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REVIEW ARTICLE

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When you can't see the wood for the trees — rare and not so rare malignancies in Nijmegen breakage syndrome: a review

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ABSTRACT

Introduction and purpose. Nijmegen breakage syndrome (NBS) is a rare genetic disease with numerous complications during its course. Patients with NBS present such clinical features as musculoskeletal abnormalities, cardiovascular impairments, microcephaly, as well as recurrent respiratory infections, and a significantly high risk of developing malignant tumors. This article aims to highlight the importance of creating guidelines and a more standardized approach to cancer prevention in NBS patients.

Malignancies in the Nijmegen syndrome. Individuals affected by NBS show a strong predisposition to develop malignancies, especially at an early age. The most frequent are those of hematopoietic origin, but solid tumors (also rare ones like medulloblastoma and rhabdomyosarcoma) are also common, as are precancerous conditions.

Conclusions. As NBS patients are prone to show the symptoms of not only lymphoid malignancies but also solid tumors and immunodeficiency-related diseases, a holistic preventive approach is strongly advised. The screening and treatment for cancer can be extremely difficult due to the radio- and chemosensitivity of individuals with NBS, followed by more common therapy-related side effects.

Keywords: Nijmegen breakage syndrome, NBS, cancer, immunodeficiency, malignancies
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Introduction

Nijmegen breakage syndrome (NBS) is a rare autosomal recessive disease that manifests itself as microcephaly at birth, usually without any primary neurological symptoms. Other clinical features that become more noticeable as the patient develops include hypertelorism (increased distance between the eyes), a short nose with a convex bridge, and low-set ears [1]. Many patients also show abnormalities in the musculoskeletal system, such as short limbs, scoliosis, knee and foot defects, and limited joint mobility [2]. Additionally, problems with the cardiovascular system, mild growth delay, or premature ovarian failure may also occur [3]. Despite progressive microcephaly, psychomotor development is not impaired; however, cognitive impairment may become apparent with age [4]. Complex deficiencies of both cellular and humoral immunity are a characteristic feature of this disease and predispose to recurrent infections, particularly in the respiratory tract. In the population of NBS patients, the most important clinical feature is the high risk of developing malignant tumors — most often of hematologic origin [5, 6].

Chromosome instability with rearrangements, inversions, and translocations affecting chromosomes 7 and 14, as well as hypersensitivity to ionizing radiation,

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are used in the clinical diagnosis of NBS. Identification of mutations in both alleles of the nibrin (*NBN*) gene complements indicates NBS [7]. The disease was first described in 1979 in a Dutch child born with microcephaly, growth and development impairment, IgA antibody deficiency, and chromosomal rearrangements on chromosomes 7 and 14. It was discovered that the patient's deceased brother presented similar symptoms. In addition to chromosomal instability, *in vitro* studies of cells from NBS patients showed similarities to those in ataxia-telangiectasia syndrome, including hypersensitivity to UV radiation or radioresistant DNA synthesis. For this reason, NBS was considered a variant of ataxia-telangiectasia syndrome, even though neither ataxia nor telangiectasia occurs in NBS [8–10].

Currently, there is no reliable epidemiological data on the incidence of NBS. However, the identification of the disease-causing gene *NBN*, has led to a significant increase in the number of patients known worldwide [11]. In addition to the approximately 150 cases described in the medical literature, there are many patients documented in national registries, in particular in the Czech Republic and Poland. The European Immunodeficiency Society manages the largest European registry of this syndrome. Although NBS appears to occur worldwide, cases are more frequently reported in Central and Eastern European populations, including the Czech Republic, Poland, Slovakia, Russia, and Ukraine [12]. Moreover, there were about 35 cases reported in the Institute of Oncology in Warsaw, as well as many more in the Polish Registry of Congenital Defects. The higher incidence is likely due to the high frequency of the main *NBN* mutation, known as c.657_661del5 (p.K219fsX19), which is estimated to affect 1 in 177 newborns. This incidence is thought to be the result of a founder effect [13]. Surprisingly, a similarly high mutation frequency was found among newborns in northeastern Bavaria, indicating a relatively large number of people of Slavic origin in this area of Europe. Cases of NBS have also been reported in North and South America, Morocco, and New Zealand [14].

