most of the fetal CHs are associated with chromosomal abnormalities (between 40% and 75%) [4, 23]. Non-septated CHs are more frequently observed (61.4%) and they are predominantly associated with trisomy 21 (Down syndrome) and cardiac malformations [23]. Septated lesions are more often characterized by Turner's syndrome (45,XO) and have an even poorer prognosis [23–25]. For this reason, when a CH is found, CVS or amniocentesis are mandatory. The examination of the fetal free deoxyribonucleic acid (DNA) from maternal blood is easier, safer for the fetus and earlier feasible, with a very high accuracy for chromosomal abnormalities more frequently associated with CH. However, in many countries (Romania included), it has no legal diagnostic value.

Somehow, contrary with the majority of reported CH, both CHs detailed by us, were severe septated forms, both with very particular karyotypes: the first, considered "normal", showing an inherited polymorphism of chromosome 1 (1qh+) and the other with 69XXX triploidy.

Although CH was long time treated as a non-inherited disease, presently, it is considered that, in the presence of "normal" karyotypes, familial occurrence has an autosomal recessive transmission [5–7, 9]. This hypothesis was not applicable in our case, since the two CHs had distinct karyotypes. We concluded that their successive occurrence was a pure unfortunate incident. However, CHs with normal karyotype can be caused by viral infections (especially with parvoviruses) [26], syphilis [27], maternal alcohol abuse during pregnancy [28] or maternal diabetes mellitus [27]. Usually, nevertheless, the etiology remains unknown [27]. It is also the case for our first reported episode of CH, as none of the above-mentioned conditions could have been identified in the patient.

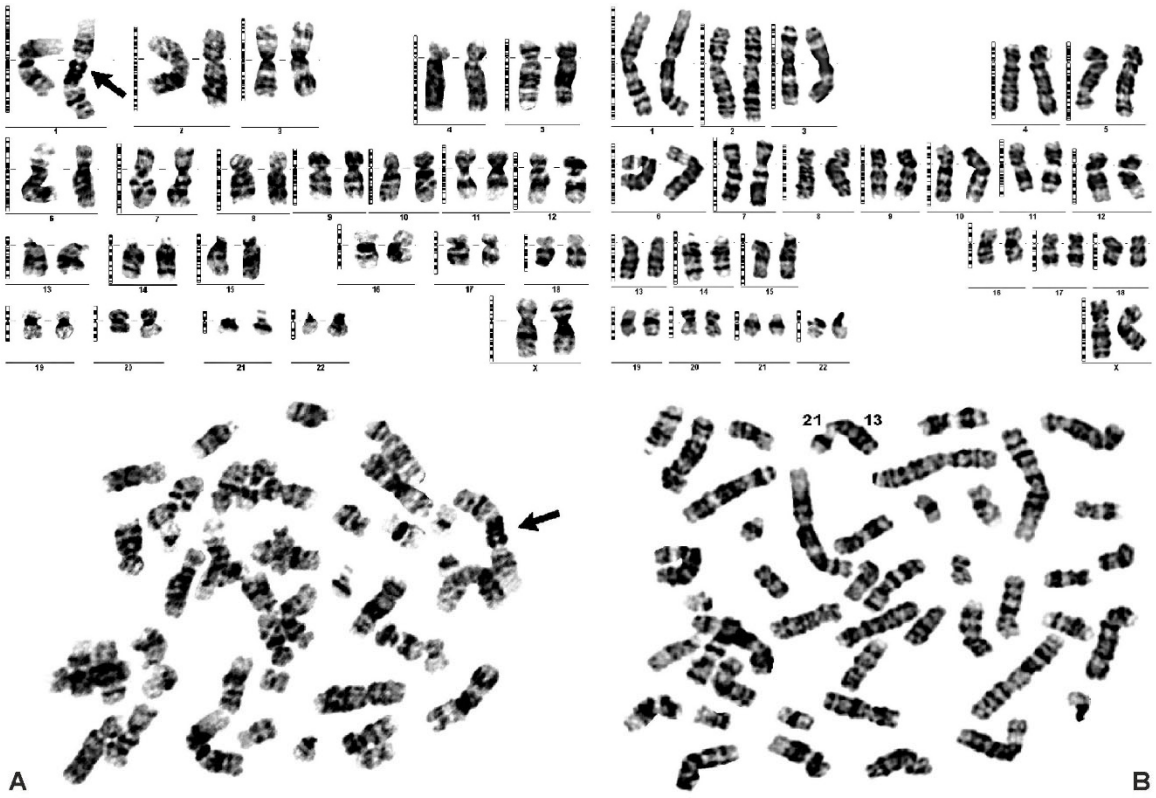

Figure 2 – ***The karyotypes of the first fetus with cystic hygroma (A) and of the mother (B): (A) An increase in length of heterochromatin on the long arm of chromosome 1 – 46XX,1qh+; (B) A heteromorphic variant of chromosome 1 (1qh+), and additionally other two chromosomal polymorphisms of the satellites on the short arm of chromosomes 14 and 21 – 46XX,1qh+,14ps+,21ps+.***

