CASE REPORT

A Case Study of Mosaic Trisomy 13 in a 2-year-old Filipino Child

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ABSTRACT

Mosaic trisomy 13 is estimated to occur in 5% of all trisomy 13 cases. Presentation of trisomy 13 mosaicism is highly variable, with cases that may present with a normal phenotype and intellectual function, to cases with grossly abnormal features and profound developmental delays. We present a 2-year-old female with trisomy 13 mosaicism, who presented with small for gestational age (SGA), polydactyly, ventricular septal defect (VSD), and poor oral feeding.

Key Words: trisomy 13, mosaic trisomy 13, genetic counseling, SNP array

INTRODUCTION

Complete trisomy 13, or more commonly known as Patau syndrome, occurs when three copies of chromosome 13 are present in every cell.[1] The incidence has been estimated at 1:5000 to 1:20,000 live births, the risk of which increases with advanced maternal age.[1-3] This genetic disorder affects a variety of organ systems, including the central nervous system, cardiopulmonary system, urogenital system, and musculoskeletal system, among others.[2] It is characterized by the triad of microphthalmia or anophthalmia, cleft lip and palate, and postaxial polydactyly, and also associated most commonly with midline defects, such as holoprosencephaly, omphalocele, and single umbilical artery.[3] Prognosis has been known to be generally poor, with a median survival time between 7 and 10 days, with 86% to 91% of live-born patients not surpassing the first year of life.[2,4] Patients with trisomy 13 who live beyond the first year of life have been found to have profound developmental delay, among other abnormalities.[5]

In cases of mosaic trisomy 13, only a certain percentage of cells contain an extra chromosome 13. It is estimated that mosaicism occurs in 5% of all trisomy 13 cases.[6] Presentation of trisomy 13 mosaicism is highly variable, with cases that may present with a normal phenotype and intellectual function, to cases with grossly abnormal features and profound developmental delays.[6] It has been noted, however, that there is a poor correlation between the percentage of cells with an additional copy of chromosome 13 and the clinical features of the patient.[6]

Counseling parents of a fetus with trisomy 13 mosaicism remains difficult because of the phenotypic variability

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associated with the condition; some patients exhibit the typical phenotype of complete trisomy 13 with very poor prognosis while others have few dysmorphic features and prolonged survival.[7]

We present a case of a female with trisomy 13 mosaicism, who presented with SGA, polydactyly, VSD, and poor oral feeding.

CLINICAL CASE

AB (not her true initials) was born full term, 37 weeks age of gestation, to a 28-year-old primigravid mother via an unremarkable vaginal delivery, with an APGAR score of 8,9. Prenatal course was uncomplicated, with regular prenatal check-ups. Her birth weight was 2,200 grams (3-10%), small for gestational age (SGA), with a length of 44 cm (10%) and a head circumference of 32 cm (10-50%). The patient was admitted to the NICU for hypoglycemia due to poor oral feeding and SGA.

At birth, the patient was pink. She was normocephalic, with fontanelles soft and flat, patent nares, palate intact and mucous membranes pink. She however had a tight frenulum and flat nasal bridge. Overall, she was non-dysmorphic. On auscultation, she had clear breath sounds bilaterally with symmetric expansion. She had a normal heart rate with regular rhythm, with a 2/6 early systolic murmur best heard at the mid left sternal border, radiating throughout the entire pericardium and both axillae. The diastole was clear. Her abdomen was soft, non-distended, with no hepatosplenomegaly or masses palpated. She had a normal female external genitalia. She had no hip clicks. However, a sacral dimple was noted. There was a post axial polydactyly on her left foot. Neurologic assessment showed age appropriate tone, with intact Moro, suck and grasp reflexes (Figure 1 A and B).

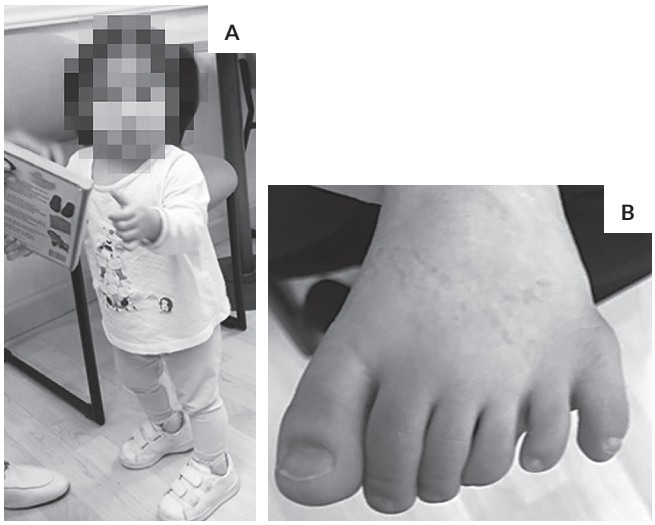

Figure 1. (A) AB at 1 year 7 months old and **(B)** extra digit in L foot.

