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EMANUEL SYNDROME (ES): NEW CASE-REPORT AND REVIEW OF THE LITERATURE

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Abstract

Multiple congenital anomalies and craniofacial dysmorphism are characterizing the so-called Emanuel or supernumerary der(22)t(11;22) syndrome (OMIM609029). Mental and developmental retardation are major clinical features. The der(22) may arise from a parental balanced t(11;22)(q23;q11.2) or can be created de novo.

Here we present a 2 years old boy with normal prenatal history, cyanotic at delivery and with ear anomalies, a preauricular tag, high-arched palate and micrognathia. There were neither microcephaly, nor heart or kidney defects. Psychological and motor testing at the age of 2 years confirmed significant mental and developmental delay. In addition, the child had seizures and an abnormal electroencephalogram. Cytogenetic and molecular analyses revealed a karyotype 47,XY,+der(22)t(11;22)(q23;q11.2). As parents refused further tests it could not be determined if the der(22) arose de novo or was parentally derived.

Overall the present report should alert physician to offer cytogenetic and/or molecular diagnostics in comparable cases.

Key words: Emanuel syndrome, congenital anomalies, derivative chromosome 22 {der(22)t(11;22)}.

Introduction

Emanuel syndrome (ES), also known as supernumerary der(22)t(11;22) syndrome (OMIM 609029) is characterized by multiple congenital anomalies, significant developmental delay and mental retardation. Craniofacial dysmorphism with microcephaly, micrognathia, high-arched palate as well as ear anomalies with preauricular tag or sinus, heart defects, kidney abnormalities, as well as genital abnormalities in male patients were reported as typical features of ES [1].

The underlying cause of ES is a supernumerary marker chromosomes (sSMC) composed of chromosomal material derived from more than one chromosome (derivative chromosome 22 {der(22)t(11;22)}, a so-called 'complex sSMC [2, 3]. The der(22) may arise from a parental balanced translocation or can arise de novo [2].

Case report

We report a 2 years old boy, progeny of young and unrelated parents. He was born after uneventful pregnancy and delivery at 39 weeks of gestation. His birth weight was 2.2 kg (< third percentile), length 46 cm (< third percentile), and head circumference 32 cm (< third percentile). He was cyanotic and hypotonic at delivery.

His face was remarkable by prominent forehead with dilated veins, and hyperthelorism with downslanting palpebral fissure. His nasal bridge was not broad, the philtrum mildly prominent, the ears large and low-set with preauricular pit. High arched palate and micrognathia were also present. In addition, he had a small penis (1.5 cm).

There was no microcephaly, and ultrasonography of kidneys and heart were without any abnormal findings. Psychological testing confirmed a significant mental and developmental delay. Karyotyping using G-banding analysis at 550 band levels identified a SMC which was suggested to be a der(22)t(11;22)(q23;q11.2). Multiplex ligation-dependent probe amplification (MLPA) assay using probes P070-B2, P036-E1,P245, including overall 15 probes for chromosomes 11 and 22 confirmed this suspicion (MRC Holland, Amsterdam, The Netherlands), (see Table 1).

Table 1

Multiplex ligation-dependent probe amplification (MLPA) assay results

	Chromosome	**Location (hg18/ build 36)**	**Method**	**Result**
1	11p15.5	195448-195520	MLPA (P070-B2 Human Telomere-5)	normal
2	11p15.5	199935-199999	MLPA (P036-E1 HumanTelomere-3)	normal
3	**11q25**	**133292680-133292754**	**MLPA (P070-B2 Human Telomere-5)**	**duplication**
4	**11q25**	**133595730-133595797**	**MLPA (P036-E1 HumanTelomere-3)**	**duplication**
5	**22q11.1**	**15959672-15959739**	**MLPA (P070-B2 Human Telomere-5)**	**duplication**
6	**22q11.21**	**16606684-16606759**	**MLPA (P036-E1 HumanTelomere-3)**	**duplication**
7	**22q11.21**	**17891318-17891378**	**MLPA (P245 Microdeletion-1)**	**duplication**
8	**22q11.21**	**18091521-18091580**	**MLPA (P245 Microdeletion-1)**	**duplication**
9	22q11.21	19565377-19565455	MLPA (P245 Microdeletion-1)	normal
10	22q12.1	27186340-27186833	QF-PCR (D22S689)	normal
11	22q12.3	35455491-35455818	QF-PCR (D22S692)	normal
12	22q13.1	39295470-39296067	QF-PCR (D22S534)	normal
13	22q13.33	49413270-49413327	MLPA (P070-B2 Human Telomere-5)	normal
14	22q13.33	49461911-49461979	MLPA (P245 Microdeletion-1)	normal
15	22q13.33	49553070-49553142	MLPA (P036-E1 HumanTelomere-3)	normal

