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M.V. Bondarenko[1], O.M. Kornutii[1], A.P. Dutchak[1], M.I. Nikolenko[2,3], S.B. Arbuzova[3]

Nuchal translucency as a potential marker of Emanuel syndrome: a case report

[1]Ivano-Frankivsk National Medical University, Ukraine
[2]Shupyk National Healthcare University of Ukraine, Kyiv
[3]Eastern-Ukrainian Specialized Center for Medical Genetics and Prenatal Diagnosis, Kyiv

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Aim: to study a clinical case of Emanuel Syndrome (ES) in a newborn child, which arose as a result of a balanced chromosomal translocation in the mother, for early detection of the syndrome.

Clinical case. A 32-year-old woman with an uncomplicated family history presented with a fetus showing increased nuchal translucency (NT) of 3.2 mm at 12 weeks of gestation. The pregnant woman refused the proposed invasive testing. Second-trimester ultrasound identified placenta previa, moderate oligohydramnios, and a hyperechoic focus in the left ventricle, with no major structural anomalies. Biochemical markers in both trimesters were unremarkable. Postnatally, the infant displayed mild dysmorphic features, severe hypotonia, and profound developmental delay. Cytogenetic and Fluorescent In Situ Hybridization analyses confirmed Emanuel syndrome due to a supernumerary chromosome der(22)t(11;22) inherited from the maternal balanced translocation t(11;22).

Conclusion. Increased NT may serve as a useful early marker for ES in prenatal screening, even in the absence of structural malformations or family history. Further research is warranted to validate NT's role in improving early detection of the syndrome.

The research was carried out in accordance with the principles of the Declaration of Helsinki. The copyright agreement from the child's parents was obtained for the study.

The authors declare no conflict of interest.

Keywords: Emanuel syndrome, prenatal diagnosis, nuchal translucency.

Комірцевий простір як потенційний маркер синдрому Емануель: клінічний випадок

М.В. Бондаренко[1], О.М. Корнутій[1], А.П. Дутчак[1], М.І. Ніколенко[2,3], С.Б. Арбузова[3]

[1]Івано-Франківський національний медичний університет, Україна
[2]Національний університет охорони здоров'я України імені П.Л. Шупика, м. Київ
[3]Східно-Український спеціалізований центр медичної генетики і пренатальної діагностики, м. Київ

Мета: вивчення клінічного випадку синдрому Емануель у новонародженої дитини, який виник внаслідок збалансованої хромосомної транслокації в матері для раннього виявлення синдрому.

Клінічний випадок. 32-річна жінка з неускладненим сімейним анамнезом звернулася зі скаргами на збільшення комірцевого простору у плода до 3,2 мм на 12 тижні гестації. Вагітна відмовилася від запропонованого інвазивного втручання. Ультразвукове дослідження у другому триместрі виявило передлежання плаценти, помірне маловоддя та гіперехогенний фокус у лівому шлуночку без значних природжених вад розвитку. Біохімічні маркери в обох триместрах були без виражених змін. Після народження в дитини простежувалися легкі дисморфічні ознаки, тяжка гіпотонія та затримка розвитку. Цитогенетичний та Fluorescent In Situ Hybridization аналізи підтвердили синдром Емануеля, спричинений надлишковою хромосомою der(22)t(11;22), яка виникла внаслідок збалансованої хромосомної транслокації в матері.

Висновки. Збільшення комірцевого простору може бути маркером у пренатальному ранньому скринінгу синдрому Емануель, навіть за відсутності структурних вад розвитку або сімейного анамнезу. Необхідні подальші дослідження для підтвердження ролі величини комірцевого простору у покращенні раннього виявлення синдрому.

Дослідження виконано відповідно до принципів Гельсінської декларації. На проведення дослідження отримано інформовану згоду батьків дитини.

Автори заявляють про відсутність конфлікту інтересів.

Ключові слова: Емануель синдром, пренатальна діагностика, комірцевий простір.

Emanuel syndrome (ES) is a rare genetic disorder resulting predominantly from a 3:1 meiotic malsegregation of a parental balanced translocation t(11;22)(q23;q11) [23,31]. Over 99% of cases involve maternal carriership of this translocation, one of the most common recurrent non-Robertsonian translocations in humans [2,4,10]. ES is characterized by significant developmental delay, intellectual disability, facial dysmorphism, and variable congenital anomalies more often affecting the cardiovascular (~50%), renal (~25%), and skeletal systems (~40%) [2–4,10,14,19.20,27]. Some patients exhibit mild congenital defects [2–4,10,19,20,27], further complicating timely

diagnosis. The syndrome ES was diagnosed in the cohort of 63 patients within the first month of the child's life in 48% [2]; in the study of 43 individuals, ES features were well evident in approximately 30% of cases [4].

