Nijmegen breakage syndrome in fraternal twins and synchronous development of non-hodgkin's lymphoma

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Case Report

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ABSTRACT

Nijmegen breakage syndrome (NBS) is an uncommon autosomal recessive chromosomal instability that is usually characterized by microcephaly, a facial structure resembling a bird, growth retardation, radiation hypersensitivity, immunodeficiency, and a propensity for malignancies. NBS patients are more likely to develop lymphomas, primarily non-lymphoma Hodgkin's (NHL). Among NBS patients, diffuse large B-cell lymphoma ranks among the most prevalent types of lymphoma. The prognosis remains poor. Here, we report the synchronous development of NHL and NBS in fraternal twins for the first time.
Keywords: Nijmegen Breakage Syndrome, Non-Hodgkin's Lymphoma, fraternal twins. chromosomal instability

Nijmegen breakage syndrome (NBS), is an extremely uncommon autosomal recessive chromosomal instability disorder that is brought on by homozygous or compound heterozygous mutations in the NBS1 gene (NBN) on chromosome 8q21. Symptoms of NBS include microcephaly, facial features resembling birds, growth retardation immunodeficiency, , a propensity for malignancies and radiation hypersensitivity. The underlying NBN gene (c.657 661del5), which codes for a protein involved in repairing DNA double-strand breaks, contains a founder mutation that makes it more common in Slavic populations. It is associated with childhood mortality, mostly due to lymphoid malignancies [1]. In a Turkish family, a homozygous 657del5 mutation was discovered before [2]. In the majority of patients, development of secondary neo-

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plasms is considered a fatal complication. Patients with immunodeficiencies, such as NBS and ataxia telangiectasia (AT), have a 250-fold increased risk of lymphomas, primarily non-lymphoma Hodgkin's (NHL), and a 50-fold increased risk of developing malignity [3]. The conclusive evaluation of NBS is based on the common clinical symptoms, elevated cell membrane responsivity to radiation exposure in an in vitro environment, and genetic and molecular research that support homozygous mutations in the NBN coding region. The 657del5 mutation of the NBN gene on 8q21 is present in approximately 85% of cases [1].

Herein, we, for the first time, report NBS in fraternal twins and synchronous development of NHL.

CASE REPORT

Two nine-month-old twins with an enlarged cervical lymph node were referred to our center with same complaints. They were born at 38th gestational week with low birth weight and microcephaly. Although immunodeficiency was not thought to be present, both twins experienced respiratory infections during infancy, including pneumonia, otitis media, and bronchiolitis. The family was of Turkish origin, who had migrated from Albania many years ago. There was no information that they were of Slavic origin. At the time of admission, both twins had a typical bird-like face appearance of NBS with microcephaly (Figure 1). When he was ten years old, the children's uncle, who also had a typical facial appearance, passed away from a lung infection (Figure 2). Physical examination of the twins revealed significant growth retardation, bilateral tonsillar enlargement, cervical lymphadenopathy, and hepatomegaly. Blood tests showed mild leukopenia with slightly increased lactic dehydrogenase (LDH) levels (596 U/l) (normal range 220-450 U/L). Immunological studies demonstrated low serum immunoglobulin (Ig) A and IgG levels with a high serum IgM concentration. Bone marrow examination results of both patients were normal. The NBS1 gene mutation analysis of theof both twins showed homozygosity for typical 5bp deletion (657del5). Anterior mediastinum was slightly enlarged on chest computed tomography (CT) scan and X-ray, and mediastinal adenopathy to right- and left-sided nodular lesions connected to pulmonary neoplastic infiltration were also seen. (Figure 3A). Tru-Cut biopsies of the tonsils were performed on both twins. Histopathological and immunohistochemical examination findings were compatible with NHL (diffuse large B-cell lymphoma [DLBCL]) in both children. A lymphoma-like growth pattern and atypically large lymphocytes with prevalent nuclei and abundant cytoplasm are seen upon histological examination. There are mitotic figures (Figure 3B). Pediatric chemotherapy regimen was initiated with Berlin-Frankfurt-Münster (BFM) protocol with reduced doses of the cytotoxic agents. Following the

