JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN (E-ISSN 2313-1519)
Original Article DOI: https://doi.org/10.23950/jcmk/14498

Nijmegen breakage syndrome – NBS: a rare clinical case in Kazakhstan

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Received: 2024-01-05.
Accepted: 2024-04-03.

J Clin Med Kaz 2024; 21(2): 95-98

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Abstract

Nijmegen syndrome is a primary immunodeficiency characterized by chromosomal instability, microcephaly, physical retardation, specific disorders of the facial skeleton, as well as a predisposition to cancer. Most patients of Slavic origin have a homozygous mutation with the del5 founder effect in the NBS gene. The frequency of occurrence is 1:100000population. The highest frequency of carriage in the population of the del5 mutation in the NBS gene in the Czech Republic is 1:154, in Ukraine – 1:182, in Poland – 1:190. This pathology is presented in our clinical practice for the first time, and therefore we would like to provide data for a wide review.

Keywords: NBS, autosomal recessive disorder, primary immune deficiency, microcephaly.

Introduction

Nijmegen breakage syndrome (NBS) is a rare autosomal recessive chromosomal disease characterized by a combined, persistent immunodeficiency condition, microcephaly and a tendency to malignant neoplasms [1]. In this case, there is a mutation in the NBN gene (early name NBS1). Gen NBN encodes nibrin, which is necessary for DNA epair and plays a critical role in all situations of double-stranded DNA synthesis. Nibrin, interacting with proteins MRE11 and RAD50, promotes the formation of a protein complex (MRN) that repairs DNA chain breaks [2,3].

As mentioned earlier, the disease manifests itself as microcephaly at birth, according to the literature without neurological disorders. The main symptoms of the disease appear with the age of the child. Children have growth retardation, frequent recurrent diseases against the background of an immunodeficiency condition, early ovarian disorders, a high risk of malignant neoplasms in childhood, more often hematological. The combined type of immunodeficiency condition (cellular, humoral) is a feature of this disease [4]. From the side of mental disorders, clinical symptoms are not very noticeable, despite microcephaly, but with the progression of the disease, cognitive impairment may occur [5].

It is known from historical data that NBS was first described in 1979 in a Dutch boy with growth and development retardation, microcephaly, IgA deficiency and chromosomal changes (chromosomes 7 and 14). The same symptoms were present in the deceased brother of this patient. In 1981, researchers from the University of Nijmegen in the Netherlands first described a new syndrome with chromosomal instability and named it Nijmegen chromosomal breakage syndrome (NBS) [6].

This syndrome is classified as rare, there are more than 150 known cases described in the scientific

literature with the identification of the NBN gene [7-10]. High prevalence of NBS among the population of Central and Eastern Europe (Czech Republic, Poland, Russia and Ukraine) [11,12]. NBS has also been reported in many other European countries [13-15], in South and North America, New Zealand and Morocco [16-18]. There are 3 known cases of NBS in Kazakhstan, in this article we will talk about the case of a child who was being treated in Corporate Fund “University Medical Center”.

An 8-year-old girl complained of cough, lag in physical development, lack of nasal conchae, facial skin lesions, purulent discharge from the nose and ears, pain, swelling in the left knee joint and diarrhea.

She has been ill since the age of 1.6 with manifestations of purulent otitis media, febrile fever, frequent streptococcal tonsillitis, stomatitis, recurrent respiratory infections. She received treatment with antibacterial drugs in the hospital, where some improvement was noted.

In 2 years, 8 months. is primary immunodeficiency, Nijmegen syndrome?, suspected for the first time. Recurrent oral aphthae, other specified anemia. She took normal human immunoglobulin, sulfasalazine, and metronidazole in treatment. There was a positive effect.

At the age of 4, during an examination at Corporate Fund "University Medical Center" the diagnosis was established: "Primaryimmunodeficiency of the humoral type. Delayed physical development, moderate pediatric malnutrition (Z-score -2.0 to -2.9). A contagious mollusk. Microcephaly (there is no data for delayed mental and motor development). Chronic bilateral otitis media. Chronic rhinopharyngitis in remission, bacilli-bearing. Pharyngomycosis. Anemia of mild severity. Recommendations were given.

The patient's condition worsens from 4 years 8 months, when recurrent stomatitis and an increase in body temperature began to bother him again. For the main disease, she received inpatient treatment: normal human immunoglobulin, antibacterial and antifungal therapy.

Before the age of 7, the child was repeatedly observed by many specialists, such as oncohematology, rheumatologists, immunologists, with the above complaints, frequent recurrent infections. The child was consulted by immunologists from Russia, Novosibirsk, where they established a new diagnosis: "Basal cell carcinoma. Secondary immunodeficiency. Protein-energy deficiency of the 2nd degree. Hypostatura".

