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Clinical course and therapeutic implications for lymphoid malignancies in Nijmegen breakage syndrome

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ABSTRACT

Nijmegen breakage syndrome (NBS, MIM #251260) is an autosomal recessive chromosomal instability disorder. Majority of patients affected are of Slavic origin and share the same founder mutation of 657del5 within the *NBN* gene encoding protein involved in DNA double-strand breaks repair. Clinically, this is characterized by a microcephaly, immunodeficiency and a high incidence of pediatric malignancies, mostly lymphomas and leukemias. Anticancer treatment among patients with NBS is challenging because of a high risk of life threatening therapy-related toxicity including severe infections, bone marrow failure, cardio- and nephrotoxicity and occurrence of secondary cancer. Based on systemic review of available literature and the Polish acute lymphoblastic leukemia database we concluded that among patients with NBS, these who suffered from clinically proven severe immunodeficiency are at risk of the complications associated with oncological treatment. Thus, in this group it reasonable to reduce chemotherapy up to 50% especially concerning anthracyclines methotrexate, alkylating agents and epipodophyllotoxines, bleomycin and radiotherapy should be omitted. Moreover, infection prophylaxis using intravenous immunoglobulin supplementation together with antifungal and antibacterial agent is recommended. To replace radiotherapy or some toxic anticancer agents targeted therapy using monoclonal antibodies and kinase inhibitors or bone marrow transplantation with reduced-intensity conditioning should be considered in some cases, however, this statement needs further studies.

1. Introduction

Nijmegen-breakage syndrome (NBS, MIM #251260) is an autosomal recessive chromosomal instability syndrome characterized by a very distinct phenotype (microcephaly, growth retardation, immunodeficiency) associated with increased predisposition to develop malignancies, particularly of lymphoid origin. The first NBS patients were described in Nijmegen in 1981 by Weemaes et al. (Weemaes et al., 1981) and the genetic background of this disease was discovered by Varon et al. (1998) and Gorski et al. (2003). They cloned a gene encoding a novel protein, nibrin (*NBN* gene), containing two modules found in cell cycle checkpoint proteins, a forkhead-associated domain adjacent to a breast cancer carboxy-terminal domain. A truncating 5 bp deletion (c.657_661del5, pK219fsX19) was identified in the majority of NBS patients. In the original report, more than 200 NBS cases were described, the majority among Slavic populations and with a founder mutation in the *NBN* gene (c.657_661del5). The prevalence of this mutation in the Slavic countries (Poland, Ukraine, Czech Republic) was subsequently analyzed, revealing unexpectedly high (1/177) carrier frequency of the founder mutation (Varon et al., 2000).

The principal clinical manifestations of the syndrome are microcephaly, present at birth and progressive with age, dysmorphic facial features, mild growth retardation, mild-to-moderate intellectual disability, and in females, primary ovarian insufficiency (hypergonadotropic hypogonadism) (Chrzanowska et al.,

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2012). Sometimes clinical manifestations are rather discrete and the diagnosis of NBS is made only on the occasion of diagnostic work-up of associated malignancy. With time, most patients develop profound immunodeficiency both of humoral and cellular type. This is frequently associated with recurrent sinopulmonary infections. The spectrum of humoral immunodeficiency is variable ranging from agammaglobulinemia to a moderate reduction in the immune response (Gregorek et al., 2002). Immunological studies reveal mild-to-moderate lymphopenia in nearly half of the patients with an evident decrease of T-cells, particularly CD4+ and CD45RA + naïve subsets (Michalkiewicz et al., 2003).

Another particular feature of NBS is the occurrence of spontaneous chromosome instability, detected via cytogenetic analysis of standard PHA-stimulated peripheral blood T cells. Inversions and translocations, involving two different loci in chromosomes 7 and 14 are particularly characteristic for NBS (Stumm et al., 2001) and are found in the vast majority of cases followed by breakpoints located in chromosome bands 7p13, 7q35, 14q11, and 14q32, which are the sites of the T-cell receptor genes (*TCRG, TCRB, TCRA/D*), and the immunoglobulin heavy chain gene (*IGH*), respectively. Since the MRN complex plays a role in normal Ig/TCR gene rearrangements, its dysfunction in NBS patients can be further confirmed by molecular detection of Ig/TCR cross-rearrangements and trans-rearrangements.

It was also demonstrated that biallelic 657del5 *NBN* mutation leads to a quantitative defect in V(D)J recombination through loss of juxtaposition of recombination activating gene-induced DNA ends. This quantitative defect affects the B-cell receptor repertoire, thus contributing to the observed immunodeficiency in NBS patients (van der Burg et al., 2010).