There is a prevailing belief, that despite some common ES features, routine second-trimester prenatal screening lacks sufficient sensitivity, largely due to the variability of ultrasound findings often not evident prenatally. While facial features, such as malformed ears with pits and tags, cleft palate, micrognathia, and flat nasal bridge are typical, they are inconsistently present and may not be echographically visible [5–7,9,11–13,16,18,25,26,29,30]. However, the diagnostic potential of early screening in the first trimester remains underexplored.

We present a case of ES with subtle prenatal and postnatal manifestations. The distinctive prenatal feature was increased nuchal translucency (NT). In this report, we explore the informativeness of first-trimester screening for ES, with a focus on NT as a potential marker.

The study was conducted in accordance with the principles of the Declaration of Helsinki. The informed consent was obtained from the child's parents.

Clinical case

A 32-year-old gravida 2, para 1 woman delivered a female newborn weighing 2,990 g at 40 weeks via Caesarean section. The father's age at the time of delivery was 34 years. The parents, unrelated and without a history of congenital anomalies or mental retardation, had a healthy first child.

The pregnancy was complicated by first-trimester placental detachment and a 34-week maternal COVID-19 infection. First-trimester screening identified the patient as high-risk for trisomy 21, with NT measuring 3.2 mm (2.1 MoM), while biochemical markers (pregnancy-associated plasma protein-A: 0.76 MoM, free beta-human chorionic gonadotrophin: 1.56 MoM) were unremarkable. The mother declined invasive testing. Second-trimester ultrasound at 20 weeks revealed placenta previa, moderate oligohydramnios, and a hyperechoic focus in the left ventricle. No gross malformations were detected. Biochemical markers were also within normal limits: alpha-fetoprotein – 0.87 MoM, free beta-human chorionic gonado-tropin – 2.4 MoM, estriol – 1.13 MoM. At the 30 week ultrasound scan, signs of fetal development delay appeared.

At birth, phenotypic signs included slight facial asymmetry, micrognathia, upward-slanting palpebral fissures, epicanthus and strabismus, short filter, wide bridge of nose, open nostrils, high-arched palate, enlarged low-set ears with a solitary right-sided preauricular tag, and a small 1st toe. The infant exhibited severe hypotonia, feeding difficulties, respiratory problems, and needed artificial respiration (Figure 1A).

At eleven months (Figure 1B), the child demonstrated profound developmental delay and convulsive ES. She is unable to sit or crawl and cannot control her head, has a microcephalic skull shape, and bilateral dislocation of the hip joints. The child reacts poorly to sounds; the hearing assessment revealed right-sided hearing loss. Brain MRI revealed mild hypoplasia of the hippocampus and cerebellar vermis. The girl was also diagnosed with moderate hypoplasia of the left kidney. A major congenital defect contributing to the child's disability was severe bilateral hip dysplasia, for which a plaster fixation splint was applied to support the pelvis and hips at the age of 16 months (Figure 1C).

