ORIGINAL ARTICLE

Phenotypic Features and Inheritance Pattern of Emanuel Syndrome: An Indian Perspective

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Abstract

Aim and objective: To study the phenotypic features and inheritance patterns in children diagnosed with Emanuel syndrome (ES).

Materials and methods: All children who underwent cytogenetic analysis at the Christian Medical College, Vellore and whose karyotypes showed the supernumerary chromosome 22 derived from an unbalanced translocation (11;22)(q23;q11.2) were included. Karyotypes of family members were retrieved from hospital records. Metaphases were obtained from phytohemagglutinin-stimulated peripheral blood cultured using standard protocols. At least 20 Giemsa-banded metaphases were analyzed and reported in accordance with the International System for Human Cytogenomic Nomenclature. The clinical features and imaging findings were retrieved from our medical records. The karyotype findings of parents and family history including the obstetric history of all mothers were recorded.

Results: There were eight children, three girls and five boys, all of whom were from unrelated families. The age at presentation ranged from 8 months to 8 years of age. Three families presented with significant family history in the form of previous sibling deaths, recurrent abortions in the mother, and maternal siblings' death. All eight children presented with global developmental delay. Preauricular sinus was found in six children (6/8,75%), while microcephaly and hypotonia in five each (5/8,62.5%). More than half of our children presented with structural cardiac and brain malformations. In three children, the der(22) was found to have originated from a maternal source of the t(11;22). All three mothers who harbored this translocation were phenotypically normal.

Conclusion: The characteristic clinical features of ES found in our study included preauricular sinus, microcephaly, hypotonia, cardiac defects, and structural brain malformations. The maternal source of the t(11;22) was the commonest mode of inheritance among children diagnosed with ES.

Clinical significance: Emanuel syndrome is a rare syndrome and it is extremely important to identify the phenotypic features of this clinical entity since early intervention can aid in appropriate counselling and offering prenatal testing. The majority of children diagnosed with ES were found to have inherited this genetic defect due to a translocation (11;22) running in the family. Hence, a clear understanding of the reproductive outcomes of the t(11;22) is of vital importance in counseling the family members and offering prenatal testing.

Keywords: der(22)t(11;22)(q23;q11.2);t(11;22), Emanuel syndrome, Inheritance, Low copy repeats quality of life.

International Journal of Infertility and Fetal Medicine (2021): 10.5005/jp-journals-10016-1228

Introduction

Emanuel syndrome (ES) or supernumerary derivative (22) t(11;22) syndrome is now a well-recognized clinical entity characterized by severe intellectual disability/global developmental delay, craniofacial dysmorphism, notably preauricular sinuses/pits, cleft palate, micrognathia, and heart defects.[1–3]

Individuals affected with ES have 47 chromosomes due to gain of a small supernumerary chromosome derived from an unbalanced translocation (11;22)(q23;q11.2) consisting of the short (p) arm, centromere, proximal part of the long (q) arm of chromosome 22, and the terminal part of chromosome 11q, resulting in partial trisomy for chromosomes 11 and 22.

This supernumerary derivative 22 is almost always formed due to a 3:1 meiotic mal-segregation of a balanced t(11;22)(q23;q11.2) in a carrier parent in the majority of children.[4]

We describe eight children with ES (supernumerary derivative 22) diagnosed by conventional cytogenetic analysis and compare our findings with the literature and discuss inheritance patterns observed in the three affected families.

Materials and Methods

All children who underwent cytogenetic analysis at the Christian Medical College, Vellore and whose karyotypes showed the supernumerary chromosome 22 derived from an unbalanced translocation (11;22)(q23;q11.2) along with parental studies were included in the study. The period of study was from 2001 through 2019. This retrospective study was approved by the Institutional Review Board, Christian Medical College, Vellore (IRB min no: 12656 [retro]).

