MUCIEK, Adrianna, MOCARSKA, Martyna, ORŁOWSKA, Anna, STRAKOWSKA, Katarzyna, OPALSKA, Laura, MARYŃCZAK, Anna, MENCEL, Jan and NITSCHKE, Nicole. Nijmegen breakage Syndrome - how much do we know about this rare condition of Slavs? - disease overview. Quality in Sport. 2024;34:56216 eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.34.56216
https://apcz.umk.pl/QS/article/view/56216

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assig589 ned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 15.11.2024. Revised: 20.11.2024. Accepted: 27.11.2024. Published: 27.11.2024.

Nijmegen Breakage syndrome - how much do we know about this rare Slavic condition? - Disease overview

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Abstract:

Nijmegen breakage syndrome (NBS) is a rare autosomal recessive defect of immunity, characterised by chromosomal instability and radiation sensitivity with a high predisposition to malignancy. The clinical manifestations of this condition include microcephaly, combined immunodeficiency, growth retardation and a range of additional abnormalities, including facial, skeletal and skin anomalies (such as café au lait spots and vitiligo). It is estimated that 40% of patients will develop cancer before reaching the age of 21 years. [1-2]

The etiology of this syndrome can be attributed to a mutation in the NBS1 gene, which is localised on chromosome 8q21 and is responsible for the production of the protein nibrin. [3] The most common mutation responsible for NBS (c.657_661del5) is consistent with a founder effect, with the majority of registered patients originating from Central and Eastern Europe and the largest cohort diagnosed in Poland. [4]

This article provides an overview of Nijmegen breakage syndrome (NBS), including epidemiology, symptoms, diagnostic pathway and patient management, as well as treatment options. The objective of this study is to enhance awareness of this condition in order facilitate an early diagnosis and screening for malignancy in patients.

Keywords: Nijmegen breakage syndrome, chromosome instability, immunodeficiency

Introduction:

The initial description of the combination of clinical features, including microcephaly, growth and developmental retardation, IgA deficiency, and chromosomal rearrangements analogous to those observed in ataxia telangiectasia (AT) or Bloom's syndrome, was first presented by researchers from the Departments of Paediatrics and Human Genetics at the University of Nijmegen in 1979. The patient's lymphocytes exhibited seven distinct chromosomal rearrangements affecting chromosomes 7 and 14. [5]

In 1981, a second case report was published concerning the brother of the initial proband, who exhibited a similar presentation of symptoms. These included recurrent upper respiratory tract infections, microcephaly, sun-sensitive erythema, café-au-lait spots, and mental retardation. [5] Although the concatenation of symptoms and cytogenic findings were not entirely consistent with those observed in ataxia telangiectasia, xeroderma pigmentosum, Bloom's syndrome, or Fanconi anaemia, the researchers proposed that this new chromosome breakage disorder be designated Nijmegen breakage syndrome. [6]

Subsequently, three further families from Czechoslovakia were identified as having a potential new syndrome characterised by microcephaly, normal intelligence, immunodeficiency and an increased risk of lymphoreticular malignancies. [7] However, further investigation revealed that these cases were found to align closely with the NBS. [8]
Over time, our understanding of this condition has evolved. Recent research indicates that there has been a notable improvement in the diagnosis of NBS over the past 25 years, with a concomitant reduction in the median age of diagnosis. [9]

Epidemiology:

Nijmegen breakage syndrome (NBS) is a rare disease, and as a consequence, it is not possible to provide an accurate estimate of its prevalence. The disease is most prevalent in Eastern European populations, particularly in Poland, the Czech Republic, and Ukraine, where the mean frequency of homozygous carriage of the "Slavic" pathogenic variant (c.657_661del5) of the NBS1 gene approaches 1:177. The highest prevalence of heterozygotes is found in the area of Nowy Sacz, with a frequency of 1/90. [10] The largest cohort registered in the ESID database is that diagnosed in Poland, comprising 118 individuals. [4]