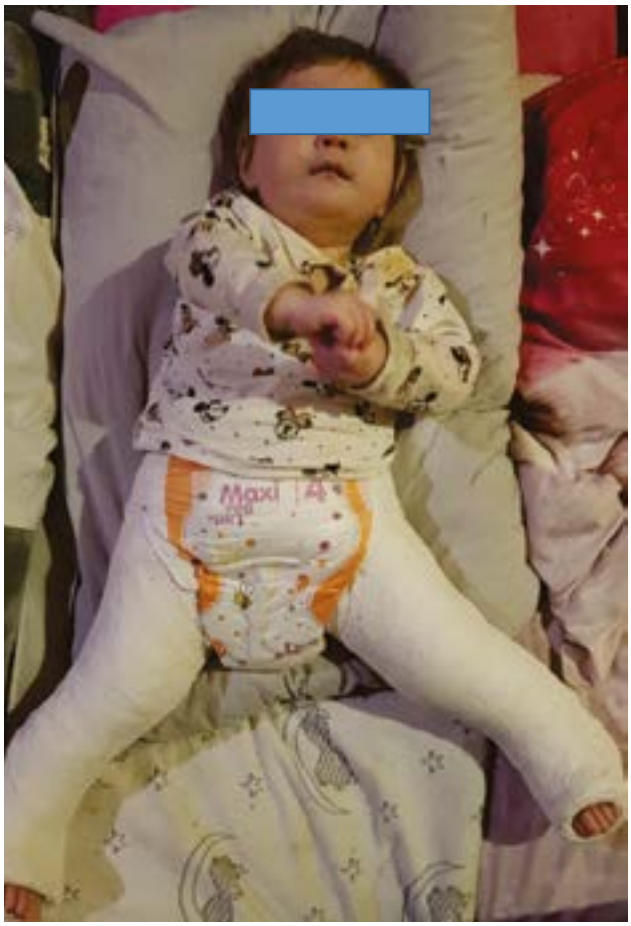
Cytogenetic and Molecular Analysis

During the analyzed period (108 days), 268 air Conventional G-banding chromosome analysis following a standard protocol (400–550-band resolution) and molecular cytogenetic analysis FISH (Fluorescent In Situ Hybridization) were provided. Metaphase plates were analyzed using IKAROS V5.7 software (MetaSystems Hard & Software GmbH, Germany) and a light microscope (Axioscope, AXIO Imager M2, Carl Zeiss Jena GmbH). FISH analysis was performed on interphase nuclei according to the protocol recommended by the manufacturer of DNA probes. A mixture of locus-specific probes for loci 22q11.21 (HIRA) and 22q13.33 (ARSA) of chromosome 22, manufactured by Cytocell Aquarius (UK), was used.

The patient's karyotyping shows a supernumerary chromosome 22, der(22)t(11;22) (Figure 2). The absence of the telomeric region 22q13.3 on derivative chromosome 22 was clarified by FISH – (ish 22(q11.2q13.3) (HIRA+, ARSA-) (Figure 3).

To ascertain the origin, the supernumerary marker chromosome cytogenetic testing was performed on both parents. The father had a normal karyotype, and the mother was found to be a carrier of balanced reciprocal translocation 46, XX, t(11;22)(q23.3;q11.2) (Figure 4).

A B



C

Fig. 1. Facial features of the child: A - at birth; B - at 11 months; C - at 16 months

Discussion

The presented case report underscores the challenges of prenatal ES diagnosis, particularly in the absence of family history or gross malformations.

The ES is known to be characterized by polymorphism of prenatal and postnatal signs of varying severity [2–7,9–14,16,18–20,25–27,29,30]. Even the most commonly observed heart, kidney defects, and diaphragmatic hernia are detected in utero in no more than 30% of cases [18]. Varying degrees of prenatal expressiveness were also noted for other malformations and facial dysmorphia [3,5–7,9,11–13,16,18,25,26,29,30], which is partly explained by oligohydramnios [6,20] and complicated timely ES detection. Although posterior fossa defects are a fairly common prenatal finding, such defects are detected in approximately half of cases [5,13,16,18,29], and there are ES cases without any adverse perinatal event [3,7,9,10,14,16,19,20,25,27]. Prenatal diagnosis is problematic if the developmental defects are not amenable to echographic imaging.

Prenatal diagnosis is especially challenging in families without a known history of t(11;22). The potential effectiveness of non-invasive prenatal testing (NIPT) for ES was shown, but mainly

