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CASE REPORT

Clinical manifestations, toxicities, and outcome of two children with Nijmegen breakage syndrome and lymphoid malignancies – case reports

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ABSTRACT

Nijmegen breakage syndrome (NBS) is a rare disease with an autosomal recessive pattern of inheritance caused by mutations in the NBN gene.

We report 2 patients with NBS and T-cell lymphoblastic lymphoma (T-LBL), in whom diagnosis and therapy were difficult challenges. Both patients were diagnosed with NBS by mutation analysis of the NBN gene, which revealed homozygosity for a typical 5 base pair deletion (657del5). The lymph node biopsy revealed T-LBL, and both patients were treated according to EURO-LB 02. Complete remission was achieved in the first patient. In the second case, bone marrow relapse was observed, and the patient died due to disease progression.

In conclusion, patients with NBS should be closely monitored because of a higher frequency of lymphoma than in the general population. The described cases indicate the importance of identifying predictive markers of cancers and developing treatment regimens for patients with NBS and malignancies.

KEY WORDS:

lymphoma, antineoplastic agents, Nijmegen breakage syndrome, microcephaly.

INTRODUCTION

Nijmegen breakage syndrome (NBS) is a rare autosomal recessive disorder of chromosomal instability that is more prevalent in Central and Eastern European populations. The *NBN* gene responsible for the entity is located on chromosome 8q21 and encodes the protein called nibrin. Most Slavic patients carry the founder mutation 657del5. This entity is clinically characterized by microcephaly, dysmorphic facial features, mild growth retardation, immunodeficiency, and a strong predisposition to develop malignancies (predominantly of lymphoid origin) [1]. A significant aberration in the peripheral T lymphocyte maturation process in patients with NBS in comparison with physiology was found in the latest studies. An increased number of senescent and exhausted T-cell populations (CD57, KLRG1, and PD1) might be related to increased suspicion of malignancy in patients with NBS [2].

We report 2 patients with NBS and T-cell lymphoblastic lymphoma (T-LBL) treated at the Department of Paediatric Haematology, Oncology, and Transplantology in Lublin in the years 2014-2020. Both patients were diagnosed with NBS by mutation analysis of the *NBN* gene, which revealed homozygosity for a typical 5 base pair

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deletion (657del5). The patients were treated according to EURO-LB 02 for the T-LBL protocol without reduction of cytotoxic drugs. Toxicity profiles during chemotherapy were classified according to the National Cancer Institute's Common Toxicity Criteria. They received anti-infective prophylaxis including oral cotrimoxazole (25/5 mg/kg/day on 3 consecutive days per week) and oral fluconazole (10 mg/kg/day). The medical records of these children were reviewed for clinical and laboratory data and outcome.

CASE REPORTS

CASE 1

A 13-year-old boy with NBS was admitted to our hospital because of a palpable, painless right supraclavicular mass and fever for 7 days. The physical examination revealed bilateral clavicular and supraclavicular lymphadenopathy (4 × 2 cm on the right side and 2 × 2 cm on the left side), microcephaly, and dysmorphic facial features of NBS, such as a sloping forehead, large ears, and prominent nose. No comorbidities or significant findings in the patient's family history were detected.

The patient was born at 37 + 1 weeks of gestation with a birth weight of 2800 g. His head circumference was 31 cm (< 3rd percentile). A genetic assessment was performed because of microcephaly and dysmorphic facial features. His mental development was normal for his age. The boy received intravenous immunoglobulins in the dose of 0.4 g/kg per month over 6 months during infancy. No severe infections were observed during childhood.

Laboratory parameters at admission are presented in Table 1. The ultrasound examination (US) of the neck showed lymph node conglomerates on both sides with reduced echogenicity and a rounded shape. Lymph node biopsy was performed for histopathological examination, and the child was diagnosed with T-LBL. Mediastinal involvement was confirmed using magnetic resonance imaging (MRI) – bilateral conglomerates of lymph nodes sized 68 × 28 × 25 mm on the right side and 67 × 20 × 19 mm on the left side. Pathological nodal masses descended and surrounded the superior vena cava, aortic arch, and trachea. Abdominal US, bone marrow biopsy, and cerebrospinal fluid examination were all normal.