A recent retrospective review of 84 NBS patients from different regions of Ukraine diagnosed between 1999 and 2023 provided new insights into the geographic distribution of patients carrying the most common founder NBS1 mutation (c.657_661del5). The largest proportion of patients (57.8%) is registered in the western regions of Ukraine. However,

recent years have witnessed an increase in the number of patients in the central and northern regions, from 0% during the period 1999-2007 to 35.7% over the past six years. [9]

The same mutation, c.657_661del5, has its origin in the Slavic population and comprises approximately 100% of variants detected in patients from Slavic countries and more than 70% of variants in patients from the United States. [11–12]

Etiology:

The disorder is caused by biallelic mutations in the NBS1 gene, which encodes the protein nibrin. [13] The most prevalent mutation in NBS is a five-base pair deletion in exon 6 (c.657_661del5), which results in the expression of a product that retains only several residual functions of full-length nibrin. [3,12]

NBN is a member of the trimeric nuclear protein complex with Mre11 and Rad50 (MRN), which is essential for checkpoint arrest and repair in response to DNA double-strand breaks (DSBs). [14-17]

Inadequate repair of damaged DNA results in the accumulation of genetic errors, which in turn lead to cell death, mutagenesis and carcinogenesis, chromosomal instability with spontaneous chromosome aberrations, increased telomere loss and sensitivity to ionising radiation.

Symptoms:

- Microcephaly and craniofacial features

Progressive microcephaly is defined as a reduction in occipitofrontal circumference (OFC) to below -2 standard deviations (SD) from the mean, as compared to a healthy population of the same age and sex. [18]

With age, dysmorphic facial features become more apparent. The prominent midface is accentuated by the sloping forehead and receding mandible, while the palpebral fissures are oriented upwards. Furthermore, the nasal prominence lends the face a distinctive "bird"-like appearance. [7, 12]

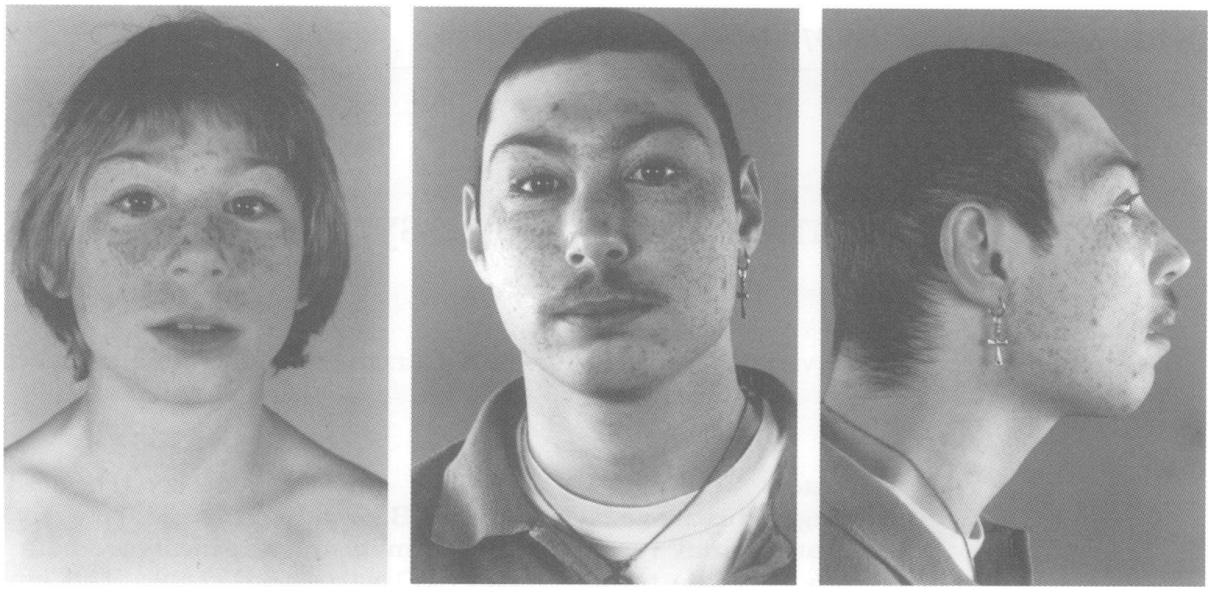

Photo 1. Left: Patient from Weemaes et al', 1981 [6] at the age of 9 years. Middle and right: The same patient at 24 years of age from van der Burgt I, 1996 [23].

