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GENETICS IN FETAL MEDICINE

Prenatal Diagnosis of Cryptic Translocation t(5p;17q) with Fluorescent In Situ Hybridization

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Abstract Reciprocal chromosomal rearrangements, de novo or inherited, often raise a concern about the foetal health and outcome of the affected pregnancies. The size and origin of the translocated chromosomes could be variable. Cryptic translocations often remain undetected and misdiagnosed. Several studies confirmed that there could be a loss of a certain amount of genomic material within breakpoints, which leads to uncertainties in predicting the pregnancy outcome. A 38 year pregnant woman approached our clinic for a genetic counselling. This was her first pregnancy, with normal foetal growth on ultrasound follow up. The amniocentesis was carried out due to the advanced maternal age. Conventional cytogenetic report showed putative deletion of short arm of chromosome 5. Cordocentesis was done additionally at 18 week of pregnancy due to the discrepancy between normal ultrasonographic finding and karyotype result. MLPA analysis showed that 5p critical region was present. FISH has been performed, using 5p;q probe (Cytocell aquarius, Cat No LPU 013), which showed cryptic de novo translocation 46,XX.ish t(5;17) (p15.1;q25). Decision to terminate the pregnancy was made due to the cytogenetic finding and reduced foetal growth recorded after 20th week. Examination at autopsy showed dysmorphism consistent with some features of cri du chat syndrome-micrognathia, hypertelorism, reduced fetal growth, as well as underdeveloped brain for gestational period. Novel technologies in molecular cytogenetics and array techniques could help in detecting minor imbalances and decrease the risk of the birth of malformed fetus. Combination of several prenatal methods -both ultrasonography and novel genetic techniques, in a small number of cases can help in the process of genetic counselling.

Keywords Prenatal diagnosis · Cryptic translocation · Fluorescent in situ hybridisation · Cri du chat syndrome · Foetal dysmorphology

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Background

Chromosomal rearrangements (CR) cause a substantial portion of multiple malformation syndromes accompanied with mental retardation. They could occur de novo or could be inherited from the parent. Both autosomes and sex chromosomes are at risk to take part in different

rearrangements [1], producing a variety of clinical presentations—from no phenotypic expression to severely malformed child. Some of the chromosomal abnormalities create easily recognisable dysmorphic patterns (trisomies, monosomy 4p, 5p). However, large proportion of them shows undistinguishable set of dysmorphic signs and malformations. There are several atlases and databases, describing more or less recognisable patterns of clinical presentations suggesting the proper diagnosis [2–4], CR in newborns and infants are presented with variety of major and minor anomalies. On the other hand, advanced ultrasonographic techniques provide a set of features that are detectable in foetuses with a certain chromosomal abnormality [5, 6]. These features allow dysmorphology as a speciality to be implemented in the field of prenatal medicine.

The frequency of reciprocal translocations relies mostly on the studies of neonatal population, referring an incidence of 1/500 newborns [6, 7]. All chromosomes are involved in the translocation events, both autosomes and sex chromosomes. However, the breakage sites are non-randomly distributed along chromosomes, hotspots are mostly positioned in regions rich with CG islands and a smaller amount of *Alu* repetitive sequences [8]. Most of the translocations are balanced and without any consequence to the individual. Data from variable studies show that translocations are present more frequently in prenatal than in postnatal series [9, 10] with no apparent clarification so far, although low survival rate of affected foetuses and advanced parental age in prenatal series have been reported as possible factors. About 30–40% of all translocations occur de novo [11, 12], and if found during prenatal genetic testing, lead to uncertainty in predicting the foetal health outcome. Recently, more advanced techniques such as fluorescent in situ hybridisation, comparative genomic hybridisation, sequencing, etc. has enabled recognition of less apparent chromosomal imbalances where reciprocal translocations occur [13]. These new techniques facilitate reliable prediction of the foetal condition, especially if the translocation is found only in foetus and not in the parents. Two events can impair the foetus phenotype: cryptic loss of chromosomal material resulting in contiguous gene syndrome with variable clinical presentation; or, less frequently, disruption of a certain gene at the chromosomal breakage site which leads to a non-functional gene.