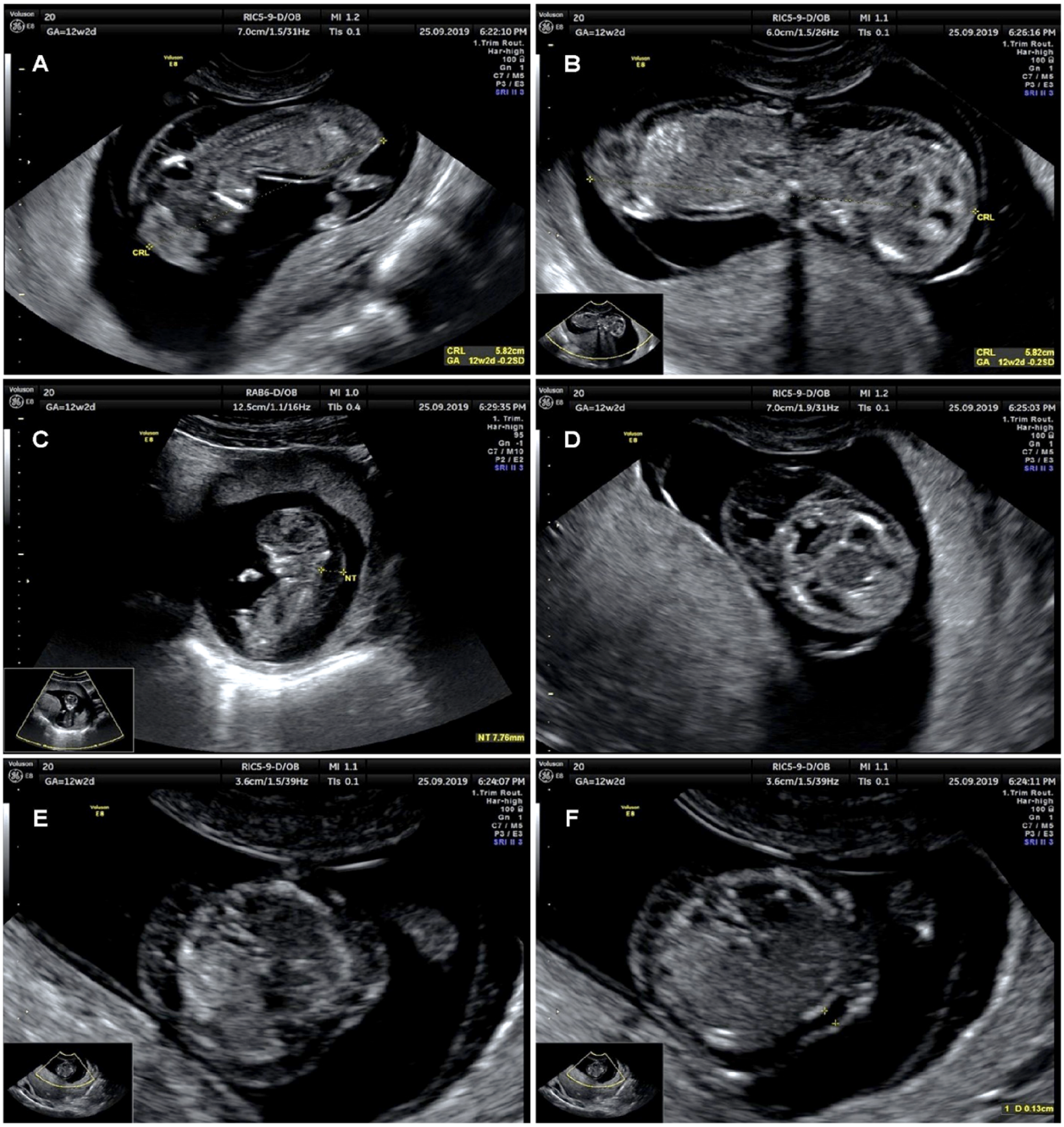

Figure 3 – ***Ultrasound images on the second fetus with cystic hygroma: (A) Sagittal views – the large septated CH, covering almost the whole back of the fetus, with a significant subcutaneous edema of the anterior body wall, can be seen; (B) Frontal view – CH is predominantly developed around the neck; (C) Sagittal view, NT 7.78 mm; (D) Head, transversal section – detail of multi thin-septated CH; (E and F) Thoracic and abdominal transversal sections – the subcutaneous edema (1.3 mm), especially over the anterior wall, can be observed. CH: Cystic hygroma; NT: Nuchal translucency.***