- Neurocognitive and intellectual development

Despite the presence of severe microcephaly, the majority of NBS children typically achieve the typical developmental milestones at the expected time. The intelligence quotient (IQ) of these children was found to range from within the normal range to mild or moderate intellectual disability. [2, 19-20]

- Sexual development

In girls, failure of puberty, poor development of secondary sex characteristics and premature ovarian failure are common occurrences. [21] In boys, puberty occurs spontaneously and progresses in a manner that is comparable to that observed in healthy peers. [22]

- Congenital anomalies

The clinical presentations of skeletal anomaly include clinodactyly of the fifth finger and partial syndactyly of the second and third toes, as well as polydactyly, cleft lip and palate. [22, 23] Skin changes include pigmentation anomalies such as café au lait spots and vitiligo spots, which are observed in approximately 50% to 70% of patients. Furthermore, alopecia, undefined ulcerative granulomas, skin sarcoidosis, and lupus-like skin changes have been documented. [4,12] The genito-urinary congenital malformations described are renal hypoplasia/aplasia, ectopic/dystopic kidney (e.g., the horseshoe or double kidney), anal atresia or hypoplasia, hypospadias, cryptorchidism or urethro-anal fistula. [4,12]

- Predisposition to infections

The majority of patients present with infections of the respiratory tract, including sinusitis, pneumonia, and bronchopneumonia. In some cases, these infections lead to bronchiectasis and death due to respiratory failure. [4-5] Upper and lower respiratory tract infections were found to be associated with the colonisation of the respiratory tract by the bacteria Pseudomonas aeruginosa and Candida albicans. [12]

Other relatively common infections include otitis media and mastoiditis, as well as urinary and gastrointestinal tract infections. [4, 23] Viral infections, particularly those caused by lymphotropic and/or hepatotropic viruses (e.g., EBV, CMV, HBV, HCV), may result in a severe and chronic course of illness. These infections frequently present with lymphadenopathy, hepatosplenomegaly, and/or pancytopenia, which may mimic a malignant state. [12]

- Predisposition to malignancies

It is observed that in excess of 40% of patients diagnosed with NBS subsequently develop a malignant disease, which is predominantly of lymphoid origin. The most common form of non-Hodgkin lymphoma of B and T cells, diffuse large B cell lymphoma (DLBCL) and T-cell

lymphoblastic lymphoma (TLBL), Burkitt and Burkitt-like lymphomas, medulloblastomas, glioma, and rhabdomyosarcoma. [13, 24]

Diagnosis:

The clinical and laboratory findings outlined below should prompt consideration of Nijmegen breakage syndrome (NBS) as a potential diagnosis.

Clinical findings:

- progressive disproportionate microcephaly
- dysmorphic facial features
- mild growth retardation
- skeletal abnormalities
- recurrent infections
- malignancies, overwhelmingly of lymphoid origin
- gradual decline of cognitive development
- failure of puberty and poor development of secondary sex characteristics in girls
- café au lait spots and/or vitiligo spots

Laboratory test results:

- **Immunological findings**

The most frequently observed deficits pertain to levels of IgG and/or IgA. Moreover, deficiencies in at least one IgG isotype were observed, with the most prevalent defect occurring in IgG4. A reduction in the absolute number of total B cells (CD19+/CD20+), CD3+ T cells, and CD4+ T cells was typically observed, with the majority of patients exhibiting a ratio of CD4+/CD8+ cells below 1.0. Furthermore, the in vitro proliferation of T and B lymphocytes to antigen and/or mitogenic stimuli was observed to be diminished. [4, 25]