Case Report

A 38 year primipara approached our clinic for genetic counselling. First trimester of the pregnancy was uneventful, with normal parameters—follow up by ultrasound showed normal foetal growth without noticeable malformations. Amniocentesis was carried out due to the advanced maternal age.

Conventional cytogenetic report showed putative deletion of the short arm of chromosome 5—46,XX,del(5)(p15.2) (Fig. 1). In order to confirm possible chromosomal rearrangement, cordocentesis had been performed at week 18 of pregnancy. MLPA probe-mix P036-E2 subtelomeres mix 1 and P070 subtelomeres mix 2 were used to detect deletion(s) and/or duplication(s) in subtelomeric regions, as well as the SALSA MLPA P373-B1 Microdeletion Syndromes-7 probe-mix that covers the critical Cri du Chat region on chromosome 5p. The analysis did not indicate the presence of a deletion/duplication of these regions. Fluorescent in situ hybridisation on metaphase spreads was performed using 5p/q probe (Cytocell aquarius, Cat No LPU 013), which showed cryptic translocation 46,XX.ish t(5;17)(p15.1;q25). The involvement of chromosome 17 in the translocation was confirmed with additional FISH slide using probe for 17p (Cytocell aquarius, Cat No LPU 007) together with the probe for chromosome 5 (Fig. 2). Maternal karyotype was normal whereas the father was not available for karyotyping at that moment, which precluded clarification if the translocation was inherited. Therefore, the decision for terminating the pregnancy was difficult. Subsequent normal karyotype of the father confirmed that the translocation in the foetus was de novo.

Reduced foetal growth was recorded after 20th week of a previously normal pregnancy. This fact together with the cytogenetic finding was decisive for the parents to terminate the pregnancy. Examination at autopsy showed minor dysmorphic features consistent with Cri du Chat syndrome (Fig. 3). The foetus was small according to the gestational age and the brain showed underdeveloped gyri and sulci for the gestational age (Fig. 4). No other organ anomalies were found.

Discussion

Chromosome 5 is frequently involved in reciprocal translocations, together with chromosomes 22, 11, 4 and 9 [8]. As shown in our previous report [14], in this case we have proven translocation events on the short arm of chromosome 5. Translocation between chromosomes 5p and 17q as in the present case have been reported previously [15], although in their report there were additional features associated with trisomy 17q. Also, there are numerous reports of translocation of chromosome 5p on other chromosomes.

Among all imbalances of the chromosome 5, 8–15% are due to the translocation; majority of the translocations (75%) arise from de novo breakage along the short arm of