Laboratory and imaging studies were done to investigate the poor oral feeding, SGA, heart murmur and extra digit on the foot. Blood and urine CMV cultures done were negative. Maternal and infant toxoplasmosis IgG were positive, but infant IgM was negative. Ophthalmologic exam demonstrated scattered bilateral retinal hemorrhages without evidence of chorioretinitis. Brain ultrasound also showed no evidence of congenital toxoplasmosis. Echocardiography revealed moderate to large perimembranous VSD with outlet extension, minimal RAE and RVE with RVH and septal flattening, normal RV function, and mild PPS. It also revealed normal LV size and function, as well as a tiny PFO with left to right flow. There was no evidence of congestive heart failure.

Since the overall features of the child did not fit a known syndrome malformation, a microarray analysis was done. SNP microarray analysis was performed using the Affymetrix Cytoscan HD platform which uses over 743 000 SNP probes and 1 953 000 NPCN probes with a median spacing of 0.88 kb. The microarray result [arr (hg19) (13)x2-3] revealed a mosaic gain of whole chromosome 13. The whole genome SNP microarray analysis has detected mosaicism for trisomy 13. The 2.25 copy number dosage observed in the array is equivalent to 25% of the nucleated blood cells (primarily granulocytes) being positive for trisomy 13.

Ultrasound of the spine showed low position of the conus at L3, with other findings unremarkable. Renal ultrasound revealed normal kidney size and overall echogenicity, mild fullness of the collecting systems, the left greater than the right but without overt hydronephrosis, and three small cysts in the right kidney, with the largest measuring 2.5 mm. Liver ultrasound was unremarkable.

Patient was discharged after 31 days of neonatal care in a hospital in the US and returned to the Philippines for continuing care. In Manila, the medical team included a geneticist, developmental pediatrician, cardiologist, nephrologist, ophthalmologist, neurologist and a team of therapists including a physical therapist, occupational therapist and early childhood specialist.

Karyotyping was performed to rule out a Robertsonian translocation. The chromosomal studies of the patient revealed 47,XX,+13[10]/46,XX[90], confirming mosaic trisomy 13 (Figure 2 A and B). Parental karyotypes were done and revealed normal studies.

Surgical correction of the VSD at age 8 months was well tolerated. She is maintained on anticonvulsant medications because of the risk of seizures. Head circumference is being monitored and is normal. Her vision is being closely monitored especially with the observation of a head tilt and occasional left eye esotropia.

Early intervention was initiated at 2nd month of age. She currently receives physical and occupational therapy and attends an early intervention program. She has age-appropriate mobility skills to explore her environment