Karyotypes were prepared from phytohemagglutinin-stimulated peripheral blood cultured using standard protocols.[5] At least 20 G-banded metaphases were analyzed and reported in accordance with the International System for Human Cytogenomic Nomenclature (ISCN).[6] Fluorescence *in situ* hybridization (FISH) was performed in all children with the supernumerary der(22) using standard protocols.[5] The clinical features were retrieved

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How to cite this article: Kamath V, Srivastava VM, Chacko MP, *et al.* Phenotypic Features and Inheritance Pattern of Emanuel Syndrome: An Indian Perspective. Int J Infertil Fetal Med 2021;12(3):60–65.

Source of support: Nil

Conflict of interest: None

from our medical records. All children had detailed clinical history and examination recorded. Other investigations such as an echocardiogram, ultrasound abdomen, and magnetic resonance imaging of the brain were also recorded. The karyotype findings and detailed family history including the obstetric history of mothers were recorded.

Results

There were eight children, three girls and five boys, all of whom were from unrelated families. The age at presentation ranged from 8 months to 8 years of age.

Three families presented with significant family history in terms of previous sibling deaths, multiple abortions in the mother, and maternal siblings' death and disability. Three mothers presented with antenatal complications in the form of oligohydramnios, deceased fetal movements, and dengue. Antenatal scan findings were not available. All children were delivered at term. Eighty percent of children were born with a birth weight of 2.5 kg and less. The newborn period was complicated by palatal insufficiency (cleft - 2 and bifid uvula - 1) in three children and anal stenosis in two.

During the infancy period, four children had recurrent respiratory tract infections requiring admissions-one child with gastroesophageal reflux and aspiration pneumonia and cardiac defect, while two were complicated with cardiac lesion and one with difficulty in passing stools.

Six children presented with global developmental delay ranging from mild to severe degree. Both children who presented above 5 years of age had intellectual disability. The average age of head control was 10.4 months (range: 6–24 months) and sitting 1.5 years (range: 1–3.5 years). Bipedal mobility was achieved for three children at an average age of 2.3 years (range: 2–3 years). Reach was achieved at a mean age of 12.8 months (range: 6–24 months). Two children achieved pincer at 2 years of age. Children who were hearing well spoke at an average age of 3.75 years (range: 3.5–4 years of age).

Febrile seizures were reported for two children and afebrile seizures for one child. Behavioral problems were reported for three children including hyperactivity and one child fulfilled the DSM (diagnostic criteria for autism spectrum disorder) criteria for autism spectrum disorder.

Three children had failure to thrive with both height and weight below the –2 SD. Microcephaly was noted in three children. Dysmorphism was noted in all (Table 1). Five children had central hypotonia with normal to brisk deep tendon reflexes. One child in infancy was noted to be floppy with sluggish deep tendon reflexes but eventually was noted to have brisker reflexes at follow-up. Visual impairment including refractory error was noted in three children and bilateral hearing impairments were noted in four. All children with hearing impairment did not have speech delays.

Five children had cardiac abnormalities in the form of the atrial septal defect (ASD), ventricular septal defect (VSD), pulmonary stenosis, pulmonary outflow obstruction, tricuspid atresia, and coarctation of the aorta.

Brain imaging studies showed structural brain malformations in five, while posterior fossa abnormality was noted in three children ranging from Dandy–Walker malformation, vermis hypoplasia to brain stem hypoplasia. Other features included were hydrocephalus, corpus callousal thinning, and choroid plexus.

Table 1: Clinical features of children diagnosed with Emanuel syndrome

Clinical features	*UID-1*	*UID-2*	*UID-3*	*UID-4*	*UID-5*	*UID-6*	*UID-7*	*UID-8*
Developmental delay	+	+	+	+	+	+	+	+
Intellectual disability	+	–	–	–	+	–	–	–
Dysmorphism	+	+	+	+	+	+	+	+
Preauricular sinus	–	+	+	+	+	+	–	+
Hypertelorism	–	–	–	+	–	–	–	+
Sparse eyebrows	–	–	–	+	–	–	+	+
Tented lips	–	–	–	+	–	–	–	+
Depressed nasal bridge	–	–	–	–	–	+	+	+
Epicanthal folds	–	–	–	+	–	+	–	–
Prominent ears	–	–	–	–	+	+	–	–
Low set ears	–	–	–	–	–	+	+	–
Microcephaly	–	–	+	+	+	+	–	+
Palatal insufficiency	+	–	–	–	+	+	–	–
Hypotonia	+	–	–	+	–	+	+	+
Seizures	+	–	–	–	–	–	+	+
Hearing impairment	+	–	–	+	–	+	–	+
Visual impairment	+	–	–	+	–	+	–	–
Speech delay	–	–	+	–	+	+	+	–
CHD	+	–	+	+	+	+	–	–
Brain malformation	–	+	+	+	+	+	–	–
Intestinal anomalies	+	–	+	–	–	–	–	+
Urogenital anomalies	–	–	–	–	–	–	–	+
Respiratory infections	+	+	–	+	+	–	–	–
Follow-up	Nil	Nil	1 year	Nil	5 years	Nil	8 years	Nil