At the age of 7 and 8 months the patient was consulted by doctors from Hadassah, Israel. Where a skin biopsy was performed twice. In the first coloring, an inflammatory process of the skin was revealed. Atypical cells (granulomatous inflammation and T-cell lymphoproliferative neoplasm) were detected for the second time. Conclusion of the molecular histological test dated 07/04/2023: does not confirm the possibility of a tumor process of lymphocytes. Sequencing of one eczema: the result is a pathogenic variant in the NBS gene according to the autosomal recessive type of inheritance of PID. Nijmegen syndrome.

Upon admission to the department, the child's condition is severe, due to the underlying disease, intoxication, joint syndrome, severe pediatric malnutrition (weight – 12 kg, height – 106 cm, BMI – 10.68 - Z-score -3.0 or greater).

Position: active. Phenotypically: characteristic features of appearance according to the type of "bird" face. The patient has a narrow face with a high forehead, corroding of the external nasal cavity, and a small lower jaw. Skin: pale in color, dry to the touch, there are foci of hyperemia on the face (Figure 1), scars, cracks, as well as the absence of an external nasal cavity (Figure 2). The subcutaneous fat layer is extremely poorly developed. Skin and joint system: swelling of the left knee joint, soreness, restriction of movement. The visible mucous membranes are pale pink, moist. Peripheral lymph nodes are enlarged to 2-3 cm in the cervical, submandibular and inguinal areas up to 1.5 cm (Figure 3).

Figure 1 – Foci of hyperemia on the face with destruction of the nasal cavity

Figure 2 – Photo of the child before and after the destruction of the nasal cavity

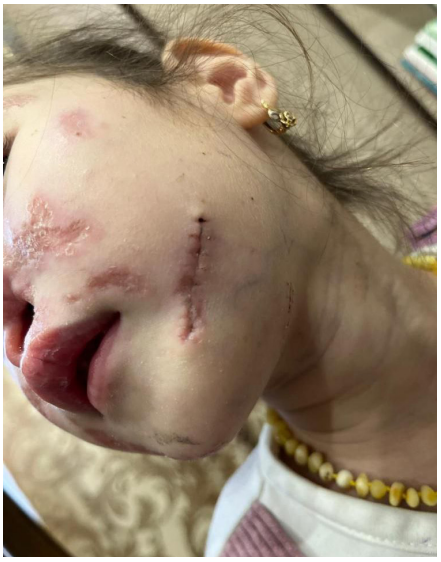

Figure 3 – The figure shows an increase in the cervical, submandibular lymph nodes, as well as a postoperative scar on the face

When examined according to immunophenotyping data, the child has an incomplete defect of the cellular and humoral links of immunity.

Immunophenotyping 10/10/2023: leukocyte count 9.76 10^9/L, lymphocyte count 27.22%, cd3- HLA-dr lymphocytes+ 7.23% (5.00 - 20.00), B-lymphocytes cd19+cd3- abs 0.17 x10^9/L (0.30 - 0.50), B-lymphocytes cd19+cd3- 6.41 % (12.00 - 22.00), mature cd3+cd19 T-lymphocytes- abs 2.08 x10^9/L (1.40 - 2.00), mature cd3+cd19 T-lymphocytes- 78.44% (66.00 - 76.00), NK cells cd3-cd16+/cd56+ abs 0.31 x10^9/L (0.10 - 1.33), NK cells cd3-cd16+/cd56+ 11.73% (4.00 - 26.00), immunoregulatory index (cd4+/cd8+) 0.75 (0.95 - 2.25). 10/10/2023 Compliment C3 1.39 g/l (0.90 - 1.80), Compliment C4 0.47 g/L (0.10 - 0.40), Immunoglobulin A 0.00 g/L (0.34 - 3.05), Immunoglobulin G 3.14 g/L (5.72 - 14.74), Immunoglobulin M 0.23 g/L (0.31 - 2.08) Immunochemical studies 11/10/2023 - TSH 4.82 mMu/ml (0.28 - 4.30), Prolactin 22.98 ng/ml (3.60 - 12.00), T4 free 16.28 pmol/L (12.50 - 21.50).