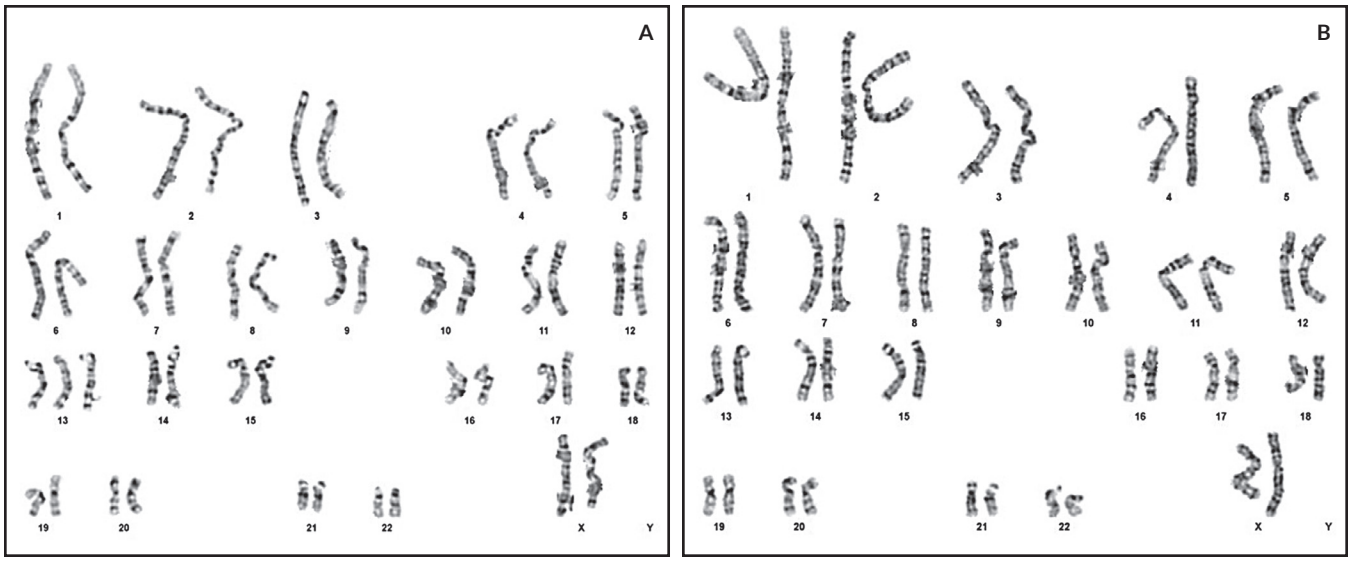

Figure 2. Chromosomal results 47,XX,+13[10]/46,XX[90]. **(A)** karyotype showing the trisomy 13 and **(B)** karyotype showing normal results.

independently and has good motor planning skills. She is attempting to do higher balance activities. Grasping and object manipulation are within age-expected range. She is able to engage in pretend play and turn taking. She understands one-step commands and gestures to indicate her needs. She has around 5-10 specific words in her vocabulary. Her developmental profile using the Bayley Scales of Infant Toddler Development – 3rd edition is as shown in Table 1.

DISCUSSION

Imataka, et al. reported survival past the first year of life in twelve patients with trisomy 13 including four with trisomy 13 mosaicism.[2] The oldest survivor with a full trisomy 13 was a 32-year-old female,[8] and the oldest survivor with a trisomy 13 mosaicism was a 38-year-old male.[9]

Table 2 presents the reported phenotype of patients diagnosed with mosaic trisomy 13. Only patients with original diagnosis of Trisomy D and further re-evaluated as Trisomy 13 by Giemsa stain or FISH are included. The review reveals the wide variability of the clinical phenotype and lifespan.[6,10-14] Two patients had fair to good developmental outcomes. Our patient (10% trisomy 13 in peripheral blood and 25% in array studies) had cognitive performance of 19 months at a chronological age of 24 months. Another patient[6] with 10% mosaicism had normal developmental milestones at age 5 years old. In both cases, chromosomal studies were done blood samples only.

Review of cases have shown that trisomy 13 mosaicism patients with typical features of a complete trisomy 13 had poorer prognosis that led to death in the neonatal period in contrast with patients with less dysmorphic features who had prolonged survival.[1] Other factors that affect prognosis are involvement of vital structures (heart or the central nervous system), degree of the malformation, association with midline facial clefts.[4,15] Life expectancy of patients with trisomy 13 has also been affected by the aggressiveness of the medical care given.[3,4,8] Although literature reports that children with full trisomy 13 usually have profound intellectual disability,[4] there are some individuals who may have mild intellectual disability.[16]

The Cytogenetics laboratory at the Institute of Human Genetics, National Institutes of Health, University of the Philippines Manila reports 4 cases (including this patient) of mosaic trisomy 13 among 104 patients with various types of trisomy presented in Table 3.

Table 1. Developmental profile using the Bayley Scales of Infant and Toddler Development – 3rd Edition (BSID-III) taken at 24 months and 7 days old

Index	Scaled Score	Composite Score	Descriptive Category	Estimated Age Equiv.
Cognitive	7	85 (78-94)	Low Average	19 months
Language	Receptive: 7 Expressive: 6 Total: 13	79 (73-88)	Borderline	Receptive: 19 months Expressive: 17 months
Motor	Fine motor: 5 Gross motor: 9 Total: 14	82 (76-91)	Low Average	Fine: 15 months Gross: 21 months