2. Molecular background of NBS

The majority of NBS patients identified to date (about 70%) had homozygous five base pair deletion in *NBN* gene (c.657_661del5, pK219fsX19) with founder effect observed in Caucasian European populations, especially of Slavic origin (Varon et al., 2000). Similar founder phenomenon was described among Pakistani patients with NBS features who were homozygous for c.C1089A mutation in *NBN* (New et al., 2005). Other mutations are uncommon (Chrzanowska et al., 2012). *NBN* gene product, nibrin protein forms a triheteromeric complex with MRE11 and RAD50 (the MRN complex). The complex is a primary sensor of DNA double-strand breaks (DSB) and is required for the effective monomerization and autophosphorylation of ATM after DNA DSB damage (Varon et al., 1998; Lee and Paull, 2005). This is an initial process in two major pathways of DNA DSB repair, e.g. homologous recombination and non-homologous end joining. Thus, all patients with biallelic hypomorphic mutation in *NBN* gene have defective DSB repair machinery, which leads to clinical features of the syndrome and are prone to develop malignancies.

3. Diagnosis of NBS

The diagnosis of Nijmegen breakage syndrome is based on clinical features including microcephaly with no or very mild psychomotor and neurological lesions, recurrent infections and occurrence of lymphoid malignancies. Patients presenting these clinical characteristics should be subjected for genetic evaluation, which includes family history, cytogenetic abnormalities involving mostly two loci on chromosomes 7 (TCR genes cluster) and 14 (immunoglobulin heavy chain gene cluster) and search for biallelic mutations in *NBN* gene with the specific focus on c.657_661del5 mutation among patients of European Caucasian origin (Chrzanowska et al., 2012).

4. Risk of lymphoid malignancy in NBS

Since by the age of 20 years, over 40% of NBS patients develop cancer, relevant markers predicting malignant transformation have been widely investigated. Kruger at al observed significant association between lymphoma incidence and the low expression level of the truncated p70-nibrin in NBS patients who were homozygous for a founder hypomorphic mutation (c.657_661del5) (Kruger et al., 2007). Based on the study performed on mouse models and cell lines the protective value of the increased p70-nibrin expression probably results from the ability of p70 protein to uphold some function of p95-nibrin such as binding to MRE11 and RAD50 and stimulation of ATM (Tauchi et al., 2001; Difilippantonio et al., 2005).

Moreover, Gregorek at al. prospectively searched for non-invasive laboratory biomarkers preceding malignancy in NBS patients by PCR analysis of the presence of viral genome, monoclonal gammapathy and clonal rearrangements of Ig/TCR genes in peripheral lymphocytes (Gregorek et al., 2010). Both EBV DNA, clonal Ig (IgH, IgK, or IgL) and TCR (B, G and/or D) gene rearrangements were found in 68% and 73% of NBS patients respectively, and preceded the diagnosis of lymphoma, on average, by 3 years. However, there is a discrepancy between results of this study and study performed by Dura-Gladkowska in a large cohort of NBS patients, which proved that EBV is not essential driver in NBS lymphoma formation (Gładkowska-Dura et al., 2008).

Nevertheless, none of predictive marker has been applied into clinical practice, probably because of the lack of well-established diagnostic and therapeutic procedure towards NBS patients exhibiting precancerous status.

5. Biological features of primary and secondary lymphoid malignancy in NBS

The adaptive component of immune system depends on genetic diversity resulting from genomic rearrangements and point mutations which occur physiologically throughout V(D)J recombination, class switch recombination (CSR) and somatic hypermutation (SHM) during lymphocyte development (Moses, 2001). Deficiency of DNA repair proteins affecting these processes reduce fidelity of replication and may lead to malignant transformation. Since NBN is involved in CSR and alternative end joining (alt-EJ) DNA repair pathway, its defect contributes to the specific targeting of B cells by genomic instability (de Miranda et al., 2011). Moreover, a quantitative disturbance of V(D)J recombination, characterized by impaired resolution of RAG-induced IgH breaks, may promote formation of complex translocations involving IgH locus in NBS lymphomas (van der Burg et al., 2010; Difilippantonio et al., 2005).

Therefore, immunological lineage of lymphomas in NBS significantly differ from Non-Hodgkin Lymphomas (NHL) entities observed in general pediatric population as well as in primary immunodeficiencies. There is a strong predominance of diffuse large B-cell lymphoma (DLBCL) and T cell lymphoblastic lymphoma (T-LBL/ALL), all showing clonal Ig/TCR rearrangements (Gładkowska-Dura et al., 2008; Seidemann et al., 1999a; Dembowska-Baginska et al., 2009). The distribution of lymphoma between T and B cell origins in the Polish Registry of NBS is almost equal and achieve 55% and 45% respectively (Chrzanowska et al., 2012). Regarding other lymphoma subtypes, a few cases of ALCL, Hodgkin's lymphoma, AILT-like B cell and

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