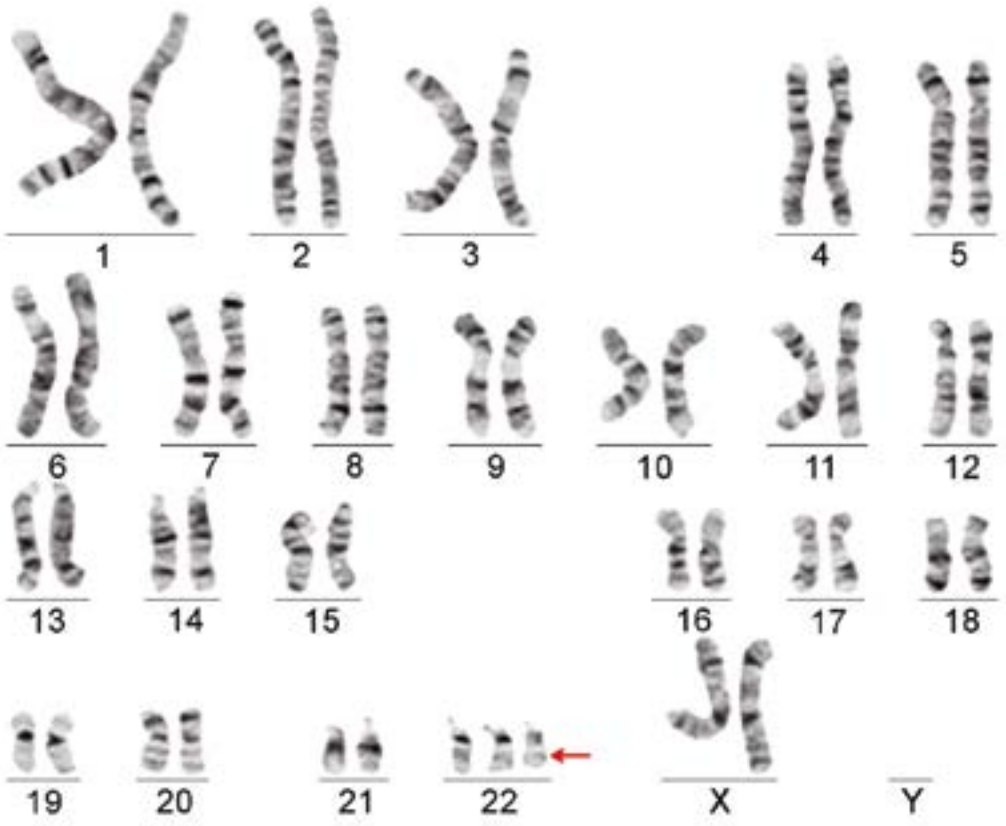


Fig. 2. The patient's karyotype using G-band analysis shows a supernumerary derivative chromosome 22 (arrowhead)

in cases with recognized carriership [16,24], and NIPT sensitivity for microduplication syndromes is still insufficient due to the small size of the involved chromosomal region and the presence of repetitive sequences. Preimplantation genetic testing may prevent affected pregnancies, but only for known carriers, and it is not applicable for population-wide screening.

Given that diagnostic testing remains the gold standard for the prenatal diagnosis of ES routine prenatal screening is an important tool for identifying high-risk groups for prenatal karyotyping. In the case of ES, the generally accepted view is that there are neither sensitive markers nor specific prenatal echographic characteristics of ES. Despite the relatively small number of publications with the description of prenatal signs of the ES, according to our knowledge, 28 cases have been summarized in several reviews and case reports [5,6,11–13,16,18,25,26,29,30], which clearly demonstrate the variability of the ultrasound picture in the second trimester. Nevertheless, the informativeness of first-trimester screening, in particular for nuchal translucency (NT), has not been particularly analyzed. Publications are about the concerning NT between 3.0 and 3.4 mm remain controversial [28].

Out of 9 cases with available data in the first trimester [5,12,13,16,18,26,29,30], NT was increased in 5 of them [5,12,18,29,30]. Most of these studies consisted of a single case with the NT measuring ranging from 3 to 4 mm. The same NT increase at 12 weeks – 3.3 mm was observed in cases described by S.K. Kee et al. [12] and L. Xu et al. [30]. In the S.K. Kee et al. case, the ductus venosus was also observed [12]. The study of P. Piwowarczyk et al. [18] presents two cases, in one of them NT was 3.9 mm. In another first-trimester case examined in this study, the NT size was within the normal range, as it was in two other case reports – 2.0 mm and 1.7mm, respectively [13,16]. In addition to the 5 cases with enlarged NT, in the study by E. Taddei et al. [26], the NT size was at the upper limit for 12^{+2} weeks – 2.4 mm (percentile 90) with a normal crown-rump length – 65.1 mm. Nevertheless, it determined that the woman's age risk was exceeded above cut-off and karyotyping was prescribed.

