

An unusual case of Trisomy 13

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Trisomy 13 is a common chromosome abnormality with a recognisable clinical phenotype, which should prompt its early diagnosis. This case report describes a patient with Trisomy 13 with unusual limb malformations and expands on the clinical phenotype of the disorder.

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Trisomy 13 (Patau syndrome) is a well-recognised, multiple congenital anomaly syndrome, characterised by the cardinal triad of orofacial clefts,

microphthalmia and postaxial polydactyly of the limbs. With an estimated worldwide live-born prevalence (after the advent of prenatal diagnosis) of 1/10 000, it is an important cause of aneuploidy.^[1] Studies conducted in South Africa (SA) many years ago estimated the prevalence of Patau syndrome at 1/24 000.^[2] Given that ~4% of birth defects in SA are formally reported (Dr H Malherbe, Chairperson of the South African Inherited Diseases Association, August 2014, personal communication), it is likely that prevalence figures are actually much higher.

While postaxial polydactyly remains the most commonly described limb anomaly in affected individuals, isolated reports of other limb anomalies, including thumb hypoplasia, oligodactyly and split hand malformation (SHM), have been documented in the literature.^[3-5] A case report follows of a patient diagnosed with Trisomy 13, with multiple congenital anomalies including bilateral SHM. This case expands on the clinical phenotype of Trisomy 13 and highlights why the diagnosis of common genetic conditions should not be confounded by unusual presentations.

Case report

A genetic consultation was requested for Baby S at the Charlotte Maxeke Johannesburg Academic Hospital in Johannesburg, SA. Baby S was born by normal vaginal delivery at term after an uncomplicated pregnancy. Her parents are a non-consanguineous couple of advanced age. The clinical examination revealed age-appropriate growth measurements, but multiple congenital anomalies. On the face, bilateral severe microphthalmia, a broad nasal tip, bilateral cleft lip, a cleft palate and small ears with

pre-auricular tags were noted. The right foot showed type A postaxial polydactyly. The upper limbs showed SHM. On the right, bidactyly was present, with absence of the middle and ulnar ray and a cleft between the presumed thumb and first digit. On the left, oligodactyly was present with a missing middle ray and a cleft between the first and third digits (Figs 1 A - E). Echocardiography and ultrasound (US) evaluation of the renal system and brain did not reveal other structural congenital malformations.

A polymerase chain reaction (PCR) aneuploidy screen performed on a peripheral blood sample diagnosed Trisomy 13. The result was confirmed on karyotype analysis (performed to elucidate the mechanism of aneuploidy) as a non-disjunction Trisomy 13

(47, XX + 13). In light of the atypical finding of bilateral SHM, a 180k oligo-array-comparative genome hybridisation (CGH) was performed by a collaborating laboratory in Belgium (Universitaire ziekenhuizen Leuven). The array result (arr Xq13.1 (70 947 014 - 71 192 496) × 3, 13q11q34 (18 348 559 -114 123 757) × 3, 15q11.2 (20 305 022 - 20 697 543) × 1) confirmed Trisomy 13 but also showed an additional small pathogenic deletion on the long arm of chromosome 15, associated with epilepsy and neuropsychiatric abnormalities, as well as a variant duplication on the X chromosome of unknown significance.

The patient's mother received genetic counselling regarding the clinical features of Trisomy 13, their aetiology and significance,



Fig. 1. A: Bilateral cleft lip and palate; B: Small posteriorly rotated ear with overfolded ear helix and pre-auricular tag; C: Bidactyly of the right hand; D: Oligodactyly with cleft of the left hand; E: Type A postaxial polydactyly of the right foot.

and the poor prognosis. She was referred for palliative care to assist with home care of Baby S. Prenatal genetic counselling with the offer of prenatal testing by chorionic villous sampling (CVS) or amniocentesis was recommended for future pregnancies in view of the mother's advanced maternal age, which would increase her risk for another baby with a chromosome abnormality.