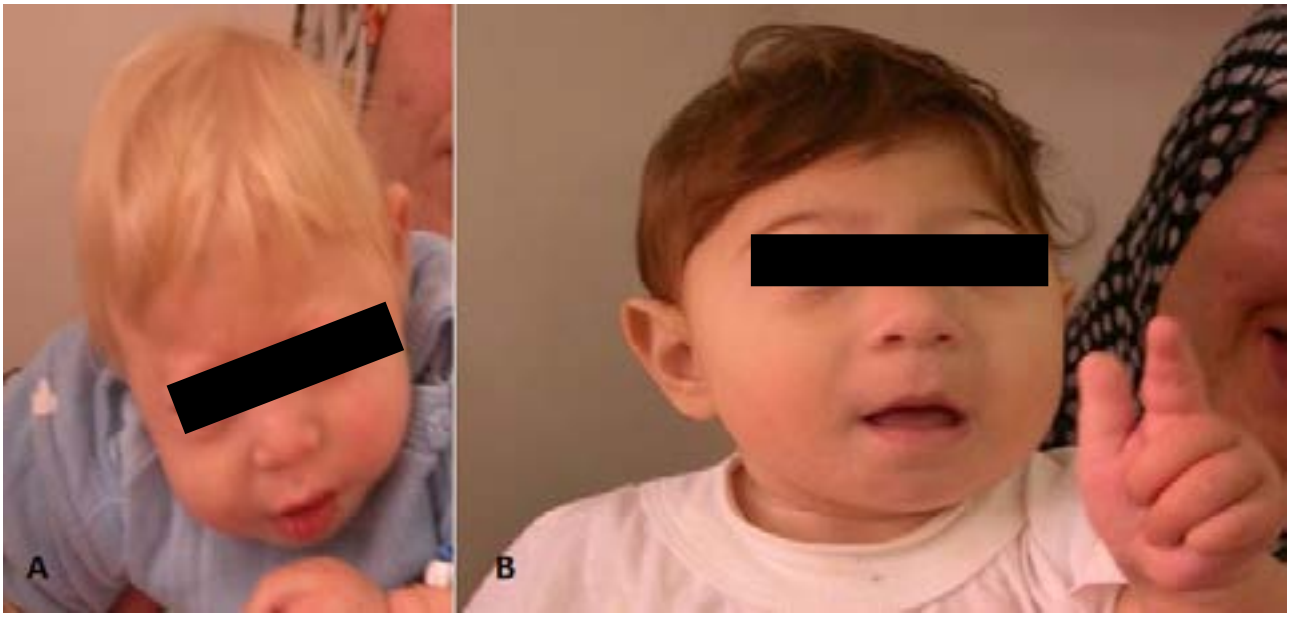

Figure1. Typical facial appearance of fraternal twins. Male(A) and female (B).

