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CASE REPORT Open Access

Emanuel syndrome due to unusual pattern

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Abstract

Background The hallmarks of Emanuel syndrome are pre- and postnatal growth retardation, microcephaly, global developmental delay, ear anomalies, and in males, heart, kidney, and genital abnormalities.

Results This study describes the atypical features of Emanuel syndrome, a rare chromosomal disorder. The patient had several physical features that are common in Emanuel syndrome, such as microcephaly, hypotonia, and ear anomalies. However, he exhibited certain unusual characteristics, including the lack of a prominent forehead, epicanthic folds, and a downward slanting palpebral fissure. There was infratentorial brain involution with a minor infarction in the left cerebral hemisphere and cerebellar hypoplasia on the magnetic resonance imaging (MRI) scan of the brain. Additionally, the patient had bilateral mild hearing loss and an aberrant epileptogenic pattern on the electroencephalogram (EEG). Orodental examination showed a long philtrum, everted fissured thick lower lip, highly attached labial frenum, and prominent median palatine raphe. The karyotype revealed 45XY t(11;22)(p15.5;q11.22), which is different from the typical karyotype of Emanuel syndrome.

Conclusions This case sheds light on the possibility of alternative genetic mechanisms, beyond chromosomal abnormalities, in patients presenting with multiple congenital anomalies and facial dysmorphism.

Keywords Emanuel syndrome, t(11;22), Dysmorphism, Intellectual disability, Microcephaly, And convulsions

Introduction

Emanuel syndrome (OMIM# 609029) is caused by the supernumerary chromosome, which consists of extra genetic material from chromosomes 11 and 22. It is an uncommon disorder characterized by multiple congenital abnormalities [1]. The reported frequency is about 1:110 000, it is characterized by delayed mental and developmental milestones and multiple congenital anomalies including ear pits (76%), micrognathia (60%), heart malformations (57%), cleft palate (54%), vision, hearing impairment, seizures, kidney abnormalities, and genital abnormalities in males [2, 3].

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Case report

The proband is the outcome of two healthy Egyptian non-consanguineous parents. He has two older female siblings: One was normal and the other had rheumatic heart disease and mental impairment. The parents' karyotypes were normal, and there was a history of prior abortions with unclear causes. No further abnormal family members have been recorded. The pregnancy history was uneventful; he was born at 40 weeks of gestation with a normal birth weight. At the presentation, the boy was 7.5 years old and complaining of delayed mental milestones, convulsions, and poor pain perception. His weight was 19 kg (− 1.1SD), his height was 113 cm (− 1.3 SD), and his head circumference was 49 cm (− 2.3). On examination, he revealed dysmorphic features: triangular face, brachycephaly, low anterior hairline, downward slanting of eyelids, synophrys, prominent frontonasal, barrel nose, thin upper lip, small posteriorly rotated low set folded ears with thick helix, widely spaced hypoplastic nipples and hypoplastic nails. The clinical examination

detected no abnormality in the chest, heart, and neurological examination. The hearing test revealed bilateral mild hearing loss. Genital examination showed normal male external genitalia. IQ was measured by Wechsler Intelligence Scale for School Children (WISC) and revealed 61 (mild mental retardation). Nevertheless, an aberrant epileptogenic pattern was seen in the EEG. The MRI brain displayed infratentorial brain involution, small infarction in the left cerebral hemisphere, and cerebellar hypoplasia. No abnormality was detected on examination of the eye, cardiovascular, gastrointestinal, and genitalia. Orodental examination showed a long philtrum, everted fissured thick lower lip, highly attached labial frenum, and prominent median palatine raphe. The clinical characteristics of Fryns syndrome and Pallister-Killian syndrome (PKS) exhibit similarities with Emanuel syndrome. Chromosome analysis always confirms the diagnosis of Emanuel syndrome and rules out other diagnoses. The karyotype was performed to explain the multiple congenital anomalies and showed abnormal karyotype 45, XY t(11;22)(p15.5;q11.22). Most Emanuel patients present with failure to thrive, hypotonia, and severe to profound intellectual disabilities.