Table 2. Clinical and laboratory findings of patients with mosaic trisomy 13

	Imataka G et al	Fogu G, et al	Cowen	Singh
Age at reporting	7 yrs 4 mos	12 yrs	9 yrs	22 yrs
Birth History	39 wks 3366 g + asphyxia	32 wks 1420 g no mention of asphyxia	- 3350 g no mention of asphyxia	full term 3400 g no mention of asphyxia
Dysmorphic Features				
Microcephaly	no mention	microcephaly	microcephaly	microcephaly
Head and Face	frontal alopecia, capillary hemangioma in forehead, high arched narrow V shaped palate	dolichocephalyhemangioma in scalp, prominent sutures, sloping forehead, long eyelashes, long smooth philtrum, micrognathia, thin upper lip, short lingual frenulum downslanting palpebral fissures, broad flat nose, high arched palate	exomphalos flat nose, and bilateral microphthalmia and colobomata	flattened occiput, sloping forehead, short neck, high arched palate
Eye and Ear anomalies	no mention	low set ears	low set ears microphthalmia cataract coloboma bilateral,	microphthalmia
Genital anomalies	cryptorchidism penis palmatus	no mention	ambiguous genitalia at birth micropenis	hypoplastic penis
Limb anomalies	narrow fingernails	flexion deformity, camptodactyly of 3rd and 4th fingers, hypoplasia of distal phalange of the 5th finger R, clubfoot, adduct metatarsus, hallux valgus, overlapping toes, cubitus valgus	Polydactyly, fingers clenched with overriding thumbs. Hyperconvex narrow finger nails, polydactyly, fingers clenched with overriding narrow finger nails	deformed claw hands; abnormally placed thumbs, clinodactyly of 5th digit, abnormal toes; equinovarus talipes; dysplastic hips
Cognitive Development	severe MR	no mention	severe MR	severe MR
Other medical problems	VSD Seizures, recurrent infections (respiratory, urinary)	recurrent infections (urinary), seizures, phylloid hypomelanosis	ASD R kidney absent	recurrent infections (chest, eye, and ear)
Laboratory Results	47, XY,+13 (G-banding karyotype); 47, XY,+13 (73.2%) / 47,XY (FISH);	Birth blood sample Iso (13q) 51%, large der (13) 49% Skin Iso (13q) 12%, large der (13) 88% 9 years, blood Iso (13q) 74.14%, large der (13) 25.86% Skin large der (13) 71% small der (13) 29%	47, XY, +13 (88%)/46,XY (9%) blood sample in 1969; 47, XY, +13 (99%)/46,XY (1%) in blood sample in 1977; 47, XY, +13 (92%)/46,XY (7%) in skin sample in 1977	Trisomy D chromosome in 1978; Reinvestigation showed 47, XY, +13 (97%)/46,XY (3%)
Parental karyotypes				"Analysis of mother's chromosomes revealed an entirely normal D Group Karyotype"

Legend: MR mental retardation; CHD congenital heart disease; VSD ventricular septal defect; ASD atrial septal defect; PDA patent ductus arteriosus

Kunwar	Delatycki and Gardner	Delatycki and Gardner	Delatycki and Gardner	This patient
24 yrs	5 yrs	10 yrs	3 yrs 6 mo	2 yrs old
- 2200 g no mention of asphyxia	41 wks 3500 g no mention of asphyxia	- 2640 g no mention of asphyxia	- - no mention of asphyxia	37 wks 2200 g no asphyxia
microcephaly	no mention	no mention	no mention	HC 32 cm (10-50%)
high arched palate, short columella, enlarged nares, bifid tongue, smooth philtrum, microtia, thin upper lip vermillion, dental malocclusion, mandibular prognathia	Low posterior hairline	no mention	no mention	non-dysmorphic
low set ears	no mention	no mention	no mention	occasional L eye esotropia
no mention	no mention	no mention	no mention	none
broad fingertip, broad hallux	no mention	no mention	no mention	post axial polydactyly
moderate MR	normal at 5 yrs and 1 mo	MR (level not stated)	no mention	At 24 months, cognitive is 19 mo; receptive language 19 mos; expressive language 17 mos; fine motor 15 mos; gross 21 months
probably with CHD due to presence of cyanosis during crying seizures	PDA	no mention	ASD	VSD S/P surgery at 8 mos hydronephrosis, small cysts in R kidney
47, XY, +13 (25%)/46,XY (75%) blood sample Interphase FISH on blood showed Trisomy 13 in blood (15%) and buccal mucosa cells (6%)	46,XX,rob(13;13) (ql0;q10) [14%]/46,XX in blood; 10% in skin fibrobalsts	At 2 yrs 4 mos, 47,XY,+13 (20%)/46,XY (80%) in blood; Repeat blood karyotyping at 10 years and 40% with Trisomy 13.	amniocentesisrevealed 1 culture with46,XX; 1 culture with 7/50 cells with 47,XX +13 and 1 culture with 47,XX +22 in 5/50 cells. Fetal sampling at 17 weeks had 100/100 with 46,XX Cord blood sample at birth, 3/100 had Trisomy 13	47,XX,+13[10]/46,XX[90] microarray result [arr (hg19) (13)x2-3] revealed a mosaic gain of whole chromosome 13
	normal			normal