Biochemical maternal serum markers did not appear to be typical for the ES. In A. Walfisch et al. series of five ES cases [29], second-trimester biochemical screening results were available in four of them, and markers were within normal

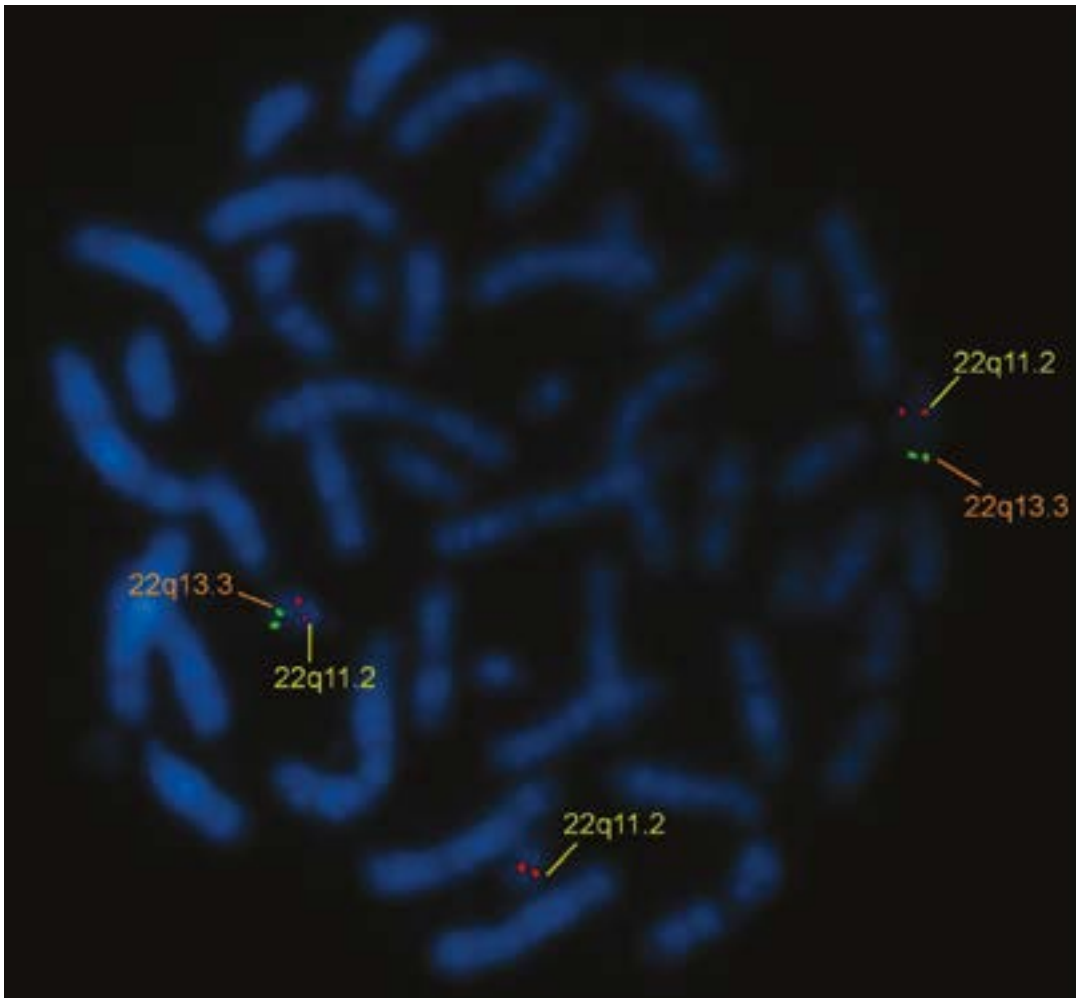


Fig. 3. Fluorescent *in situ* hybridization image with der(22)t(11;22); green signals the 22q13.3 and red signals the 22q11.2 region

limits. The first-trimester screening was available in one case, both markers were less than <0.5 MoM: PAPP-A – 0.25; free beta-human chorionic gonadotropin – 0.49. Similar results were shown in another case report presented by D. Kilijanova et al. [13]: PAPP-A – 0.28, βhCG – 0.66. In a series of six ES cases described by X. Hao et al [5], three had biochemical screening, and in all cases, results were unchanged. Available data fail to suggest a consistent specific pattern. Most likely, the altered biochemical markers in those two cases were associated with the presence of other abnormalities. Nasal bone aplasia also does not appear to be the definitive characteristic of the syndrome ES. This marker was noted in two of the six cases in the X. Hao et al. series [5]. Given that other descriptions of first-trimester ultrasound screening did not report this finding, it might be assumed that it was not observed.

In our case, among the first-trimester markers, only an increased NT was present – 3.2 mm at 12 weeks. That is, together with our report, increased NT in ES fetuses was observed in 6 out of 10 cases (60,0%), excluding the case with a borderline value. Notably, NT thickening was the most prominent feature in fetuses with complete trisomy 22 [22]. Although the rarity of the ES and limited prenatal data preclude reliable assessment of the sensitivity and specificity of the NT, these results are noteworthy and suggest that NT measurement could serve as a valuable tool for identifying at-risk fetuses, warranting further prospective studies.