Plus (+): present; Minus (–): not present

Table 2: Karyotypes and inheritance patterns of children with Emanuel syndrome

UID number	*Sex*	*Age (years)*	*Karyotype findings in children with Emanuel syndrome*	*Parental karyotype*
UID 1	F	6	47,XX,+der(22)t(11;22)(q23;q11.2)mat	Mother: 46,XX,t(11;22)(q23;q11.2) Father: 46,XY
UID 2	M	<1	47,XY,+der(22)t(11;22)(q23;q11.2)mat	Mother: 46,XX,t(11;22)(q23;q11.2) Father: 46,XY
UID 3	M	2	47,XY,+der(22)t(11;22)(q23;q11.2)	Not available
UID 4	F	4	47,XX,+der(22)t(11;22)(q23;q11.2)	Not available
UID 5	F	3	47,XX,+der(22)t(11;22)(q23;q11.2)mat	Mother: 46,XX,t(11;22)(q23;q11.2) Father: 46,XY
UID 6	M	2	47,XY,+der(22)t(11;22)(q23;q11.2)	Not available
UID 7	M	8	47,XY,+der(22)t(11;22)(q23;q11.2)	Not available
UID 8	M	3	47,XY,+der(22)t(11;22)(q23;q11.2)	Not available

In three children, parental samples were subjected to karyotype analysis. All three mothers were found to have an abnormal karyotype in the form of a balanced t(11;22)(q23;q11.2), while all three fathers had a normal karyotype. The three mothers who harbored the t(11;22) were phenotypically normal (Table 2).

Discussion

There have been several reports of children with abnormal phenotypes which differed from Down syndrome and were considered to be due to trisomy 22.[7–9] Studies on affected families after the advent of chromosomal banding techniques[10] demonstrated that the trisomy 22 was a supernumerary der(22), which originated from a parent who carried the balanced t(11;22)(q23;q11.2).[11,12] This supernumerary chromosome was seen to consist of the short (p) arm, the centromere, the proximal part of the long (q) arm of chromosome 22, and the terminal part of chromosome 11q resulting in partial trisomies for the terminal and proximal segments of chromosomes 11 and 22.

Further studies revealed that in 99% of cases, supernumerary der(22) was inherited, and only rarely was it *de novo*.[4,13] Segregation analysis in 16 families with the t(11;22) conducted by Shaikh et al.[11] confirmed that the supernumerary derivative chromosome 22 was a product of a 3:1 mal segregation at meiosis I in a carrier of a balanced t(11;22). Thereafter, several studies verified the events of mal segregation wherein one gamete receives three homologs (one normal chromosome 11, one normal chromosome 22, and the derivative 22) while the other receives only the derivative 11.[3,11] A zygote formed from the gamete carrying the derivative 22 will then show a gain of a structurally abnormal supernumerary derivative 22 comprising of segments of both chromosome 22 and chromosome 11. As the segments involved in this process were small, the zygote could be viable and hence, could result in a live-born child with a chromosome imbalance.