The child was classified as stage III and started on treatment in July 2014, according to the EURO-LB 02 protocol (Table 2). The patient achieved complete remission on the 33rd day of induction. Phase Ia was complicated by anaemia, febrile neutropaenia, oral mucositis grade 3, and peripheral neurotoxicity grade 2. The delay in the next course of chemotherapy in our patient was 7 days, due to an upper respiratory tract infection. After the first administration of high-dose methotrexate (HDMTX) a grade 3 epileptic seizure was observed, which responded to diazepam (0.1 mg/kg body weight). Subsequent infusions of HDMTX were well tolerated. No severe complications were observed during re-induction or maintenance. Currently, in the 4-year follow-up, the child is alive and well.

CASE 2

A 3-year-old boy was admitted to our hospital because of submandibular lymphadenopathy with fever for 7 days and a 2-month history of pain in the lower limbs. The patient was treated with amoxicillin with no improvement for 3 days. The physical examination on admission revealed bilateral clavicular and submandibular lymphadenopathy (5 × 4 cm), enlargement of the inguinal lymph nodes, and splenomegaly. Microcephaly and dysmorphic facial features, such as a sloping forehead and prominent nose, were observed. No comorbidities or significant findings in the patient's family history were detected.

The patient was born abroad at 36 + 6 weeks of gestation with a birth weight of 2530 g. The boy was microcephalic, with his head circumference at one month being

TABLE 1. Clinical and laboratory characteristics of T-cell lymphoblastic lymphoma in the first and the second cases

Parameter	Case 1	Case 2
Sex	Male	Male
Age (years) at diagnosis	13	3
Histology	T-LBL	T-LBL
Stage of disease	III	IV, BM-positive
WBC (l)	8.94×10^9	28.10×10^9 ↑
Neutrophils (l)	7.19×10^9	12.34×10^9 ↑
Lymphocytes (l)	1.06×10^9 ↓	10.02×10^9 ↑
Monocytes (l)	0.69×10^9	4.67×10^9 ↑
Hb (g/l)	131	130
PLT (l)	256×10^9	384×10^9
AspAT (U/l)	29	13 ↓
AlAT (U/l)	9	11
LDH (U/l)	384 ↑	559 ↑
CRP (mg/l)	7.50 ↑	2.18
Uric acid (mmol/l)	0.276	0.179
IgA (g/l)	0.95	0.24 ↓
IgM (g/l)	0.88	0.72
IgG (g/l)	9.23	4.43 ↓
IgG1 (g/l)	4.5	2.25 ↓
IgG2 (g/l)	2.5	0.2 ↓
IgG3 (g/l)	0.33	0.22
IgG4 (g/l)	0.14	0.01
anti-EBV VCA IgG	Negative	Positive
anti-EBV VCA IgM	Negative	Negative

T-LBL – T-cell lymphoblastic lymphoma; WBC – white blood cells; Hb – haemoglobin; PLT – platelet count; AlAT – alanine aminotransferase; AspAT – aspartate aminotransferase; LDH – lactate dehydrogenase; CRP – C-reactive protein; CR – complete remission; BM – bone marrow, anti-EBV VCA – anti Epstein-Barr virus viral capsid antigen

TABLE 2. Characteristics of treatment protocol EURO-LB 02

Course of protocol	Drugs
Cytoreductive pre-phase	Prednisone 60 mg/m^2/day
Induction, phase Ia	Prednisone 60 mg/m^2/day, vincristine 1.5 mg/m^2/day, daunorubicin 30 mg/m^2/day, *Escherichia coli* asparaginase 10,000 IU/m^2/day
Induction, phase Ib	Cyclophosphamide 1000 mg/m^2/day, cytarabine 75 mg/m^2/day, 6-mercaptopurine 60 mg/m^2/day
Consolidation, phase M	6-Mercaptopurine 25 mg/m^2/day, HD-methotrexate 5 g/m^2/day
Re-intensification, phase IIa	Dexamethasone 10 mg/m^2/day, vincristine 1.5 mg/m^2/day, doxorubicin 30 mg/m^2/day, *Escherichia coli* asparaginase 10,000 IU/m^2/day
Re-intensification, phase IIb	Cyclophosphamide 1000 mg/m^2/day, cytarabine 75 mg/m^2/day, 6-thioguanine 60 mg/m^2/day
Maintenance	6-Mercaptopurine 50 mg/m^2/day, methotrexate 20 mg/m^2/day

33 cm (< 3rd percentile). Medical investigations made in the United Kingdom did not include NBS. Computed tomography revealed no structural brain lesions. His mental development was normal for his age. He experienced recurrent upper respiratory tract infections when he attended kindergarten. The diagnosis of NBS was established after the manifestation of lymphoma at the Department of Paediatric Haematology and Oncology and Transplantology in Lublin by sequencing exon 6 of the NBN gene, which revealed homozygosity for a typical 5 base pair deletion. The karyotype of peripheral blood lymphocytes also revealed chromosomal instability involving chromosome 7.