Many carriers of balanced t(11;22) are identified only after reproductive challenges or the birth of an affected child, as was the case in our report. The translocation t(11;22) is not only the most common recurrent non-Robertsonian constitutional translocation in humans. Based on its geographic distribution [4], the frequency of this mutation may be much higher than ~1 in 16,000 as was estimated in a single study [17]. In addition to the implications for prenatal diagnosis, there

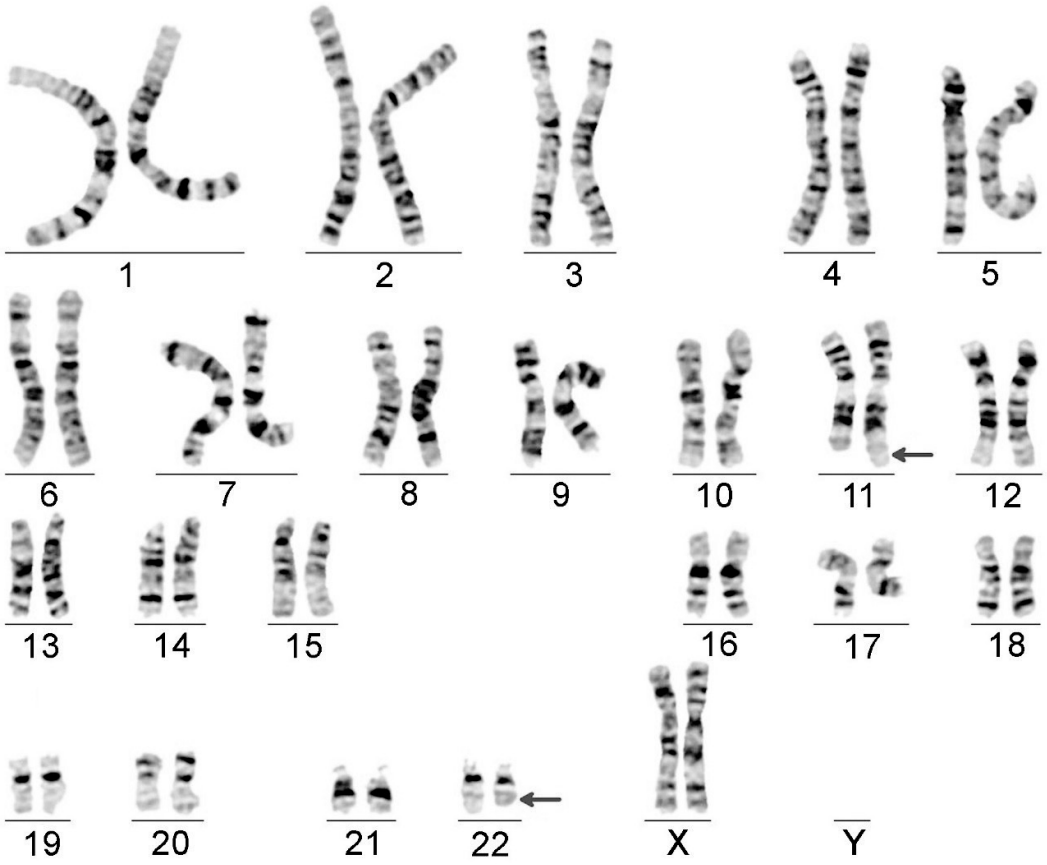


Fig.4. The mother's karyotype shows a balanced non-Robertsonian translocation between chromosome 11 and chromosome 22 (arrowheads).

is another important aspect connected with timely detection of carriers since several studies suggest long-term health risks for carriers of balanced t(11;22) translocations, including an increased risk of breast cancer and other malignancies [1,8,15,21]. This underscores the importance of genetic counseling for both reproductive and broader health management.

Conclusion

This case and literature review suggest that increased NT may serve as a potential early marker for ES. Although limited by small sample sizes, existing evidence underscores that NT measurement may provide a valuable tool for identifying at-risk pregnancies. Future prospective studies are needed to validate NT's diagnostic potential in ES.