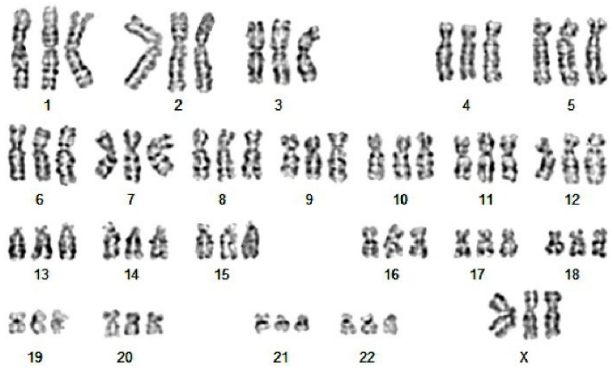

Figure 4 – ***The karyotypes of the second fetus with cystic hygroma – 69XXX triploidy (GTC banding).***

The prognosis of fetal CH remains very poor: around 90% of the fetuses are dying before birth [4, 23], 2% will die in the neonatal period or will maintain abnormal karyotype and/or other malformations [29], with a mortality rate in the first year of around 12 % [30]. Only 8% of them will be in good health [4, 23, 29]. Sixty percent of CHs evolve to HF, with a very bad prognosis [4]. When this lethal aspect occurs, the cystic lesion associates one or several other abnormalities, such as: ascites, uni- or bilateral pleural or pericardial effusions and subcutaneous edema (greater than 5 mm thick) [3, 4]. Therefore, if a CH is diagnosed, a carefully US search for all these negative aspects should be done [3].

Both HF reported by us, associated CH with

subcutaneous edema, especially located on the anterior body wall.

Only a small percent of CHs spontaneously disappear before 20 weeks, but this does not exclude chromosomal abnormalities and/or severe fetal malformations [4] and reappearance is also possible [29].

Chromosomal aneuploidy [4], septated CHs [23] and the lack of spontaneous resolution [4] suggest a poor prognosis [4, 23]; however, the absence of these factors is not a guaranty for a favorable development [4]. Ascites and/or pleural fluid (especially bilateral), oligohydramnios or polyhydramnios, are factors for an even worse prognosis [3].

The secondary constriction of chromosome 1 (1qh+), as showed by the inherited karyotype of the first CH reported here, is considered a "normal" and "healthy" polymorphism of chromosome 1 [31]. This general appreciation is concordant with the fact that our patient was in a very good health, with a high intelligence level (university graduate).

However, there are some authors that report a lower fertility of women with such polymorphisms [32]. This was, also, not valuable in our case, who already had a healthy boy and another two voluntary TOP, with the previous husband, before the first CH.

Nevertheless, such a "healthy" 46XX(1qh+) karyotype did not exclude the occurrence, in our case, of a severe form of septated CH with HF.

The karyotype of the second fetus with septated CH is absolutely unique, the present case being the first reported having a 69XXX triploidy. This abnormality is frequently associated with partial hydatidiform mole [33] and is life incompatible [34]. However, since the second CH had a significantly more severe aspect compared with the first one, it can be speculated that the 69XXX triploidy could be the cause for the second abnormal fetus (Figures 1 and 3).

There are very few recurrent CHs with different karyotypes described in the literature, [8], but our case is the first one reported recurrent CH showing such particular genetic features.

Conclusions

We report, on our knowledge, the first case of a recurrent CH, each of the subsequent embryos with a such karyotype: inherited 46XX (1qh+) and 69XXX. The etiology of the first fetal CH remains unknown and the large secondary constriction of chromosome 1 (1qh+) was not a cause for the first CH appearance. Furthermore, this "particular" genetic aspect did not associate with any maternal abnormality and behaved itself as a "normal" karyotype, fortuitously co-existing with a CH. The 69XXX triploidy, in the second episode, could be a cause of this disease or, even more, for its higher severity. Neither the CHs' appearance, nor their recurrence seemed to be family-linked, the two CHs having distinct genetic profiles. Once CH is diagnosed, a careful US examination is compulsory for the determination of subcutaneous edema, ascites, pleural and pericardial effusions and cardiac or renal abnormalities and the patient should be advised on the very poor fetal outcome. CVS or amniocentesis are mandatory, because a defective karyotype is a supplementary bad prediction factor; however, a "normal" karyotype does not significantly improve the fetal prognosis.

Conflict of interests

The authors declare that they have no conflict of interests.

Acknowledgments

The patient agreed for publication of all her private data.

The study was supported by PanMed S.R.L. Grant 119.1/26.02.2019.

The authors are very grateful to the Department of Genetics, University of Medicine and Pharmacy of Craiova and to the Dr. Cristina Gug Laboratory of Genetics, Timişoara, Romania.

Authors' contribution

Oana Sorina Tica and Cristina Gug equally contributed to this paper.

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Received: May 28, 2020

Accepted: March 8, 2021