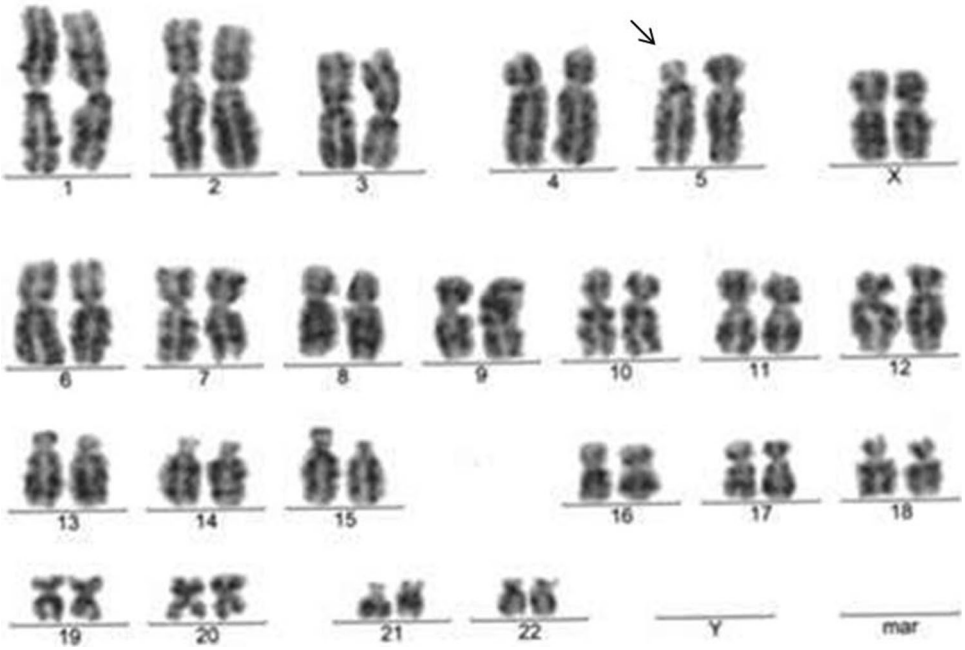

Fig. 1 Karyotype of the amniocytes showed deletion of the chromosome 5p without visible changes in other chromosomes

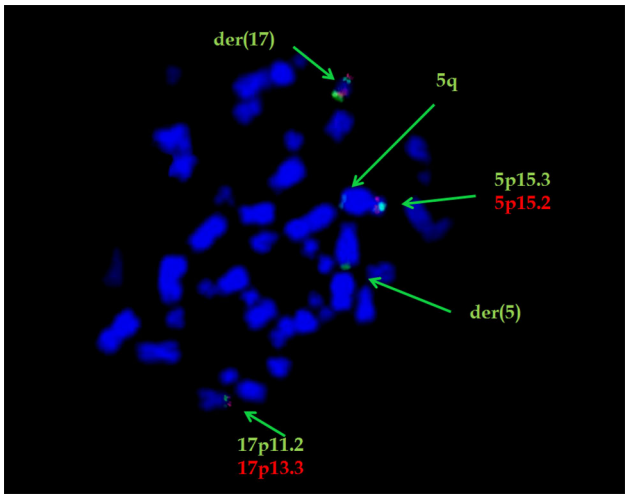

Fig. 2 FISH results using probe of chromosome 5p (p15.3—green signal and 15.2—red signal), 5q (green signal) and chromosome 17. Arrows point to normal and rearranged chromosome

chromosome 5 [16]. The breakpoints occur mostly on *Alu-GC* + R band [8], between bands 5p13-p15. Follow up studies of children, showed that most of the breakage events are associated with chromosomal imbalances and have variable expression in affected individuals that are not always dependent on the length of the involved region [17].

Discrepancy between the lack of visible malformations of the foetus during the second trimester, normal result on MLPA analysis covering 5p15.31 and 5p15.33 region; and the result of the karyotype showing deletion of 5p made the decision about the discontinuation of the pregnancy cumbersome. The method of fluorescent in situ hybridisation has been proven to be effective and fast in detecting cryptic chromosomal rearrangements [18, 19]. However, in this particular case, the major concern about the foetal health arose from the fact that paternal karyotype was unavailable for examination, which furthermore gave uncertainty towards the risk of the translocations to have been occurring de novo. Since most of the breakage events of chromosome 5 reported in the literature cause chromosomal imbalance and variable degree of mental retardation [20], the decision for termination of pregnancy was made in this case. The foetus was examined at the autopsy and had many minor facial dysmorphic features related to Cri du Chat syndrome (triangular face, broad nasal root, micrognathia, hypertelorism, low set ears, etc.). Although microarray was not performed, both the karyotype and the presence of two signals in FISH analysis (5p15.2 and 5p15.3) pointed to the fact that a very small segment centromeric to 5p15.2 was deleted and produced minor dysmorphism and growth retardation in the foetus. Mainardi [16] in his cohort of patients with 5p deletion demonstrated that the deletion in this region is associated with mild mental retardation.

Moreover, ultrasonographic evaluation in foetuses with small chromosomal imbalances could be uneventful during the second trimester, notably if no major structural anomaly were present [21]. Growth retardation could be late-appearing trait as it was in our case, which was mostly due to the placental alteration in foetuses with CR, and should have been considered as a major feature of a syndrome [22]. Minor facial dysmorphic features typical for Cri du Chat syndrome are rarely described prenatally [23, 24], although many of them are noticed post-mortem (i.e. short nasal bone, hypertelorism, micrognathia). Evaluation of the foetus described above revealed some of the Cri du Chat