All performed procedures were in accordance with the Declaration of Helsinki and received approval from the Ethics Committee of Ivano-Frankivsk National Medical University, Ukraine (148/3/12/24). Parental written informed consent was obtained for the publication of this case report including the images. All authors declare that they have no competing interests.

References/Література

1. Carter MT, Barrowman NJ, St Pierre SA, Emanuel BS, Boycott KM. (2010). Risk of breast cancer not increased in translocation 11;22 carriers: analysis of 80 pedigrees. Am J Med Genet. 152A: 212-214.
2. Carter MT, St Pierre SA, Zackai EH, Emanuel BS, Boycott KM. (2009). Phenotypic delineation of Emanuel syndrome (supernumerary derivative 22 syndrome): Clinical features of 63 individuals. Am J Med Genet. 149A: 1712-1721.

3. Choudhary MG, Babaji P, Sharma N, Dhamankar D, Naregal G, Reddy VS. (2013). Derivative 11;22 (Emanuel) syndrome: a case report and a review. Case Rep Pediatr. Epub 2013 Apr 18. 2013: 237935. doi: 10.1155/2013/237935. PMID: 23691404; PMCID: PMC3652044.
4. Fraccaro M, Lindsten J, Ford CE, Iselius L. (1980). The 11q;22q translocation: a European collaborative analysis of 43 cases. Hum Genet. 56: 21-51.
5. Hao X, Wu J, Fu W et al. (2022). Prenatal diagnosis of fetuses with Emanuel syndrome: results of ultrasound examination and invasive genetic testing. Prenat Diagn. 42: 469-477.
6. Hou JW. (2003). Supernumerary chromosome marker Der(22)t(11;22) resulting from a maternal balanced translocation. Chang Gung Med J. 26: 48-52.
7. Jancevska S, Kitanovski M, Laban N, Danilovski D, Tasic V, Gucev ZS. (2015). Emanuel Syndrome (ES): new case report and review of the literature. Pril Makedon Akad Nauk Umet Odd Med Nauki. 36: 205-208.
8. Jobanputra V, Chung WK, Hacker AM, Emanuel BS, Warburton D. (2005). A unique case of der(11)t(11;22),-22 arising from 3:1 segregation of a maternal t(11;22) in a family with co-segregation of the translocation and breast cancer. Prenat Diagn. 25: 683-686.
9. İkbal Atli E, Gürkan H, Vatansever Ü, Ulusal S, Tozkir H. (2016). A case with Emanuel syndrome: extra derivative 22 chromosome inherited from the mother. Balkan J Med Genet. 18: 77-82.
10. Iselius L, Lindsten J, Aurias A et al. (1983). The 11q;22q translocation: A collaborative study of 20 new cases and analysis of 110 families. Hum Genet. 64: 343-355.
11. Kazandı M, Turan V, Zeybek B, Argon A. (2010). Emanuel Syndrome. Ege J Med. 49: 209-211.
12. Kee SK, See VH, Chia P, Tan WC, Tien SL, Lim ST. (2013). Differential out-comes in an extended family with constitutional t(11;22)(q23.3;q11.2). J Pediatr Genet. 2: 37-41.
13. Kilijanova D, Hynek M, Prosova B, Hejtmankova M, Smetanova D. (2017). Prenatal diagnosis of Emanuel syndrome: a case report. Ultrasound Obstet Gynecol. 50: S312. https://doi.org/10.1002/uog.18509.
14. Kim HJ, Kim YM, Lee HB, Kim JH, Seo EJ, Yoo HW. (2012). A case with Emanual syndrome resulting from a maternal translocation. J Med Gen. 9: 35-37.
15. Lindblom A, Sandelin K, Iselius L et al. (1994). Predisposition for breast cancer in carriers of constitutional translocation 11q;22q. Am J Hum Genet. 54: 871-876.
16. Luo Y, Lin J, Sun Y et al. (2020). Non-invasive prenatal screening for Emanuel syndrome. Mol Cytogenet. 13. https://doi.org/10.1186/s13039-020-0476-7.
17. Ohye T, Inagaki H, Kato T, Tsutsumi M, Kurahashi H. (2014). Prevalence of Emanuel syndrome: Theoretical frequency and surveillance result. Pediatr Int. 56: 462-466.