In our study, we confirmed the maternal inheritance (Fig. 1) in three children harboring der(22) (Table 2). According to Carter et al.,[1] in 90% of children diagnosed with ES, the der(22) originated from the maternal source. Zackai et al.[4] in his segregation analysis demonstrated that the female heterozygotes harboring a balanced t(11;22) carried a risk of 10%, while a significant risk was also borne by male heterozygotes, of having progeny with an unbalanced karyotype. Furthermore, the risk of recurrence among siblings was 3.7% when the mother was a carrier and 0.7%, if the father carried this translocation.[14] The propensity of female carriers to stand a higher chance of bearing an abnormal embryo with der(22) was not yet clear. Few studies have also described reduced fertility among male carriers which could possibly explain the increased risk among female carriers in bearing an abnormal progeny, although this could be a result of ascertainment bias.[15]

Interestingly, when a female is a carrier, nearly 70% of her phenotypically normal offsprings were carriers and >50% of the progeny carriers were females.[16]

Carriers of the t(11;22) are usually ascertained following the birth of an offspring with an abnormal phenotype due to der(22). Kurahashi et al.[17] in their experiments on healthy males were able to demonstrate that the de novo translocation events of the t(11;22) occurred in the sperms at a frequency of $1.24–9.46 \times 10^{-5}$.[18] Hence, he concluded that most *de novo* translocations were paternal in origin. Men harboring the t(11;22) either presented with infertility or repeated miscarriages in their partners.

By far, the t(11;22) is one of the most common recurring translocations, and the interesting contributions of its recurrence nature have been attributed to the presence of low copy repeats (LCR) on chromosome 11q, band 23.3 and chromosome 22q, band 11.2, which are susceptible to breakage and recombination.[19]

This is because these LCRs have centrally placed palindromic AT-rich repeat sequences (PATRRs) which are prone to form secondary structures such as hairpin bends and cruciform structures, the ends of which may undergo double-stranded DNA breaks.[17,20] Another mechanism that favors breakage and recombination is the asynchrony of DNA replication of LCR regions on chromosome 22.[21] Double-stranded breaks in the regions of chromosomes 11 and 22 which have similarities to PATRRs predispose to non-homologous end-joining of these chromosomes resulting in the translocation (11;22).[20] The likelihood of the formation of these configurations decides the rate of recurrence of the translocation.

The outcomes of carriers of the t(11;22) varied from normal fertility, miscarriages, to viable pregnancies with offspring affected with an unbalanced genetic make-up.[22]

Three families in our study had a significant family history in terms of previous sibling deaths, repeated miscarriages in the mother, and maternal siblings' death and disability. Therefore, establishing a carrier status plays a crucial role in family counseling since it predicts the reproductive outcomes in the couple.

Three mothers presented with pregnancy-related complications and the neonatal period was complicated by palatal insufficiency and anal stenosis in five children. Sparse literature related to

pregnancy and neonatal complications with respect to the t(11;22) and ES has been described so far.

In the early 2000s, the phenotype associated with supernumerary chromosome 22 was termed ES. Over 100 individuals with ES have been reported to date.[1–4,7–9] The dysmorphic features and congenital anomalies most frequently seen in ES have been well described in the literature.[1–3] Some of these studies have recorded findings, while others are based largely on parental reporting of abnormalities. We compare our findings with the literature.

Commonly seen dysmorphic features in our patients with der(22)t(11;22)(q23;q11.2) (Fig. 2) were preauricular sinus (75%) which was similar to that reported by Carter et al. (Table 3). On the contrary, we found microcephaly in 62.5% of children vs 23% as reported by Carter et al. We found palatal insufficiency in only three children (37.5 vs 54%) as compared to reports by Carter et al. Other variable dysmorphic features described by Carter et al.[1] which were observed in our group included hypertelorism, epicanthic folds, sparse eyebrows, depressed nasal bridge, and large ears and were seen in only two to three children (Table 1).