Patients and methods

G-banding: Peripheral blood lymphocytes were cultured for 72 h. At 37 °C in 4 ml, PRMI 1640 culture medium was supplemented with 1 ml fetal bovine serum and 0.1 ml of phytohemagglutinin. Cultures were exposed to 0.1 mg/ml of 0.05 colchicine solution for 1 h followed by 5 ml of hypotonic solution (0.58% potassium chloride or 0.7% sodium citrate) at 37 °C for 30 min and repeated fixations in methanol/acetic acid (3:1). Slides were air-dried and stained with 10% Giemsa solution. Karyotyping was performed, and 100 metaphases were analyzed to record the presence of chromosome abnormalities following the International System for Human Cytogenetic Nomenclature according to Seabright (1971) and Verma and Babu (1995).

Fluorescence in situ hybridization (FISH) technique was applied on metaphase nuclei from peripheral blood according to modification of Pinkel et al., (1986) and manufacturer instructions by using:

1. Whole chromosome painting of chromosome 11 spectrum red, and whole chromosome painting of chromosome 22 spectrum green, 50 metaphases were analyzed to confirm translocation.
2. DiGeorge VCFS N25 Region + 22q13.3 Region Probe supplied by Cytocell Aquarius Diagnostics [4] to confirm 22 deletions.

Results

See Figs. 1, 2, 3, 4 and Table 1.

Discussion

The patient in our investigation displayed mental and developmental impairment, as documented in several other studies [2, 12, 17]. The likelihood of recurrence depends on whether the proband's chromosomal

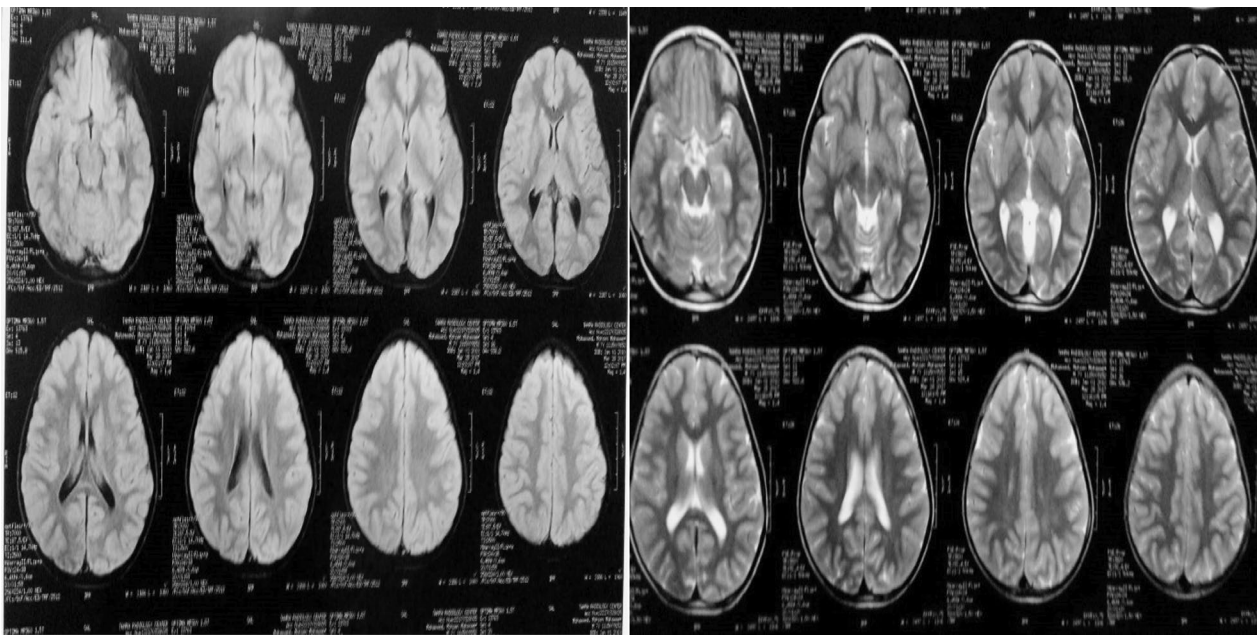

Fig. 1 MRI brain displayed infratentorial brain involution with a small infarction in the left cerebral hemisphere with cerebellar hypoplasia