During hospitalization, the child was consulted by narrow specialists such as a phthisiologist (conclusion: there is no data for the tuberculosis process during the examination), an oncologist, since CT showed signs of polysegmental bilateral pneumonia with signs of atelectasis S5 of the right and S5, S8, S9 of the left lungs, with the presence of traction dilated bronchi in S5 of both lungs and deformity, bronchial dilation in the lower lobe of the left lung. Pronounced intrathoracic lymphadenopathy,

bilateral subclavian, axillary lymphadenopathy (lymphoma?). Further, to exclude the oncological process, a biopsy of the skin and lymph node was performed (conclusion: in the examined bone marrow sample, the population of cells with the immunophenotype: CD 117+/ CD34+ /CD33+/ Hla-DR+/ CD7-/ CD19-/CD10- is 0.63%; B lymphocytes are represented by regenerating cells bone marrow in the amount of 2,14%. Conclusion: Immunophenotypic data for acute leukemia have not been obtained. Myelogram (conclusion: No abnormal cells were found).

Histological examination of 1 block preparation of surgical biopsy material (IV category of complexity) from 20/10/23 were sent to Moscow, to the Dmitry Rogachev National Medical Research Center for Pediatric Hematology, Oncology and Immunology. Where was the conclusion received: The studied material shows signs of polymorphic lymphoproliferative disorder EBV+ in a patient with a congenital abnormality of the immune system. A picture of granulomatous lymphoproliferative disorder rich in CD8 lymphocytes in conditions of congenital abnormality of the immune system was revealed in the skin.

In the hospital, the child underwent immunoglobulin replacement therapy, antibacterial therapy, prevention of pneumocystis pneumonia (sulphanilamide group), and symptomatic therapy.

Discussion

Typical clinical manifestations of NBS are: microcephaly, severe and progressive (from birth or develops progressively in the first months after birth); characteristic facial skull: "bird-like" face (sloping forehead, decreased lower jaw, protruding middle part of the face with a large nose), mongoloid eye incision; skeletal disorders: clinodactyly 5th finger and/or partial syndactyly of the 2nd and the 3rd fingers, polydactyly is observed in half of the described patients; mental retardation in 60% of patients; stunting and delayed physical development; pigmented spots ("coffee with milk"); infectious and autoimmune pathology; predisposition to the development of malignant neoplasms; fibrosis and absence of thymus are also described.

In our clinical case, the patient has frequent recurrent bacterial nasopharyngitis, otitis media, less often bronchitis and pneumonia, phenotypically characteristic features of appearance according to the type of "bird" face. The patient has a narrow face with a high forehead, a small lower jaw, as a complication of repeated abscessing, corroding of the external nasal cavity. There is also a proven result of a genetic examination performed in July 2023. In Israel (see above in the article). Structural changes were also revealed in the MRI of the brain with contrast from October 2023 in the form of microcephaly, however, cognitive impairment was not detected in the psycho-emotional status corresponding to age. The complications of this case are lymphadenopathy and protein-energy malnutrition 3 grade. As a result of the examination, the diagnosis of lymphoma was excluded. Since the radical treatment for Nijmegen syndrome is HSCT, HLA typing was taken to find a donor. According to the results of HLA typing SSP, the patient's parents are not compatible. The result of the patient's HLA typing has been submitted to the international donor database. Currently, the child is at home, receiving human immunoglobulin G subcutaneously once a month on an outpatient basis.

Conclusion

Thus, dynamic monitoring of patients with NBS is mainly carried out by a pediatrician and an immunologist. A specific treatment method is hematopoietic stem cell transplantation and replacement intravenous administration of human immunoglobulin, which in many patients can reduce the frequency of infectious episodes. Patients need to undergo periodic medical examinations for early detection of cancer. Since Nijmegen syndrome is one of the types of chromosomal instability syndromes, it is necessary to use X-ray research methods in a limited way and replace them with other imaging diagnostic methods (ultrasound and nuclear magnetic resonance imaging) [6]. During the examination of this patient, a rare genetic anomaly was revealed in the Kazakh population in the form of Nijmegan syndrome, which had not been previously encountered. HSCT is recommended for this patient in the near future, as it reduces the risk of developing malignancy [19].

Author Contributions: Conceptualization, A.Y., E.B.Y. and İ.G.; methodology, A.Y., E.B.Y. and İ.G.; validation, A.Y., E.B.Y. and İ.G.; formal analysis, A.Y.; investigation, A.Y. and İ.G.; resources, A.Y., E.B.Y. and İ.G.; data curation, A.Y., E.B.Y. and İ.G.; writing – original draft preparation, E.B.Y.; writing – review and editing, A.Y., E.B.Y. and İ.G.; visualization, A.Y., E.B.Y. and İ.G.; supervision, A.Y.; project administration, A.Y.; funding acquisition, A.Y., E.B.Y. and İ.G. All authors have read and agreed to the published version of the manuscript.

Disclosures: There is no conflict of interest for all authors.

Acknowledgments: None.

Funding: None.

Patient informed consent: This clinical case is presented after parental consent

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