Table 3. Trisomy 13 at the Institute of Human Genetics, National Institute of Health from 1991-2017

	N	
Full Trisomy 13		
47,XX,+13	44	
47,XY,+13	50	
Subtotal		94
Mosaic trisomy 13		
47,XX,+13/46,XX	3	
47,XX,+13/47,XY,+15	1	
Subtotal		4
Robertsonian Translocation Trisomy 13		
46,XX,+13,der(13;13)(q10;q10)	2	
46,XX,+13,der(13;14)(q10;q10)	3	
46,XY,+13,der(13;14)(q10;q10)	1	
Subtotal		6
Total		104

Several papers have reported there is no clear association between the level of mosaicism, the severity of the phenotype and potential survival at birth. Griffith et al. reported a patient with normal neurodevelopmental outcome with 40% trisomic cells in leukocytes and 45% of trisomic cells in fibroblasts.[1,3] In some studies, it has also been noted that the percentage of abnormal cells decrease over time, and might be possibly due to a natural selection against the abnormal cells.[3,5,6,9]

Diagnosis is a challenge among patients with mosaicism. Our patient did not have the classical features of trisomy 13. Microarray testing was done because of non-specific findings of SGA, polydactyly, VSD, and poor oral feeding. Parental G-banded karyotypes revealed normal studies. Genetic counseling is difficult knowing that prognosis will be unpredictable.

Two large studies have addressed the origin of trisomy 13 using microsatellites and demonstrated that the majority of cases are maternal in origin, with almost equal meiosis I and II errors as well as markedly reduced recombination but only 2 cases of mosaic trisomy 13 were included. SNP array provides both genotype and copy number information and is useful in studying mechanisms of complex mosaic aneuploidy and UPD.[17]

In a study of chromosome mosaicism in 22,000 amniocenteses, Hsu et al. found true chromosome mosaicism in 50 cases (0.27%), including two cases of mosaic trisomy 13.[18] Robinson et al. found that the majority of cases of mosaic trisomy 13 were associated with trisomic fertilization compatible with a meiotic origin of the extra chromosome and with postzygotic loss of one chromosome.[19] Mosaic trisomy 13 at amniocentesis has been reported to be associated with normal or near-normal liveborn. Delatycki and Gardner reported two cases of mosaic trisomy 13 at amniocentesis with a favorable outcome. One case with level II mosaic trisomy 13 was normal at age 3 years and 6 months, and the other case with level II mosaic trisomy 13 was normal at age 17 months.[6] Di Giacomo et al. reported a case of mosaic trisomy 13 at amniocentesis with a favorable outcome. The child was normal with no dysmorphic features at age two years.[20] The mother of our patient did not undergo prenatal diagnosis.

Our patient continues to develop within normal range, albeit borderline skills in her language and fine motor development. The close follow up on our patient will provide a better picture on the future outcome of the patient.

CONCLUSION

This paper reported a female patient who presented with SGA, polydactyly, VSD, and poor oral feeding, wherein microarray and chromosomal analysis revealed trisomy 13 mosaicism. Counseling remains to be an important part of management, with emphasis on continued follow-up to monitor the progress of the patient, as well as to be able to refer to the necessary services to improve and maximize the quality of life.

For patients with minor dysmorphic features, microarray studies have shown to be useful for resolution of diagnosis. For patients with mosaicism, they will benefit from further studies on skin fibroblasts to better assess the level of mosaicism as this information will be important for long term outcome.

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Statement of Authorship

All authors participated in data collection and analysis, and approved the final version submitted.

Author Disclosure

All authors declared no conflicts of interest.

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