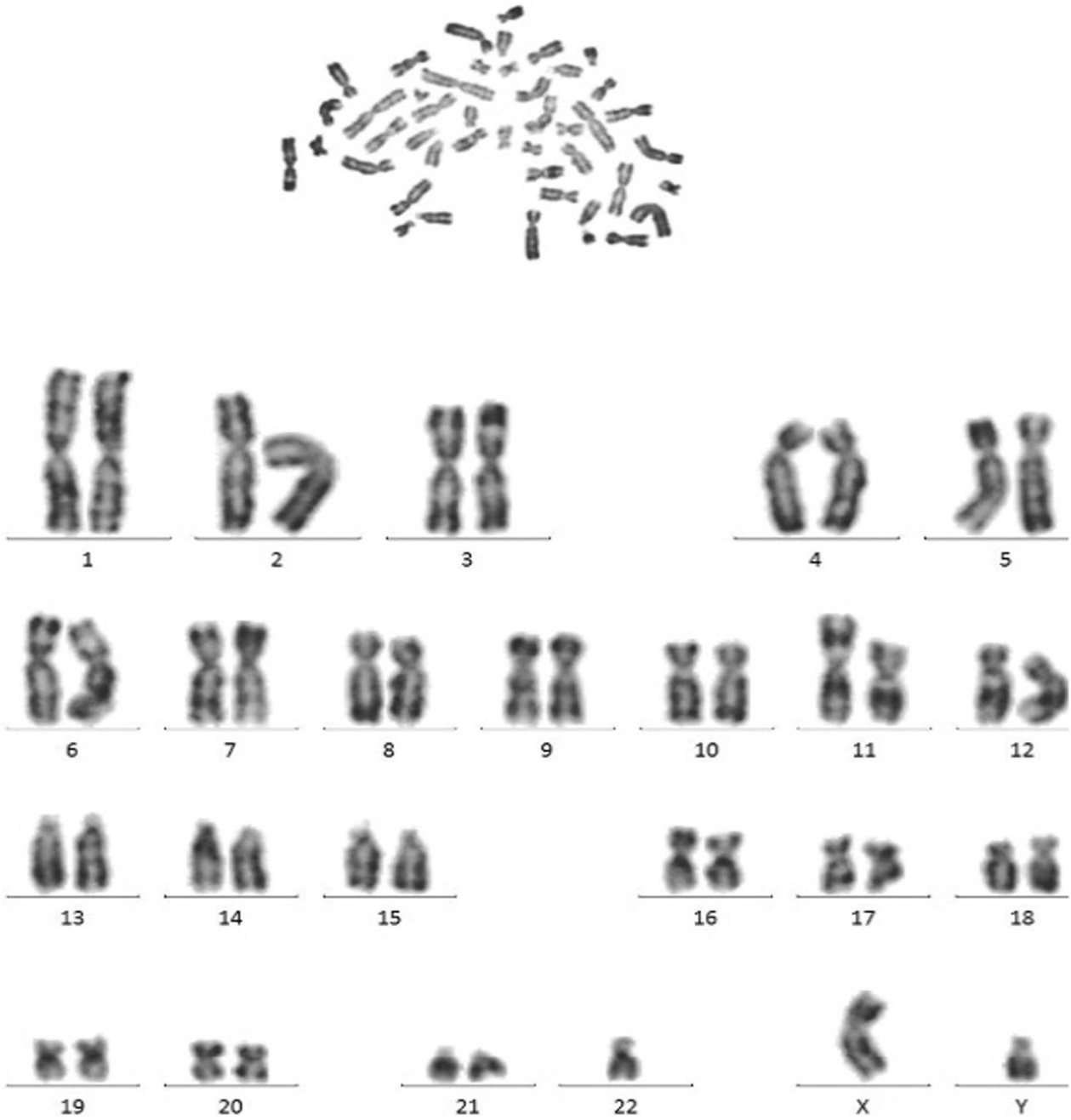

Fig. 2 The karyotype is: 45, XY, t(11;22)(p15.5;q11.2)

abnormality is inherited or developed spontaneously. The karyotypes of both our patient's parents were normal. However, it was noted by Saxena et al. (2018) and Vorstman et al. (2006) that in 99% of the cases, one of the parents is a carrier of a balanced translocation between chromosomes 11 and 22 [18, 19]. The results of this study support those of earlier research, demonstrating that the features of the craniofacial dysmorphism included brachycephaly, low anterior hairline, downward slanting of palpebral fissures, synophrys, prominent frontonasal root, barrel nose, thin upper lip, small posteriorly rotated low set folded ears with thick helix, widely spaced hypoplastic nipples, and hypoplastic feet nails [20]. This study describes abnormal findings that have not been previously reported in patients with Emanuel syndrome. The patient in this study did not have the following features