The laboratory parameters at admission are presented in Table 1. The child was diagnosed with T-LBL on histopathological examination. Chest MRI revealed lymph nodes in the area of mandibular angles – 10 × 13 mm on the right side and 8 × 11 mm on the left side. On both sides of the supraclavicular pits, several lymph nodes sized up to 6 mm in the short axes were observed. In the area of the anterior mediastinum, bilateral conglomerates of lymph nodes sized 78 × 32 × 31 mm on the right side and 78 × 18 × 24 mm on the left side were found. Pathological nodal masses descended to the mediastinum, surrounding the superior vena cava, aortic arch, and trachea. The nodal masses were strengthened after the administration of a paramagnetic contrast agent. Abdominal US demonstrated lymphadenopathy and conglomerates 44 × 22 mm in size in the abdomen. Small pericardial effusion (pericardial thickness 3 mm) was observed on echocardiography. The evaluation of cerebrospinal fluid excluded central nervous system involvement. Bone marrow aspirate showed the presence of 6% lymphoblasts.

He was classified as stage IV and started on treatment in August 2019, according to the EURO-LB 02 protocol (Table 2). The boy received intravenous immunoglobulins in the dose of 0.4 g/kg body weight per month during all courses of chemotherapy. On the 15th day of induction, MRI and US revealed decreased neck, breast, and abdominal masses, and parietal remission was achieved. Phase Ia was complicated by peripheral neurotoxicity grade 3 (according to the National Cancer Institute's Common Toxicity Criteria). The delay of the next Ib induction phase in our patient was 7 days. During this phase of therapy (on day 58) hepatotoxicity grade 2 occurred (alanine transaminase 138 IU/l, aspartate transaminase 58 IU/l). Chemotherapy was delayed by 9 days. After consolidation (phase M), progression of the disease was reported with bone marrow and mediastinal relapse. The boy was qualified for haematopoietic stem cell transplantation due to progression of the disease. The treatment was changed, and second-line therapy was implemented. The detailed therapy schedule is presented in Table 3. The boy received chemotherapy according to IntReALL HR 2010 protocol. He received an HIB course with the proteasome inhibitor bortezomib and achieved partial regression. This phase was complicated by a grade 3 seizure episode. During the next HC1 course, disease progression in the neck and me-

TABLE 3. Therapy for T-cell lymphoblastic lymphoma administered due to disease progression in the second patient

Course of protocol	Drugs
IntReALL HR 2010	
Induction, course HIB	Dexamethasone 20 mg/m^2/d, vincristine 1.5 mg/m^2, mitoxantrone 10 mg/m^2, PEG-Asparaginase 1000 U/m^2, bortezomib 1.3 mg/m^2/day
HR consolidation block 1 — HC1	Dexamethasone 10 mg/m^2/d, vincristine 1.5 mg/m^2/d, ARA-C 2 g/m^2, methotrexate 1 g/m^2, cyclophosphamide 200 mg/m^2, PEG-asparaginase 1000 U/m^2
Subsequent treatment*	
	Cyclophosphamide 200 mg/m^2/day, etoposide 75 mg/m^2/day, bortezomib 1.3 mg/m^2/day

**Therapy administered due to further disease progression.*

diastinum was observed. Subsequent treatment consisting of a combination of bortezomib and cytotoxic agents was implemented. However, we still observed progression of the disease, and the patient subsequently died.

DISCUSSION

The analysis shows the highest prevalence of NBS in Poland (3.1/1,000,000) and in the Czech Republic (3.1/1,000,000) [3-5]. Overall, Sharapova *et al.* estimated the highest prevalence of NBS cases in the Vistula watershed as the geographical hot spot of NBS [5]. Microcephaly at birth has been described as the leading symptom of NBS [1]. Therefore, the significance of a detailed diagnostic approach to microcephaly in childhood is important for identifying patients with NBS, to optimize medical support and cancer prevention. Recording the patient's medical and family history and a clinical examination are the first step in the diagnosis. Subsequently, cranial MRI or cerebral US with genetic assessment should be performed. Routine metabolic screening of patients with primary microcephaly is not required [6].