18. Piwowarczyk P, Massalska D, Obodzińska I et al. (2022). Prenatal diagnosis of Emanuel syndrome - case series and review of the literature. J Obstet Gynaecol. 42: 2615-2620.
19. Saffren BD, Capasso JE, Zanolli M, Levin AV. (2018). Ocular manifestations of Emanuel syndrome. Am J Med Genet. 176: 1964-1967.
20. Saxena D, Srivastava P, Tuteja M, Mandal K, Phadke SR. (2018). Phenotypic characterization of derivative 22 syndrome: case series and review. J Genet. 97: 205-211.
21. Schoemaker MJ, Jones ME, Higgins CD, Wright AF et al. (2019). Mortality and cancer incidence in carriers of constitutional t(11;22) (q23;q11) translocations: A prospective study. Int J Cancer. 145: 1493-1498.
22. Schwendemann WD, Contag SA, Koty PP, Miller RC, Devers P, Watson WJ. (2009). Ultrasound findings in trisomy 22. Am J Perinatol. 26: 135-137.
23. Shaikh TH, Budarf ML, Celle L, Zackai EH, Emanuel BS. (1999). Clustered 11q23 and 22q11 breakpoints and 3:1 meiotic malsegregation in multiple unrelated t(11;22) families. Am J Hum Genet. 65: 1595-1607.
24. Soster E, Dyr B, Caldwell S, Sussman A, Magharyous H. (2023). Prenatal cfDNA Screening for Emanuel Syndrome and Other Unbalanced Products of Conception in Carriers of the Recurrent Balanced Translocation t(11;22): One Laboratory's Retrospective Experience. Genes (Basel). 14(10): 1924. https://doi.org/10.3390/genes14101924.
25. Sou S, Takabayashi T, Sasaki H et al. (1987). Prenatal diagnosis of partial trisomy 22 derived from a maternal t(11;22) (q23;q11). Tohoku J Exp Med. 153: 389-393.
26. Taddei E, Sartori E, Raio Bulgheroni L, Papadia A. (2021). Early detection of Emanuel syndrome: a case report. Case Reports in Perinatal Medicine. 10. https://doi.org/10.1515/crpm-2020-0049.
27. Toyoshima M, Yonee C, Maegaki Y et al. (2009). Vertebral fusion in a patient with supernumerary-der(22)t(11;22) syndrome. Am J Med Genet A. 149A: 1722-1726.
28. Vriendt MDE, Rooryck C, Madar H, Coatleven F, Vincienne M, Prier P et al. (2025, Apr). Outcomes associated with fetal nuchal translucency between 3.0 and 3.4 mm in the first trimester. Acta Obstet Gynecol Scand. 104(4): 629-636. Epub 2025 Feb 17. doi: 10.1111/aogs.15055. PMID: 39962853; PMCID: PMC11919737.
29. Walfisch A, Mills KE, Chodirker BN, Berger H. (2012). Prenatal screening characteristics in Emanuel syndrome: A case series and review of the literature. Arch Gynecol Obstet. 286: 299-302.
30. Xu L, Wang Z, Mao Q, Lu W. (2018). A case report for the fetus with Emanuel Syndrome. Chin J perinat Med. 21: 822-824.
31. Zackai EH, Emanuel BS. (1980). Site-specific reciprocal translocation, t(11;22) (q23;q11), in several unrelated families with 3:1 meiotic disjunction. Am J Med Genet. 7: 507-521.

Відомості про авторів:
Бондаренко Майя Вікторівна — лікар мед. генетик, акушер-гінеколог, к.мед.н., доц. каф. медичної біології і медичної генетики, ІФНМУ.
Адреса: м. Івано-Франківськ, вул. Галицька, 2. https://orcid.org/0000-0002-2113-4433.
Корнутій Олександр Миронович — студент V курсу ІФНМУ. Адреса: м. Івано-Франківськ, вул. Галицька, 2. https://orcid.org/0009-0006-7620-2452.
Дутчак Анастасія Петрівна — студентка V курсу ІФНМУ. Адреса: м. Івано-Франківськ, вул. Галицька, 2. https://orcid.org/0009-0002-2124-5536.
Ніколенко Маргарита Іванівна — д.мед.н., асистент каф. акушерства, гінекології та перинатології НУОЗ України ім П.Л. Шупика.
Адреса: м. Київ, вул. Дорогожицька, 9. https://orcid.org/0000-0002-0231-7496.
Арбузова Світлана Борисівна — д.мед.н., проф., чл.-кор. НАМНУ, Східноукраїнський центр медичної генетики і пренатальної діагностики.
https://orcid.org/0000-0002-5846-1067.

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