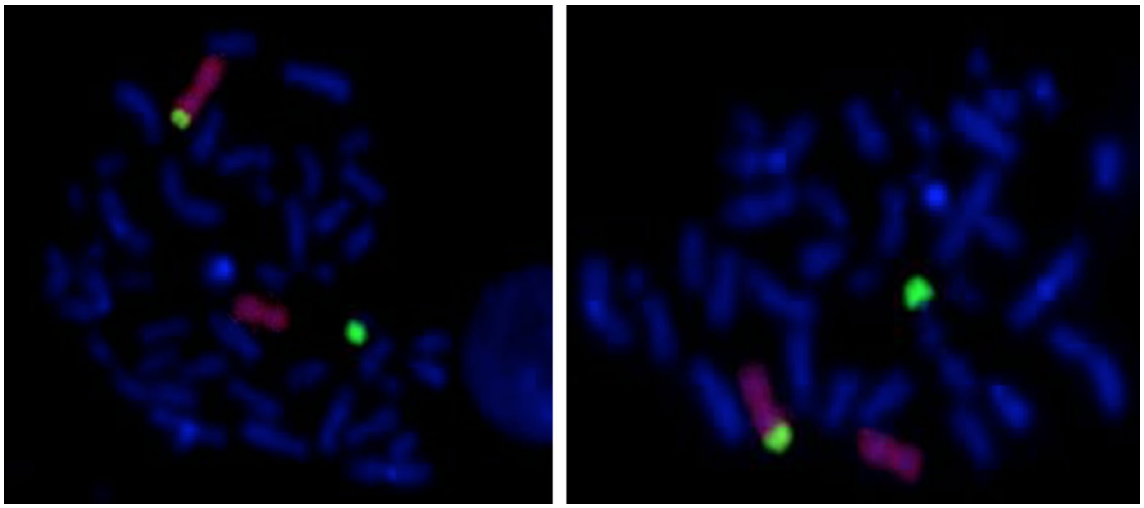

Fig. 3 FISH showing t(11;22) using whole chromosome painting of chromosome 11 spectrum red, and whole chromosome painting of chromosome 22 spectrum green

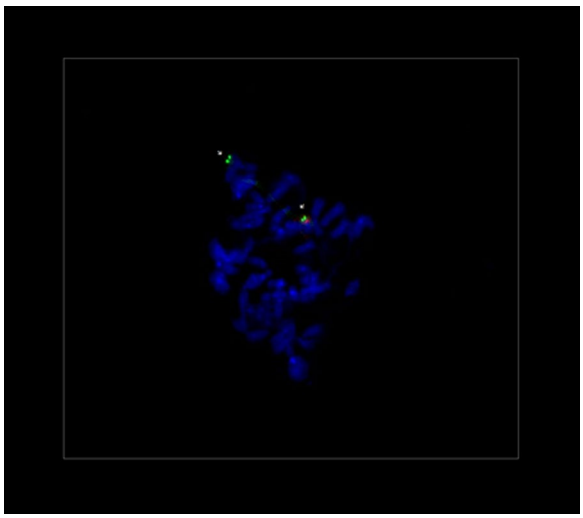

Fig. 4 ish del(22)(q11.2)(D22S75-){40/200}

that are commonly seen in Emanuel syndrome including a prominent forehead, epicanthic folds, a broad and flat nasal bridge, a long-pronounced philtrum, abnormal auricles, and preauricular ear pits.

However, the patient did have hearing loss, which is a known feature of Emanuel syndrome. Other studies have also reported hearing loss in patients with Emanuel syndrome [2, 21]. The findings of this study suggest that there may be a wider range of clinical features in Emanuel syndrome than previously thought. This is important to increase the awareness of this syndrome for proper diagnosis and management. The patient had seizures and an abnormal epileptogenic pattern. This is consistent with the findings of Jancevska et al. [3]. The MRI of the brain showed infratentorial brain involution, a small infarction in the left cerebral hemisphere, and cerebellar hypoplasia. This is similar to the findings of Zaki et al., who described a patient with a maldeveloped corpus callosum and hindbrain [1].

No abnormalities were detected on examination of the eyes, cardiovascular system, gastrointestinal tract, or genitalia. This is consistent with a prior study by Jancevska et al. [3], that described an Emanuel syndrome patient without microcephaly, heart defects, or kidney abnormalities. However, other studies have noted that Emanuel syndrome is characterized by congenital heart diseases, kidney abnormalities, and genital anomalies in males [1, 3, 22]. The patient's karyotype revealed 40 out of 200 (20%) cells with a 22q deletion. This suggests that the patient has a mosaic form of Emanuel syndrome.