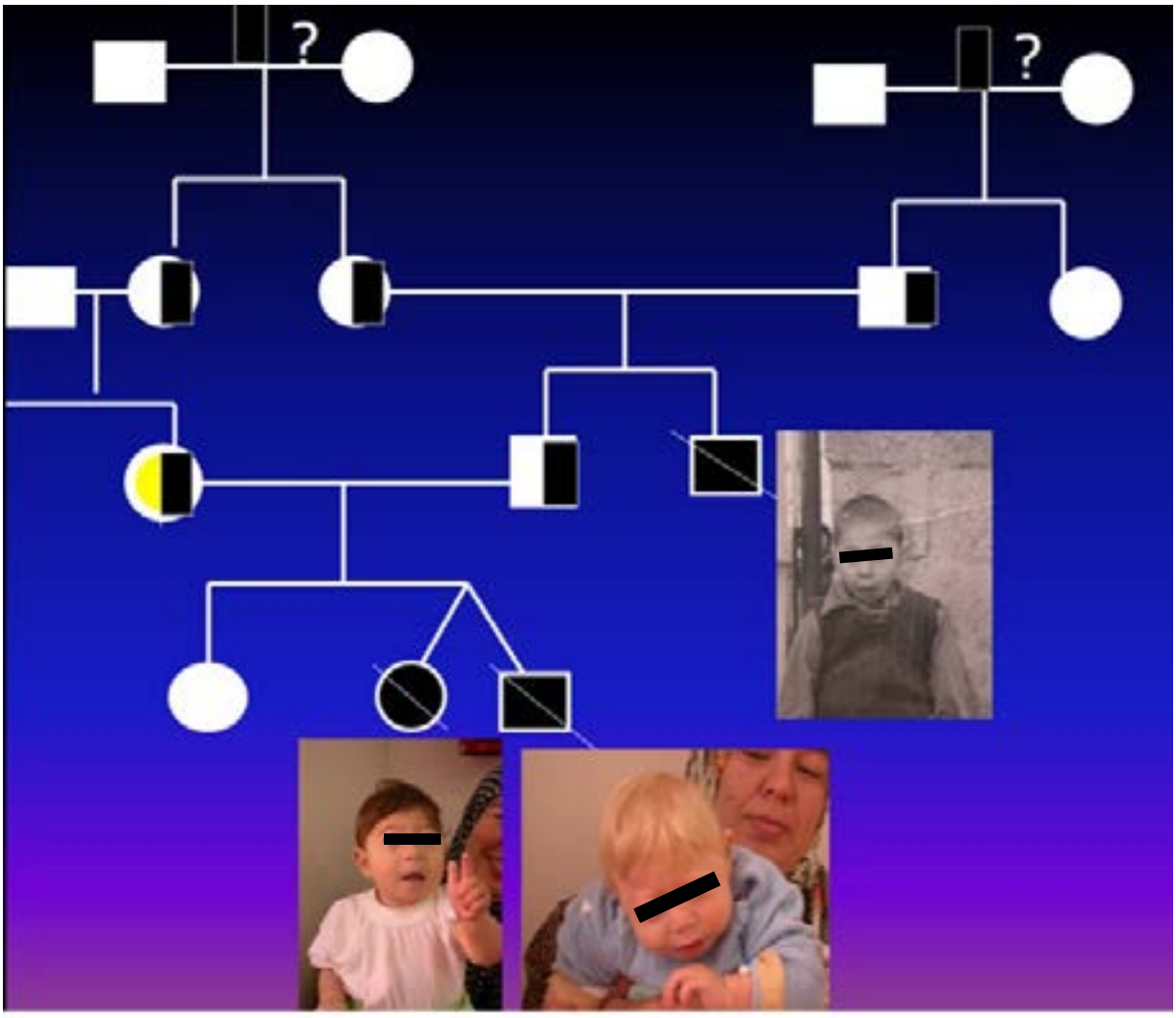

Figure2. The family pedigree

first cycle of chemotherapy, severe febrile neutropenia and infections occurred and both patients died from sepsis and massive hemorrhage within three weeks.

DISCUSSION

Nijmegen breakage syndrome is a relatively uncommon condition DNA repair disorder. Recent studies have demonstrated that NBS is caused by mutations in the gene that code for nibrin. [1]. Malignancies usually develop in nearly half of NBS patients before the age of 21 years [4]. The most frequent neoplasms related with NBS are lymphoblastic T cell lymphoma (T-LBL) and diffuse large B-cell lymphoma (DLBCL); even though medulloblastoma and rhabdomyosarcoma are also documented in the literature. [1]. Fanconi anemia, Xeroderma pigmentosum, Rothmund-Thomson syndrome, and Werner syndrome are the most frequent cancers in people without immunodeficiency, whereas immune-deficient patients of disrupted DNA repair, such as above with an NBS, Bloom Syndrome, Ataxia-telangiectasia (AT), and, show a higher propensity to develop lymphomas. [5]. Although several biomarkers predicting malignant transformation have been widely investigated in recent studies, but the reasons for an increased predisposition of immunocompromised patients for lymphoproliferative diseases have not been fully understood, yet.