Purpose

This article aims to highlight the importance of providing complex care for NBS patients. Affected individuals may present not only with recurrent respiratory infections and musculoskeletal malformations but also with hematopoietic cancers as well as solid tumors. There is a strong need for continued research on effective treatment options for NBS patients to lengthen their life expectancy and improve their quality of life, as well as create standardized treatment protocols.

Cause of the disease

Nijmegen breakage syndrome, like ataxia-telangiectasia syndrome, Fanconi anemia, and Bloom's syndrome, belongs to a group of diseases associated with chromosomal instability, inherited mainly in an autosomal recessive manner. In NBS, a mutation in the *NBN* gene, encoding the protein nibrin, causes impaired repair of double-strand breaks (DSBs) — a disruption of phosphodiester bonds in both strands of the DNA double helix. As a result of the above-mentioned instability, DNA repair mechanisms are weakened, which results in an increased risk of cancer and immune deficiencies. Patients with NBS have a particular predisposition to cancers of the lymphatic system, and the most common cancers developing in this group are non-Hodgkin's lymphomas. Cancer is one of the most common causes of death in this group of patients; it is estimated that 40% of patients under 20 years of age will develop cancer [15–19]. Figure 1 depicts the pathogenesis of malignancies in NBS.

Most NBS patients have a common founder mutation — a deletion of 5 nucleotide pairs in exon 6 of the *NBN* gene (c.657_661del5, p.K219fsX19), which occurs mainly in the Czech, Polish, Slovak, Russian, and Ukrainian populations. Cases of the disease are diagnosed all over the world, but due to the founder effect and the resulting higher frequency of mutations in the population (according to sources about 1/177 newborns), most diagnoses of the syndrome are recorded in the region of Central and Eastern Europe [16–18]