- **Chromosomal instability**

The most frequently observed chromosomal aberration in NBS is inv(7)(p13;q35), followed by t(7;14)(p13;q11), t(7;14) (q35;q11), t(7;)(p13;q35) and t(14;14)(q11;q32) in descending order of prevalence. [23]

- **Radiation hypersensitivity**

The colony survival assay (CSA) and the radio-resistant deoxyribonucleic acid synthesis (RDS) assay have previously been employed to facilitate the diagnosis process. [12]

Genetic testing:

The available molecular genetic testing tools comprise single-gene testing (targeted analysis for the common founder variant c.657_661del5) and a multigene panel including NBN and other genes of interest considered in differential diagnosis. [26] Single-gene testing

may be regarded as a screening test, given that in the majority of affected individuals from Poland, the Czech Republic, and Ukraine, as well as approximately 70% of individuals tested in the USA, the aforementioned pathogenic variant is present in a homozygous state. [11] Furthermore, **Western blot** analysis enables the detection of the nibrin protein and assessment of its correct size.

The procedure for establishing a definitive diagnosis of Nijmegen Breakage Syndrome is illustrated schematically below.

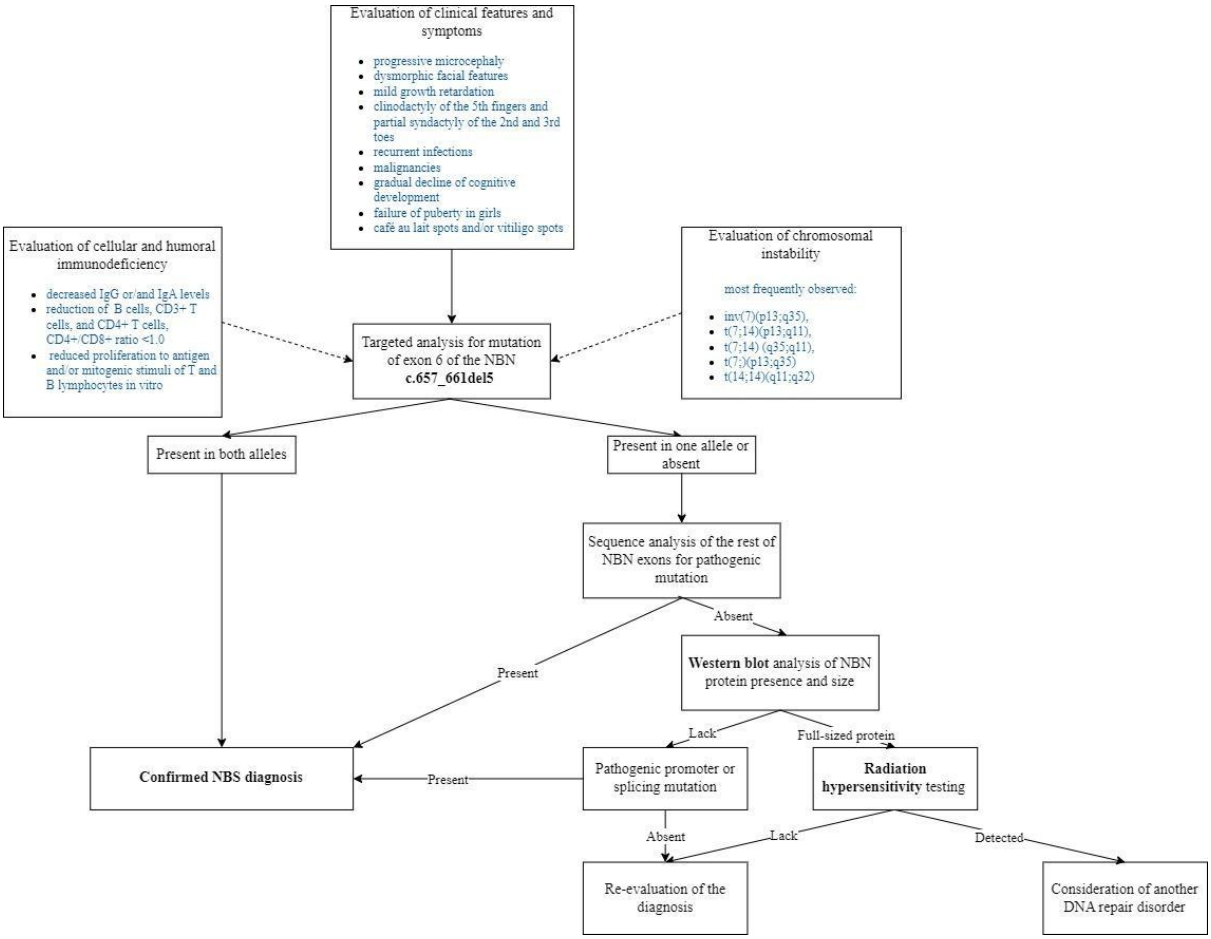

Figure 1. NBS diagnostic process.

Differential diagnosis:

A differential diagnosis of NBS should encompass other genomic instability conditions, including those affecting the DNA repair process. Moreover, the presence of early growth failure can indicate other well-established disorders of growth, such as thyroid hormone or growth hormone deficiency, or primary disorders of bone growth.

The table below presents a selection of potential alternative diagnoses.

Clinical picture	Microcephaly Growth retardation Chromosomal instability	Microcephaly Immunodeficiency	Chromosomal instability
Alternative diagnosis	NBS NBSLD NHEJ1 syndrome FA Seckel syndrome 1 Bloom syndrome WBS	NBS NHEJ1 syndrome	NBS and A-T NBSLD and ATLD
A-T ataxia telangiectasia, ATLD ataxia telangiectasia like disease, FA Fanconi anemia, NBSLD NBS-like disease, NHEJ1 syndrome- severe combined immunodeficiency, WBS Warsaw breakage syndrome			

Figure 2. Suggestions for alternative diagnosis.

Treatment:

Currently, there is no established therapeutic approach for NBS. However, given the underlying immunodeficiency and sensitivity to IR, a multidisciplinary medical management plan and long-term follow-up are essential. [27]