Carter et al.[1] and Lin et al.[23] have reported heart defects, which are usually acyanotic in 57% and 62% of ES, respectively. Similarly, we found heart defects in 62.5% of children of which ASDs were detected in 60%, while VSDs in 40%. Other heart defects detected in our children were coarctation of the aorta, pulmonary outflow obstruction, pulmonary stenosis, and tricuspid atresia in one each. These findings have also been reported by other studies.[1,22] Four of our children presented with more than one cardiac defect. None of our children presented with complex heart defects such as tetralogy of Fallot, transposition of great vessels, or truncus arteriosus as described previously.[23,24]

We found intestinal anomalies in three children (37.5%) in the form of anal stenosis in two and malrotation of the gut in one, which is slightly higher than the previous reports.[1,2] Renal malformations have been reported in 19–36% of ES;[1,2] however, none of our children had renal malformations. Genital abnormalities have been reported to be a variable finding[1,2] in males with ES. One child presented with bilateral undescended testes.

All eight children in the present study had undergone brain imaging studies. Structural malformations of the brain were detected in five children (62.5%) (Table 3). In a literature review on 79 cases of ES, authored by Pallotta et al.,[25] 30% of children were reported to have structural brain malformations of which recurrent malformations included ventricular dilatation in seven, hypoplasia of cortex and cerebellar vermis in four each, trigonocephaly in three, and hypoplasia of corpus callosum and Dandy–Walker malformation in two each. In our study, hypoplasia of corpus callosum, Dandy–Walker malformation, choroid plexus cysts,