Many children are still diagnosed with NBS after cancer presentation. The median age at diagnosis of NBS is approximately 5 years, and 27% of patients have been diagnosed with malignancies [7]. In Case 1, a genetic diagnosis of NBS was made after birth. In Case 2, the NBS was genetically confirmed during the disclosure of lymphoma when the boy was 3 years old. Earlier investigations due to microcephaly and dysmorphic facial phenotype did not include NBS. Sharapova *et al.* described malignancy in 62 (45.6%) patients with NBS. The median age at cancer presentation was 9.31 years [5]. In our first case, lymphoma was diagnosed when the patient was 13 years old. The cumulative cancer incidence was approximately 40.21% and 77.78% at 10 and 20 years of follow-up, respectively [7].

A holistic preventive approach is essential for children with NBS. The first signs of lymphoma are often misdiagnosed by paediatricians because of their similarity to immunodeficiency-related diseases. Lymphoid malignancies should be considered in the differential diagnoses. Research has been carried out to identify the parameters that would enable patient prognosis. Cooperation between an oncologist, a geneticist and a clinical immunologist seems to be significant in the preventive approach for children with NBS. Wolska-Kuśnierz *et al.* emphasized the importance of monitoring the levels of immunoglobulins due to their correlation with the severity of respiratory tract infections and cancer predisposition. Statistical analysis showed a significant impact of the degree of IgG, IgG1, IgG4, and/or IgA deficiency [3]. In Case 1, we reported normal immunological parameters during the diagnosis of lymphoma. The patient received immunoglobulin therapy during childhood. The levels of immunoglobulins including serum IgA and IgG, IgG1, and IgG2 were decreased in Case 2. The patient received regular IVIG therapy during chemotherapy. NBS patients with latent Epstein-Barr virus (EBV) infection should be carefully monitored. The median viral load is higher in patients with lymphoma [8]. In the second case, elevated levels of anti-EBV viral capsid antigen IgG antibodies were observed.

Characteristic cellular features of NBS include spontaneous chromosomal aberrations, usually affecting T-cell receptor gene cluster and immunoglobulin heavy chain gene cluster [9]. In Case 2, chromosomal instability involving chromosome 7 was described by karyotype analysis. Additionally, telomere attrition also mediates chromosomal instability, which may explain the high incidence of lymphomas in patients with NBS [10].

Hypersensitivity to ionizing radiation triggers changes during initial staging of lymphoma in patients with NBS. MRI or US should be used instead of computed tomography or X-ray [1]. In Case 1 and Case 2, the diagnosis was made using MRI and US.

There are no specific protocols for the treatment of lymphoid malignancies in children with NBS. The decision to reduce cytostatic agents depends on the oncologist and is based on the detailed medical history of every patient. In the literature, cases of successful treatment of lymphomas with reduced doses of cytotoxic agents have been described [11]. In Russian's cohort studies, conventional unmodified regimens were well tolerated in 65% of patients with malignancy [12]. Our Case 1 and Case 2 patients received chemotherapy courses at the scheduled dose without any modification according to the EURO LB-02.

It is well known that therapy-related side effects are more common among patients with immunodeficiencies. Wolska-Kusnierz *et al.* reported that infectious complications (85%) were the most frequent cause of treatment-related toxicity [7]. Similarly, Zawitkowska *et al.* observed 44% of microbiologically documented infections in immunocompromised children [13]. In contrast, Landmann *et al.* reported 65 severe adverse effects in 51 patients with lymphoblastic lymphomas without immunodeficiencies. The most frequent toxicities were haematological toxicity, coagulation problems, infection, and liver toxicity [14]. In our patients, we observed 4 grade 3 adverse events – oral mucositis and 3 episodes of epileptic seizures. Moreover, fatal infectious complications, especially of fungal aetiology, are visibly more common in NBS patients (16%) compared with immunocompromised patients (2%) [3].

The outcome of these patients is extremely poor. Complete remission is achieved in less than 40% of patients, which is visibly less than in the general paediatric population. The 5-year overall survival rate in NBS patients is 25% and the median survival is 3.8 years, compared to immunocompromised patients, in whom it is 82% and 10.3 years, respectively [3]. Most children with T-LBL die due to disease relapse. The second patient died due to progression of the disease. There is a great impact of haematopoietic stem cell transplantation on the long-term survival of patients with NBS and malignancies,

including T-LBL. Patients who received haematopoietic stem cell transplantation had a significantly higher 20-year overall survival rate (42.7%) in comparison with the patients who did not (30.3%). The median follow-up time of patients with NBS and malignancies is 13 years [7].

CONCLUSIONS

Our reports highlight that a standardized approach is essential for the immediate identification of frequent causes of microcephaly. Patients with NBS and lymphoid malignancies are particularly vulnerable to high incidence progression of disease and therapy-associated toxicity.

DISCLOSURE

The authors declare no conflict of interest.

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