The early diagnosis of NBS can prevent infectious and malignant complications and avoid unnecessary exposure to IR. This may be achieved by, for example, preferring MRI or ultrasound examination.

A multidisciplinary medical care team should include a paediatrician or general practitioner with expertise in the condition, an immunologist, an oncologist, an endocrinologist and a gynaecologist in cases of female patients. Moreover, ensuring the enhancement of quality of life and optimal development of patients may necessitate the provision of psychological, social, and educational support.

It is recommended that NBS patients undergo regular immunological evaluation. In patients who are in good clinical condition, control tests of the immunological profile should be performed once a year. In patients who manifest evident progression of immune system deterioration over time, control tests should be performed at 3-4 month intervals. [12] In cases of IgG deficiency, gamma-globulin replacement therapy should be considered. Additionally, NBS is a contraindication to vaccinating with live bacterial or viral vaccines. [27]

A fundamental element of the care of NBS patients is the periodic assessment and treatment of malignant conditions. The prevention of leukaemia and lymphoma requires the avoidance of radiation, the utilisation of sun protection measures, and the administration of the HPV vaccination. Routine blood work is no longer recommended for screening of acute lymphoblastic leukaemia (ALL) and lymphoma in asymptomatic patients. It should be performed only for patients exhibiting indications and suggestive symptoms. The dose of chemotherapy should be reduced due to preexisting comorbidities and vulnerability to toxicity. [28] Additionally, radiotherapy should be avoided. [27]

A review of the literature indicates that patients with NBS who receive allogeneic haematopoietic cell transplantation (HCT) for haematologic malignancies have a superior survival rate than those who do not. However, it is not indicated to perform this procedure routinely [29]. The data on HCT are insufficient to allow the formulation of standardised recommendations, which remains a procedure with a significant risk for individual patients. Consequently, it should only be recommended in patients with life-threatening complications, such as severe immunodeficiency that cannot be controlled with prophylactic measures or haematological malignancy. [30]