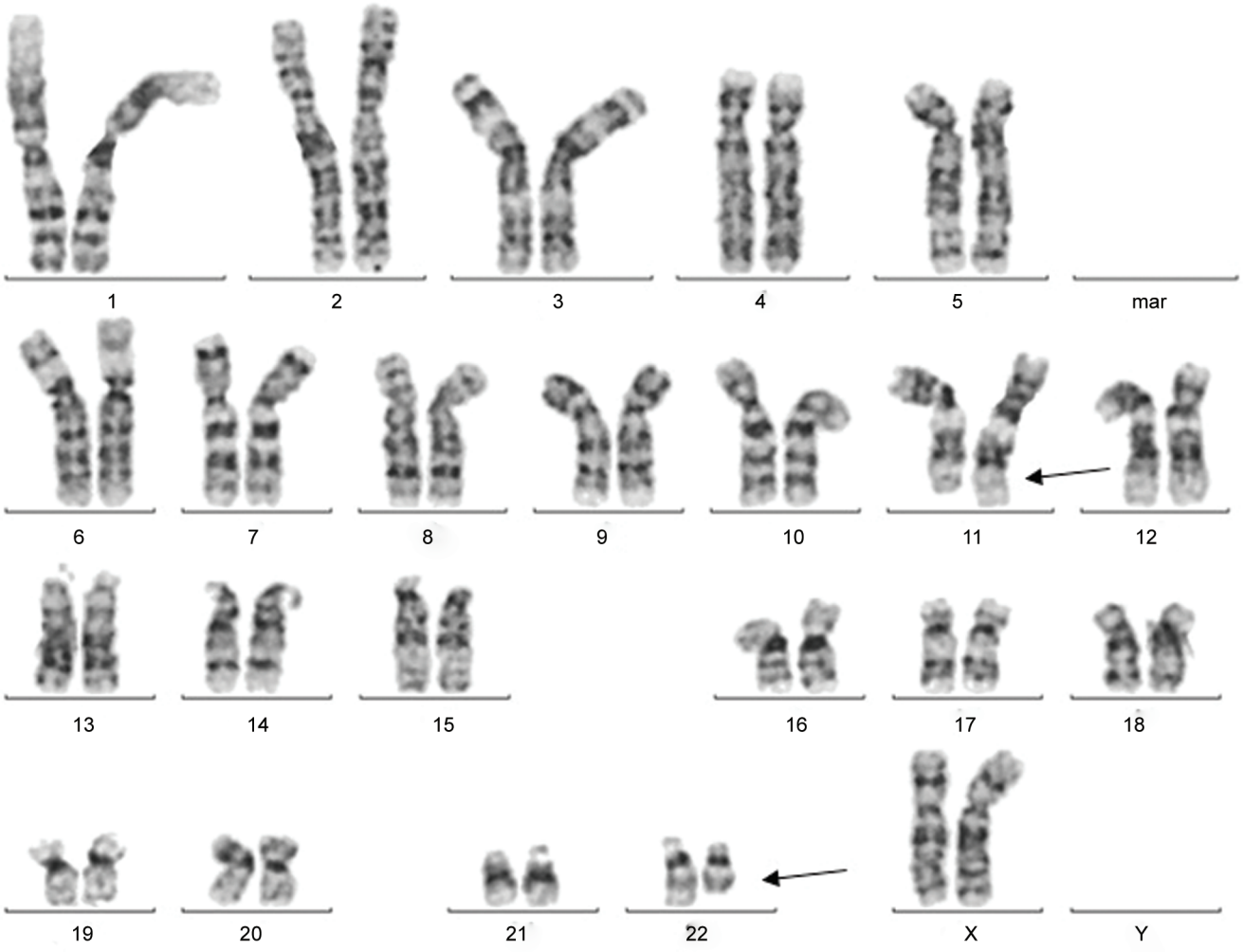

Fig. 1: G-banded karyotype shows the t(11;22)(q23;q11.2)

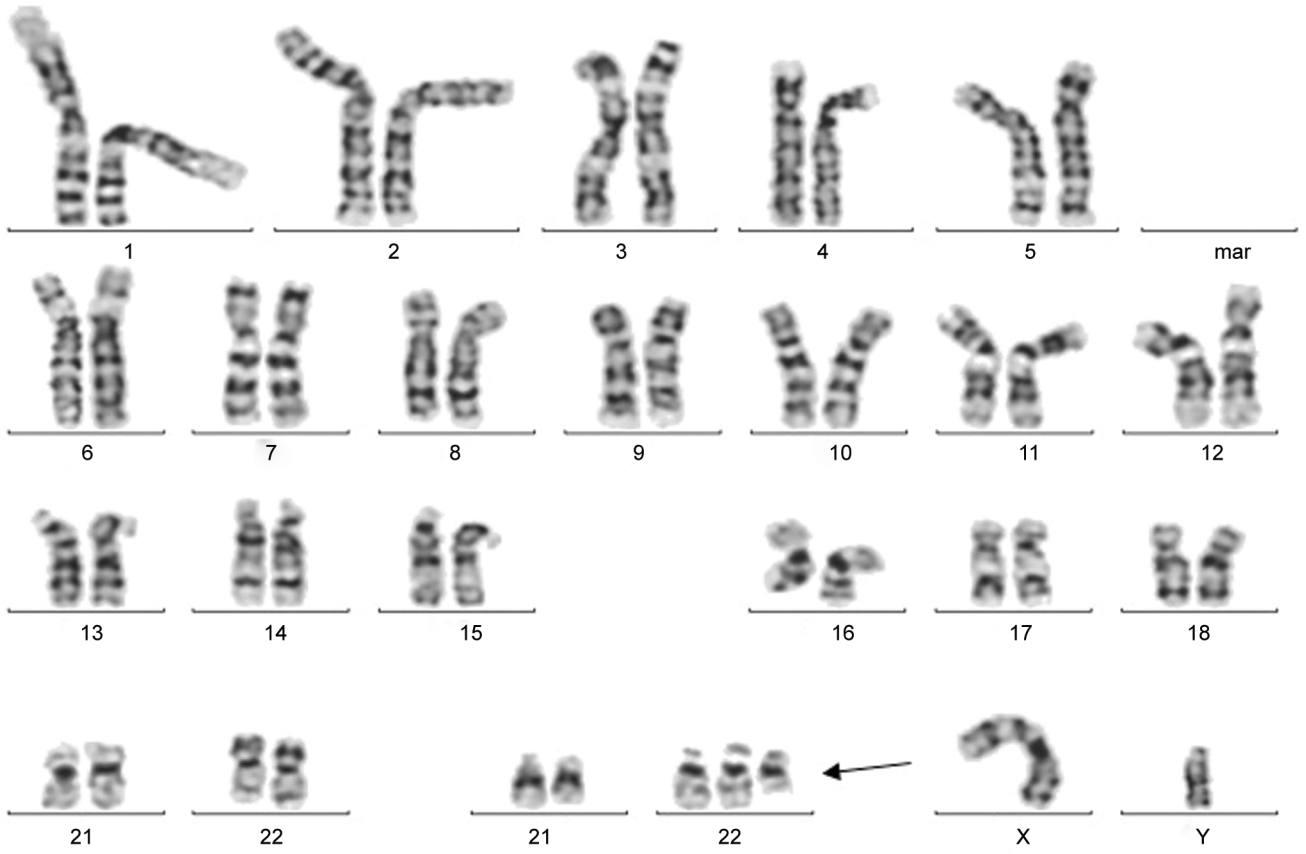

Fig. 2: +der(22)t(11;22)(q23;q11.2)