Orodental examination showed a long philtrum, everted fissured thick lower lip, highly attached labial frenum, and prominent median palatine raphe. These findings are consistent with those reported by previous researchers. However, they also described other orodental findings, such as the delayed eruption of primary and permanent teeth, oligodontia, and short-root anomaly of central incisors [12].

Researchers have suggested that the loss of a particular gene on chromosome 22 may account for the distinctive signs of Emanuel syndrome, such as dysmorphic features, hearing loss, and behavioral problems [17].

Although other researchers reported 47, XY,+der(22) t(11;22)t(q23;q11.2), our patient's karyotype exhibited 45,XY t(11;22)(p15.5;q11.22), monosomy 22, and ish del(22)(q11.2) [3]. The identified 22q11 deletion was

Table 1 Comparing clinical features reported in Emanuel syndrome and our patient

Affected system	Clinical presentation	Our patient
1. Growth and development	Delayed milestones, delayed speech and language development [5]	Delayed milestones and delayed speech
2. Craniofacial dysmorphism	Brachycephaly, prominent forehead, epicanthal folds, downwards slanting of palpebral fissures, broad and flat nasal bridge, long pronounced philtrum, abnormal auricles, preauricular ear pits and/or tags (76.0%) [6]	Brachycephaly, low anterior hairline, downward slanting of palpebral fissures, synophrys, prominent frontonasal root, barrel nose, thin upper lip, small posteriorly rotated low set folded ears with thick helix, widely spaced hypo-plastic nipples and hypoplastic feet nails
3. Hearing test	Deafness and otitis media [7]	Mild hearing loss
4. Central nervous system	Microcephaly, seizures, failure to thrive, and delayed psychomotor development MRI brain revealed hypoplastic corpus callosum in 20% [8]	Mild mental retardation (61), seizures EEG showed an abnormal epileptogenic pattern. MRI brain revealed infratentorial brain involution, small infarction in the left cerebral hemisphere, and cerebellar hypoplasia
5. Cardiac defects	Congenital heart defects such as atrial septal defect (60%), ventricular septal defect, tetralogy of Fallot, and patent ductus arteriosus [9]	Normal echo heart
6. Genito-intestinal defects	Diaphragmatic hernia, anal atresia, inguinal hernias, biliary atresia, small penis (64.0%), and cryptorchidism (46.0%) [10]	Normal
7. Musculoskeletal defects	Most commonly, centrally based hypotonia, congenital hip dislocation, arachnodactyly, club foot and joint, syndactyly of the toes, delayed bone age, and hyperextensibility of joints [11]	Bilateral clinodactyly in the fourth toe and hypoplastic nails in the toes
8. Oral findings	Cleft palate (50.0%), micrognathia (60.0%), angular mouth pits, bifid uvula, and facial asymmetry [12]	Long philtrum, everted fissured thick lower lip, highly attached labial frenum, and prominent median palatine raphe
9. Immunological defects	Congenital immunological deficiency [13]	Normal
10. Renal defects	Renal defects (36.0%) [14]	Normal
11. Karyotype of parents	99% of parents are balanced translocation [15]	Normal
12. Karyotype	47, XY, + der(22)t(11;22)(q23;q11.2) [16]	45, XY t(11;22)(p15.5;q11.22)

abnormal and did not overlap the CATCH crucial area. In another investigation, the first instance of monosomy with the karyotype 45, XY, der(11)t(11;22)(q23; q11.2) was described [23].

Therefore, the combined cytogenetic and molecular analyses can achieve a more accurate diagnosis of congenital abnormalities. Furthermore, genetic disorders on 22q11 may expand our knowledge of chromosomal rearrangements and phenotype/karyotype correlation. This case has implications for genetic counseling in families with 22q11, as proper genetic counseling should be given to clarify that chromosome mosaic deletion could affect their children subsequently.

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Author contributions
HTE and MS designed and supervised the study, EAA and KH were responsible on clinical examination of the case. MR was responsible on dental examined. MS and AEA were responsible on cytogenetic investigations, and all authors participated in writing and revising the manuscript.

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Availability of data and materials
It is available with the corresponding author upon request.

Declarations

Ethics approval and consent to participate
Written consent was taken from patient guardian. The study was approved by the Medical Research Ethics Committee of the National Research Centre (NRC), Cairo, Egypt.

Consent for publication
Not applicable.

Competing interests
There are no conflicts of interest.

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