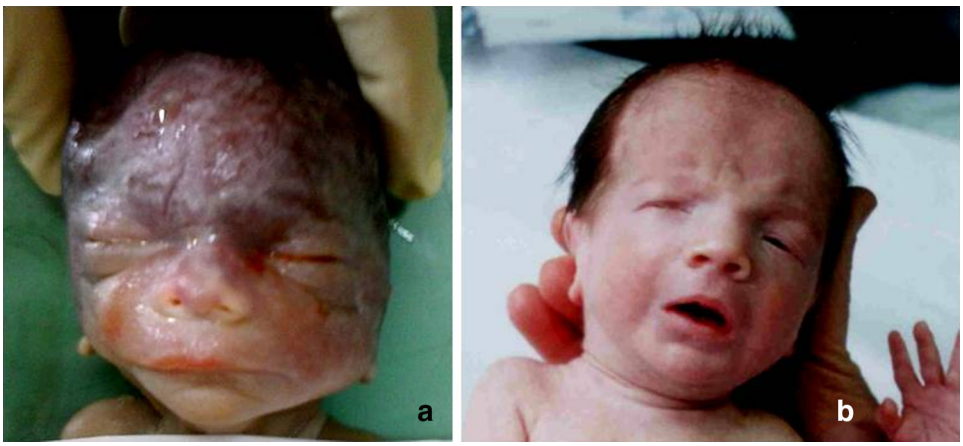

Fig. 3 Similar dysmorphic features in post-mortem evaluation of the foetus (**a**) and newborn with classical Cri du Chat syndrome (**b**)

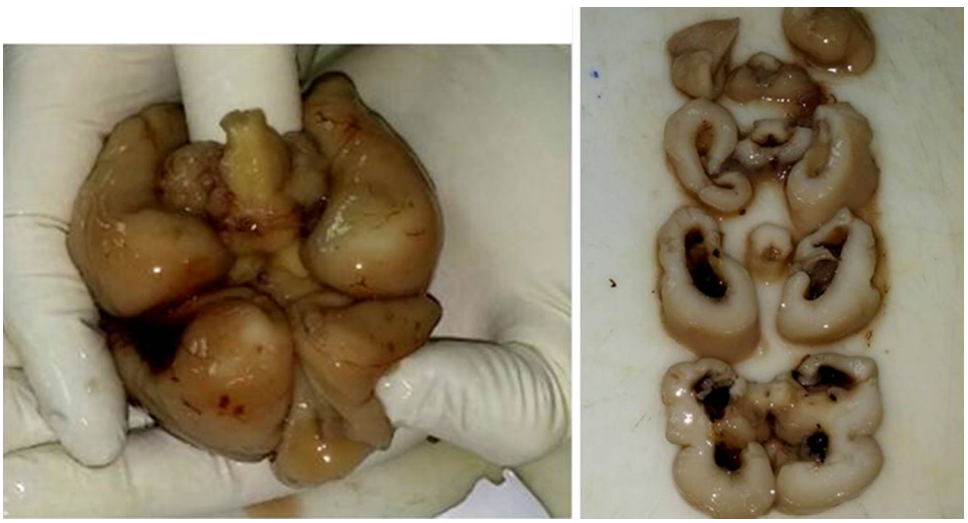

Fig. 4 Cross section of the foetal brain detecting underdevelopment of the brain surface for the gestational age

syndrome features—broad forehead, hypertelorism, low-set ears, wide nasal bridge, micrognathia. However, others as round face, downslanted palpebral fissures and short philtrum were not present. Dysmorphic profile of the foetus and absence of major anomalies (congenital heart defect, hernia, cleft palate), was established previously in patients where deletion between bands 5p15.2 and 15.1 was present [16]. Yet, in order to detect minor chromosomal imbalances of chromosome 5p prenatally, further delineation of ultrasonographic minor dysmorphic features are warranted.

Conclusion

Combination of several cytogenetic and molecular techniques is needed in decision making for terminating the pregnancy where chromosomally imbalanced foetus is suspected. However, despite recent advances in cytogenetic and ultrasonography methods, there is uncertainty in foetal prognosis in cases where de novo translocations occur.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed Consent Informed consent was obtained from all individual participants included in the study. Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

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