Table 3: Comparison of the clinical features of the current study with the published literature

Clinical features	*Carter et al. (n = 63) (%)*	*Fraccaro et al. (n = 43)*	*Pallotta et al. (n = 79)*	*Present study (n = 8) (%)*
Developmental delay	100	100	NA	100
Facial dysmorphism	100	100	NA	100
Microcephaly	23	30	NA	62.5
Hypotonia	65	46.8	NA	62.5
Seizures	48	NA	NA	37.5
Congenital heart defects	57	42.5	NA	62.5
Anal atresia	14	12.7	NA	25
Renal anomalies	36	19	NA	0
Hearing loss	72	4.2	NA	50
Vision impairment	38	NA	NA	37.5
Brain malformations	NA	NA	30	62.5

NA, not available

pontine hypoplasia, vermis hypoplasia, and hydrocephalus was found in five children. A better understanding of the structural malformations associated with ES would help to conduct detailed antenatal ultrasound scans for specific abnormalities.

More than half of children as reported by Carter et al.[1] had seizures, whereas only three of our children (37.5%) presented with seizures. Our findings are similar to that of Carter et al.[1] with respect to hypotonia (62.5%) and visual impairment (37.5%) (Table 3). Fraccaro et al.[2] documented hypotonia in approximately half of the affected children.

Hearing loss and speech delay have been reported in up to two-thirds of cases with ES.[1] In our study, bilateral sensorineural deafness and speech delay were found in 50% of children. Only one child had both hearing loss and speech delay. Early intervention in terms of administering speech therapy and hearing aid would improve the quality of life in these children.

The features of ES such as intellectual disability and developmental delay, cleft palate, renal malformations, heart defects, and structural brain malformations have also been detected in those with partial trisomy 11q[26] since ES shows a partial trisomy 11q in addition to partial 22q trisomy. However, ES differs from the other syndromes associated with gain of chromosome 22 material, namely, cat-eye syndrome (CES) or supernumerary isodicentric 22q resulting in tetrasomy for 22q, with respect to

the presence of intellectual disability and developmental delay, which is either absent or mild in CES. The plausible explanation for this is the presence of a gain of unique chromosome 22 material. Nevertheless, preauricular sinus, congenital heart defects, and anorectal malformations have been found in both CES and ES.[1–3,27]

Conclusion

The distinctive clinical features found in children diagnosed with ES in our study include global developmental delay/intellectual disability, heart defects, brain malformations, hypotonia, and dysmorphism in the form of preauricular sinus and microcephaly. Probands inherited der(22) from the maternal source of t(11;22). Therefore, it becomes extremely important to conduct family studies to identify carriers to predict reproductive risks which would aid in offering prenatal testing and providing appropriate counseling.

Clinical Significance

Emanuel syndrome is a rare syndrome. Identification of characteristic features would aid in early diagnosis which would be of benefit to children in seeking intervention for disabilities such as hearing, vision, and speech delay as well as mobility concerns which form an integral component of development since life expectancy is likely to be longer in uncomplicated cases. Furthermore, identification of the t(11;22)(q23;q11.2) carriers would also aid in assessing reproductive risks and offering appropriate family counseling.

Limitations of the Study

We could not study the inheritance pattern in all children diagnosed with ES, since all parents were not subjected to karyotype testing.

This could possibly be due to the rarity of this syndrome by itself and sparse literature associated with regard to the characteristic features of the syndrome and its inheritance pattern.

Acknowledgments

All the authors of this manuscript have significantly contributed toward the writing of this manuscript.

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