Discussion:

Nijmegen Breakage Syndrome (NBS) is a rare disease with an unfavorable prognosis that remains insufficiently known. The primary cause of mortality is cancer progression and treatment-related mortality, which is predominantly associated with infectious complications. [4] There is a dearth of awareness and knowledge about this condition, as evidenced by the average delay in diagnosis of NBS, which has been reported to be 4–5 years. [29] A recently published retrospective study from Ukraine demonstrated an improvement in the diagnosis of NBS over the past 25 years, with an increase in the number of diagnosed patients and a shift in the percentage of patients from the western regions of Ukraine to other regions. [9] This trend indicates that greater awareness of NBS among physicians and improved accessibility to genetic diagnostics may facilitate an improvement in the diagnosis of NBS. An early diagnosis is fundamental to the management of NBS patients, as it allows for the prevention of infections, the diagnosis of malignancies, the avoidance of radiation exposure and the selection of an appropriate treatment strategy.

In Poland, where the largest cohort of patients is located and the prevalence of the major NBS1 mutation (657del5), also referred to as the "Slavonic mutation," is the highest, healthcare professionals are faced with the challenge of establishing the genetic diagnosis of the syndrome and providing appropriate clinical management to prevent oncological and infectious complications. [10, 24]

At present, there is no specific targeted therapy available for NBS, nor are there any established protocols for the treatment of lymphoid malignancies in children with NBS. Consequently, further meta-analysis is essential to establish the optimal monitoring and treatment regimen for patients with NBS and lymphoid malignancies.

Furthermore, there is a paucity of well-documented, long-term observations of the effectiveness of HSCT. The most recent recommendations indicate that HSCT may be a potential option for patients in their first remission of a haematological malignancy, as well as for those exhibiting clinically apparent immunodeficiency, such as recurrent infections, with the objective of restoring their immune function. [23] Given the current limitations in data, there is a pressing need for multicentre prospective studies to evaluate the efficiency of HSCT in patients with NBS.

The neonatal screening of T-cell excision circles (TRECs) and kappa-deleting recombination excision circles (KRECs) represents a promising avenue for further research in newborn screening (NBS), with the potential to facilitate an early diagnosis in the future. [29]

It is anticipated that further fundamental research will result in further improvements for patients.

Additionally, examination of the cellular defect in patients with a mild manifestation of the disease may potentially contribute to the development of innovative therapeutic strategies.

Authors' contributions statement

Conceptualization: [AM] [MM] [AO] [KS] [LO] [AMA][JM][NN]
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Formal Analysis: [AM] [MM] [AO] [KS] [LO] [AMA][JM][NN]
Funding Acquisition: Investigation: [AM] [MM] [AO] [KS] [LO] [AMA][JM][NN]
Methodology: [AM] [MM] [AO] [KS] [LO] [AMA][JM][NN]
Project Administration: [AM] [MM] [AO] [KS] [LO] [AMA][JM][NN]
Resources: [AM] [MM] [AO] [KS] [LO] [AMA][JM][NN]
Software: [AM] [MM] [AO] [KS] [LO] [AMA][JM][NN]
Supervision: [AM] [MM] [AO] [KS] [LO] [AMA][NN]
Validation: [AM] [MM] [AO] [KS] [LO] [AMA][NN]
Visualization: [AM] [MM] [AO] [KS] [LO] [AMA][NN]
Writing- original Draft: [AM] [MM] [AO] [KS] [LO] [AMA][NN]
Writing- Review and Editing: [AM] [MM] [AO] [KS] [LO] [AMA][NN]

All authors have reviewed and agreed to the publication of the final version of the manuscript.

Conflict of Interest Statement: No conflicts of interest.

Funding Statement: The study did not receive any specific funding.

Informed Consent Statement: Not applicable.

Ethics Committee Statement: Not applicable.

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