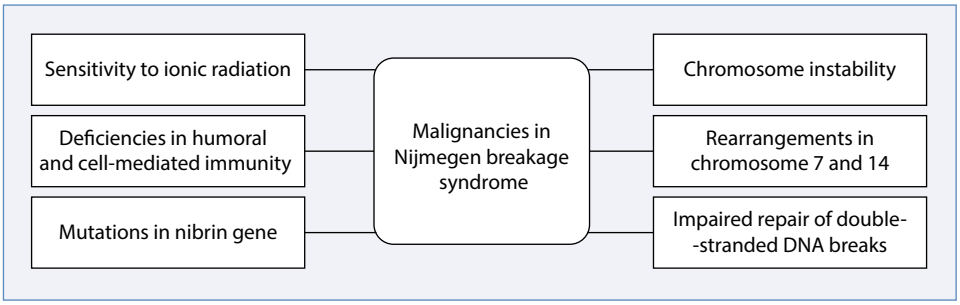

Figure 1. Malignancies in Nijmegen breakage syndrome

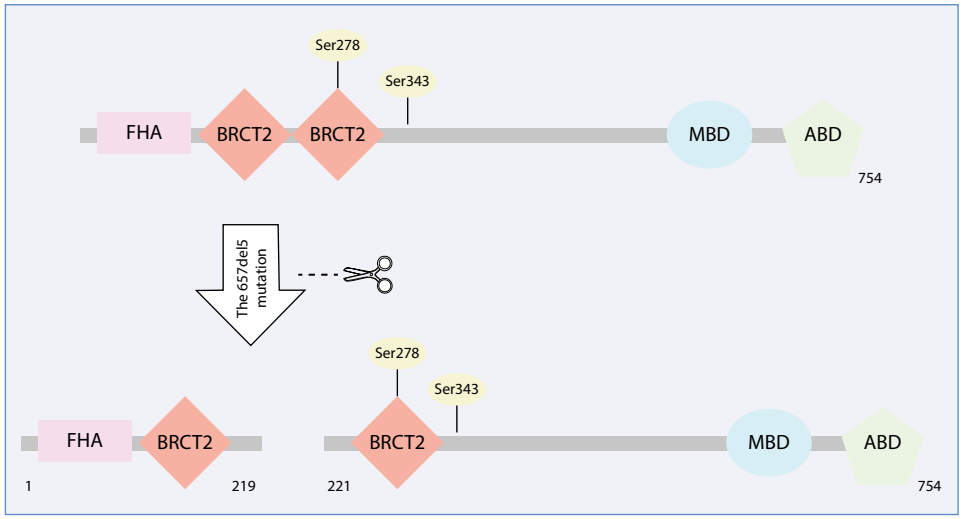

Figure 2. Schematic diagram representing the wild type and mutated NBN proteins

Protein NBN is part of the MRE11-RAD50-NBN (MRN) protein complex, which is involved in the repair of DSBs. Physiologically occurring DSBs play an important role in DNA replication, the recombination of genetic material occurring during meiotic divisions, and the development and adaptation of immune system cells [16]. The c.657_661del5 mutation, characteristic of NBS, leads to the expression of fragments of nibrin molecules with a molecular weight of 26kDa (p26) and 70kDa (p70). The smaller fragment, p26, contains the FHA domain and the BRCT-1 domain. The BRCT-2 domain is present in the p70 fragment and allows it to bind to MRE11, maintaining the function of normal nibrin. Thanks to this arrangement, despite mutations in the *NBN* gene, the MRN complex remains active and plays its role in recognizing, signaling, and participating in DSB repair pathways, such as non-homologous end joining (NHEJ) and homologous recombination (HR). The separation of BRCT domains (Fig. 2) is the probable cause of impaired interactions of cell cycle regulation proteins, such as p53, BRCA1, and CHK2, which in turn translates into disturbances in the genetic stability of cells and an increased risk of cancer [15, 16, 19].

Malignancies — the lymphatic system

The majority of cancers in NBS occur in the lymphatic system (nearly 90%), mainly T-cell non-Hodgkin's lymphomas. The most frequently observed subtypes of lymphomas in Nijmegen syndrome are diffuse large B-cell lymphoma (DLBCL), T-lymphoblastic lymphoma (T-LBL), and peripheral T-cell lymphoma (PTCL). Burkitt's lymphoma, Burkitt-like lymphomas, and Hodgkin's lymphoma are less common. The most common leukemia occurring in NBS is acute lymphoblastic leukemia (ALL). Approximately 25% of patients are diagnosed with another cancer within 10 years of achieving remission of the first cancer. It is worth noting that oncological treatment in NBS is significantly difficult due to the accompanying immunodeficiencies, hypersensitivity to ionizing radiation, and chemotherapy. Patients with NBS require modification of standard treatment regimens due to developing complications, such as infectious diseases or organ failure [15, 17, 18, 20].

It has been discovered that in NBS patients, an increased level of nibrin with a higher molecular weight (p70) is associated with lower risk of developing lymphomas, so its level may be a predictive value of predisposition to cancer [17].

The study of the most common lymphomas in this group of patients, DLBCL and T-LBL, showed monoclonal rearrangements in the Ig or TCR loci [21]. Histopathological analysis of tumor tissue collected from children with NBS diagnosed with DLBCL showed that lymphomas in this group of patients resemble the adult variant of DLBCL. Moreover, mutations in TP53, STAT3, KMT2D, HIST1H1B, and amplifications in programmed death-ligand 1 (PD-L1) were detected in these cells [22].

Malignancies — solid tumors and gonadal tumors

It is worth noting that patients with NBS require thorough pediatric evaluation for rare cancers. There was a case of a 14-year-old girl with persistent abdominal pain who was ultimately diagnosed with primary gastric Hodgkin's lymphoma. The patient underwent two cycles of OEPA chemotherapy (vincristine, etoposide, prednisone, and doxorubicin) at doses of 30–40% of

the standard dose [23]. Additionally, cases of medulloblastoma (medulloblastoma) have been reported. The basis of treatment for this cancer is radiotherapy, which in patients with NBS more often than in the general population, results in serious skin damage, post-radiation inflammation of the gastrointestinal mucosa, and even cardiorespiratory failure, which may lead to death [26, 27]. It is believed that radiotherapy should be avoided in patients with NBS [23]. It is worth mentioning that the risk of medulloblastoma has been shown to be several times higher in patients with heterozygous mutations in the *NBN* gene (c.511A>G and c.657_661del5) [26]. Additionally, several cases of rhabdomyosarcoma located in the perianal area can be found in the literature [29, 30]. This is an extremely rare location for this type of cancer and, therefore, should raise the suspicion of NBS in patients, as the diagnosis allows for appropriate modification of treatment and planning of additional tests.

Carriers of the 657del5 mutation in the *NBS1* gene have a significantly increased risk of prostate cancer, and cancer cells in this group of patients lose the normal allele of the NBS1 gene [30].