Discussion

ES is a rare syndrome (~350 patients reported so far (http://ssmc-tl.com/chromosome-22.html). ES patients have a karyotype 47,XX,+der(22)t(11;22)(q23;q11) in females or 47,XY,+der(22)t(11;22)(q23;q11) in males [2, 6–11]. The supernumerary chromosome can be of maternal [9–11] or paternal origin [12, 13]. It is of note that ES is the most frequently observed, recurrent, non-Robertsonian translocation in humans. As karyotype 46,XN,der(22)t(11;22)(q23;q11) is not compatible with life, most if not all ES patients result from monosomic rescue of the intact chromosome 22 and have a uniparental isodisomy 22, besides the complex sSMC [14].

The facial dysmorphism in ES is prominent and characteristic [1]. It is of note that our patient had only mild facial dysmorphysm. Although the forehead was prominent, epicanthal folds were small, palpebral fissures were not downslanting, nasal bridge was not broad, and the philtrum was only moderately long. There was a moderate micrognathia, without cleft or high-arched palate. The auricules were large with a preauricular ear pit. The lack of prominent features was probably due to the fact that facial features of ES coarsen over time [6]. The patient did not have cleft palate (observed in 54% of the cases) [1]. Most importantly our patient did not have microcephaly [1]. Nevertheless, the boy had developmental delay and intellecttual disability. He was ambulatory and his speech was scant.

As most ES children [1] he was floppy and his growth was below the 3rd percentile.

His weight was appropriate for his height and he had no feeding difficulties. Renal malformations were not present in our patient, although they are found in ~30% of ES [1]. Also, there were no cardiac malformations, while they were present in ~57% of the cases [1]. The present patient had not cryptorchidism as observed in 46% of the ES-cases [1], but his penis was small (64% of ES; 1). Computer tomography of the brain was normal. He had recurrent seizures and his electroencephalogram was abnormal.

Clinical phenotype is not sufficient for the diagnosis. Thus, genetic testing should be offered to the families. It is of note that carriers of the balanced constitutional t(11;22) translocation are phenotypically normal, but they have a 10% risk of having a progeny with supernumerary der(22)t(11;22) syndrome, as a result of malsegregation of the der(22) [5]. Prenatal diagnosis is possible and has to be offered [15–16]. In addition, carrier testing of the unaffected siblings could be also offered in timely manner. While balanced translocation carriers can only be detected by cytogenetics, ES patients also may be picked up by accompanying PCR [17] or MLPA testing [18].

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Р е з и м е

ЕМАНУЕЛ СИНДРОМ (ES): ПРЕЗЕНТАЦИЈА НА НОВ СЛУЧАЈ И ПРЕГЛЕД НА ЛИТЕРАТУРАТА

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Повеќе вродени аномалии и краниофацијална дизморфија се карактеристични за т.н. Емануел синдром, или прекуброен der(22)t(11; 22) синдром (OMIM609029). Главни клинички карактеристики се ментална и физичка ретардација во развојот. Der (22) може да потекнува од родителска избалансираност t(11;22)(q23;q11.2), или настанува de novo.

Презентираме 2-годишно дете со нормална пренатална историја, аномалии на аурикули, преаурикуларна ресичка, висок свод на непцето и микрогнатија. Не се детектирани микроцефалија, срцеви или бубрежни дефекти. Психолошките тестови и тестовите на моториката на возраст од 2 години потврдуваат значајни ментални нарушувања и доцнење во развојот. Покрај тоа, детето има конвулзии и абнормален електроенцефалограм. Цитогенетската и молекуларната анализа се 47,XY,+der(22)t(11;22)(q23;q11.2). Родителите не прифатија понатамошни тестови, што оневозможува да се утврди дали der (22) настанал de novo или потекнува од родителите.

Овој труд треба да им укаже на лекарите да побараат цитогенетска и/или молекуларна дијагностика во случаи со слични карактеристики.

Клучни зборови: Емануел синдром, вродени аномалии, дериват хромозом 22 {дер(22)t(11;22)}.