Discussion

The diagnosis of Trisomy 13 was suspected in Baby S on the basis of the indicative cardinal triad of features. However, the finding of bilateral SHM was very unusual. To date, only five other cases of Trisomy 13 have been described with SHM.^[3-5] Prior to the PCR result, the major differential diagnosis in Baby S was 'ectrodactyly, ectodermal dysplasia, clefting syndrome' (EEC), which is caused by mutations in the *TP63* gene and which is inherited in an autosomal dominant manner.^[6] While we have not excluded *TP63* mutations (testing is not available in SA) in Baby S and co-occurrence of Trisomy 13 and EEC is possible, this dual pathology has not been previously reported to our knowledge. Furthermore, Baby S did not have clinical features of an ectodermal dysplasia (including hair and nail anomalies), which would make dual pathology less likely. Neither of the two other copy number variations detected by array-CGH is known to be associated with SHM. We concluded thus that SHM was part of the spectrum of limb malformations in this infant with Trisomy 13.

Trisomy 13 is a common condition of aneuploidy worldwide. The majority of cases (80%) are caused by the presence of an additional chromosome 13 owing to non-disjunction (usually in maternal meiosis I); ~10 - 20% are due to translocations, usually an unbalanced 13:14 Robertsonian translocation.^[1]

Apart from the classic triad of features (in 60 - 70% of cases),^[1] multiple other dysmorphic features and congenital anomalies are described. Growth deficiency is common and is related to the aneuploidy as well as to poor feeding associated with orofacial clefts, gastrointestinal malformations and gastro-oesophageal reflux. Cardiac malformations are present in up to 80% of patients,^[1,7] with atrial septal defect, patent ductus arteriosus and ventricular septal defect reported as the most common anomalies in one series of cases.^[7] Renal pathology, particularly cystic dysplasia, is reported in over 30% of patients.^[1,8] Significant ocular pathology (microphthalmia, colobomas, retinal dysplasia and cataracts) occurs in up to 50% of patients, and sensorineural hearing loss has been reported.^[1] Other anomalies include limb defects (postaxial polydactyly, oligodactyly, limb deficiency and rarely SHM),^[3] omphalocele, cutis aplasia of the scalp and neural tube defects.^[8] Structural malformations of the central nervous system (CNS), including the holoprosencephaly spectrum, cerebellar hypoplasia and hypogenesis of the corpus callosum are described^[1] and occurred in 76% of patients in one series.^[8] Central apnoea, related or unrelated to CNS malformations, may explain the increased mortality rate, with 90% of affected patients passing away before 1 year of age.^[1,8] Surviving patients have profound mental retardation.^[1]

Pre- and postnatal diagnosis of Trisomy 13 in SA is often made on PCR aneuploidy screen, which detects triplicate copies of short tandem repeat sequences on chromosome 13. The test is also used for confirming the diagnosis of Down syndrome (Trisomy 21) and Trisomy 18. PCR aneuploidy testing does not elucidate the mechanism of the trisomy or provide recurrence risk information, and as such, karyotype analysis can also be used as a first-line investigation in suspected cases. Trisomy 13 can be suspected on antenatal US by 20 weeks' gestation in 90 - 100% of cases.^[9] Apart from structural anomalies, other indicators of Trisomy 13 include intrauterine growth restriction, echogenic cardiac foci, hypotelorism and poly- or oligohydramnios.^[8,9] Invasive prenatal testing, including CVS (11 - 13 weeks' gestation) or amniocentesis (16 - 20 weeks'

gestation), can be offered to women of advanced maternal age who are at increased risk of aneuploidy or those whose antenatal US has detected fetal anomalies.

While it is generally agreed that affected infants have a poor prognosis and significant disability if they survive, recent discourse has questioned the care that should be afforded these individuals. Traditional views of palliative care and the withholding of life-saving treatments are now being challenged by families and healthcare practitioners who advocate life-saving interventions. A review of this discourse is beyond the scope of this report; however, it is recommended that a balanced approach be taken when counselling families at the time of diagnosis and thereafter, and that parental autonomy be seriously considered. Each case should be treated on an individual basis with personalised care, based on the social and financial resources of the family as well as the best interests of the child.^[10,11] Genetic counselling is beneficial not only in terms of understanding the diagnosis and its implications, but also in supporting families to make particularly difficult decisions for future care and family planning.

Conclusion

Trisomy 13 can be suspected from the clinical phenotype of the affected infant. While unusual features may suggest a different diagnosis or a more complicated aetiology, they do not exclude the possibility of aneuploidy. As simple tests to detect aneuploidy can be readily accessed, common genetic conditions, including Trisomy 13, should be considered in the differential diagnosis and actively excluded even in the presence of unusual manifestations. Referral to a genetic counselling clinic is advocated whenever possible, although care of the affected infant and support for the family can and should be offered by all healthcare practitioners.

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