It is worth mentioning that precancerous conditions may occur in patients already in the early years of life, as evidenced by the presence in a skin biopsy of a 9-year-old patient with NBS of a fibroblast cell line with numerous aberrations regarding their high proliferative potential and much shorter telomeres [32].

Pure gonadal dysgenesis is more common in girls with NBS because nibrin is involved in the proper development of the ovaries. Several cases of ovarian cancer have been described in this group of patients, including concurrent ovarian germ cell tumors — dysgerminoma and gonadoblastoma [33]. Accurate but minimally invasive gynecological diagnostics is recommended in girls with NBS. It includes palpation, pelvic ultrasound, and basic hormonal tests [34]. Prophylactic gonadectomy is not recommended, but if a patient already has a tumor in one gonad, early ovariectomy of the remaining dysfunctional gonad should be considered to avoid tumor recurrence [35]. We also described a case of a 62-year-old NBS carrier with a heterozygous mutation in RAD50, which plays a key role in the recognition of double-stranded DNA lesions and repair by joining non-homologous DNA ends (NHEJ). The patient initially developed serous ovarian cancer and was treated with surgery and adjuvant chemotherapy based on paclitaxel and carboplatin. After a few months, she developed numerous nodules that turned into cauliflower-like masses up to 6 cm in diameter. The examination showed that these were ovarian cancer metastases [36].

Discussion

Cancer therapy in NBS patients is particularly difficult due to mutations in the nibrin gene and impaired DNA repair capacity, as well as cellular (T and B cell deficiency) and humoral (IgA and IgG) deficiency [37]. Moreover, hypersensitivity to ionizing radiation and chemotherapy excludes radiotherapy from the treatment regimen and requires a reduction in doses of standard chemotherapy drugs [37]. Magnetic resonance imaging (MRI) and ultrasonography (USG) are the recommended imaging modalities for patients with NBS to reduce exposure to X-rays used in computed tomography and traditional X-rays. Care of patients affected by this syndrome requires a multidisciplinary approach and regular diagnostic tests to quickly detect a potentially ongoing cancer process and initiate treatment based primarily on surgical resection of the tumor and/or chemotherapy in lower-than-standard doses.

The cause of treatment-related deaths in NBS patients is mainly sepsis, but deaths from anthracycline-induced cardiomyopathy [38] have also been reported. In the case of lymphatic system cancers, the most common type of cancer in the population of NBS patients, the use of hematopoietic stem cell transplantation (HSCT) seems promising. In five of six patients, HSCT restored T-cell immunity. After a follow-up period of 2.2 years, the patients were in good condition. Experiential data suggest that HSCT should be considered in NBS patients because this form of therapy may correct immune deficiencies and effectively treat cancer [39].

The authors of studies on_NBS draw attention to methodological problems related to its specificity. One of the key problems affecting the current state of knowledge about this disease is the rarity of its occurrence, which translates into relatively small study groups and, therefore, limits the universality of the conclusions drawn in research. A related issue is the short follow-up period of these patients, resulting from the late discovery of the disease (the first case was described in 1981) and the relative newness of research and therapeutic methods to diagnose, treat, and monitor NBS patients. To this day, the molecular basis and pathophysiological mechanisms of NBS have not been fully understood and remain of interest to specialists in biochemistry, molecular biology, genetics, oncology, and pediatrics. An additional difficulty is the sociological and political turmoil related to political changes in the Czech Republic, Slovakia, and Poland in the 1980s and 1990s — i.e., in the countries where the highest incidence of NBS is recorded, consequentially the awareness about NBS and patient longitudinal management may not have been as well-known as it should be.

Conclusions

Current medical efforts related to patients with NBS are aimed primarily at alleviating symptoms and supporting psychomotor development. However, scientific activity to develop diagnostic guidelines and modify treatment protocols to take into account the specific needs of NBS patients is equally important. Databases collecting information on registered NBS cases should be consistently expanded, and therapeutic strategies based on analysis of praxis and the latest treatment methods should be improved. Moreover, it is extremely important to carefully monitor and document the course of the disease in individual cases, as well as to record the positive and negative effects of the treatment. Due to the significant radio- and chemosensitivity associated with NBS, it is also particularly important to monitor possible complications of both the disease and its therapy, taking into account their nature, severity, reversibility, and impact on the prognosis.

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Author contributions

All the authors present the same contribution to the article.

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Conflict of interest

The authors declare no conflict of interest.

Supplementary material

None.

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