In general, patients with primary immunodeficiencies and NHL are younger than non-immunocompromised patients with NHL. In a BFM study with 1,569 newly diagnosed NHL patients, it was found that 0.06 percent of the patients had NBS (n = 4) or AT (n = 5) [6]. In this study, the median age of NHL diagnosis was nine years old, which was similar to other pediatric NHL cases (median 9.3 years) [7]. Similar to our patients, two of these patients with NBS were diag-

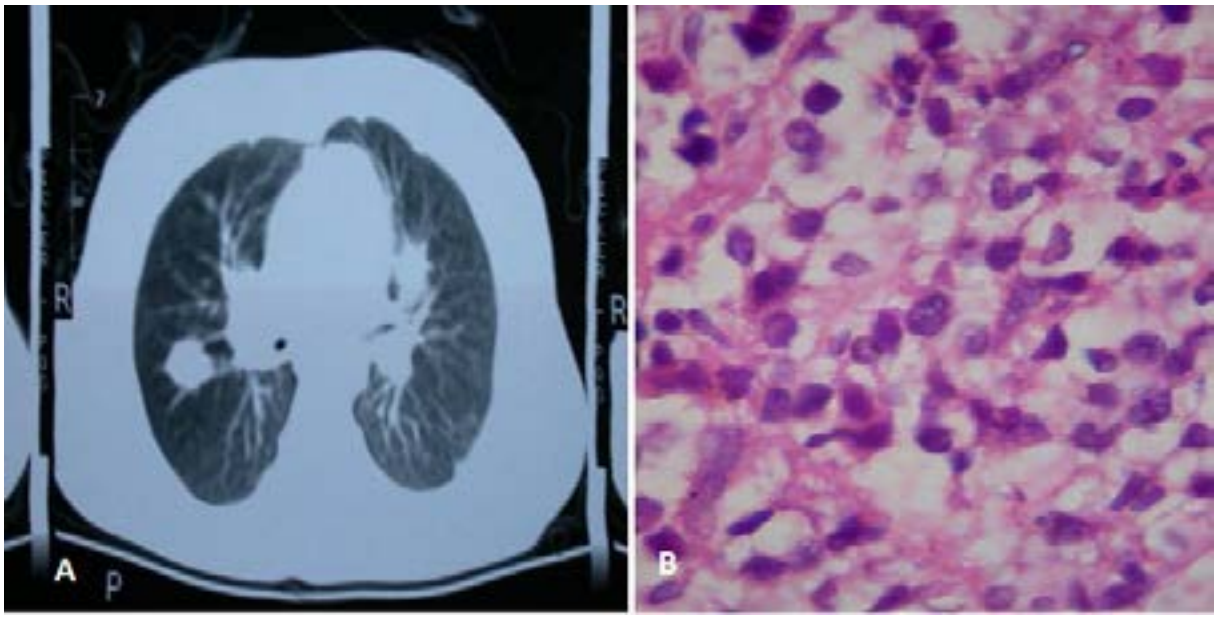

Figure3. (A), A thoracic computed tomography (CT) image of male case. (B) Tru-Cut biopsies of the tonsils from male case. Mitotic figures are present (arrows). (Hematoxylin and Eosin stain x100).

nosed based on immunological examination after the diagnosis of NHL. In their previous article, it was also reported 19 patients with primary immunodeficiency (NBS n=4) in BFM studies. Two of them were siblings aged 6.5 (female) and 9 (male) years, respectively [8].

17 NBS patients with a median age of 9.5 years who received treatment for NHL were the subject of another study [9]. Their youngest patient with NHL was 3.8 years old. There were also reported 38 patients with primary lymphoid cancer and chromosomal instability syndromes (NBS n = 19 and AT n = 19 and) [10]. The youngest patient with NBS who was diagnosed with NHL was 4.3 years old and five of them were not considered syndromic cases, until the definite diagnosis of lymphoma. More recently, the European Society for Immunodeficiencies (ESID) dataset between 2004 and 2012 revealed that 63 (42%) of a total of 149 patients were diagnosed with 80 malignancies, with the median age for the initial episode of neoplasms being 10.25 years (range, 2 to 26). However, there is no NBS case with lymphoma aged under two years in this database [11].

As far as we are aware, there are no published cases of NBS and NHL occurring before the age of two. Similarly, there is no reported case of fraternal twins with NBS and NHL. Therefore, we believe that our cases are the first NBS cases who synchronously developed NHL. In addition, DLBCL is one of the most prevelant types of lymphoma in NBS patients, as in our cases.

However, NBS patients have demonstrated significant variation in immunodeficiency over time in both the same patient as well as between different patients [1]. Our patients were IgA and IgG-deficient which were unable to be detected before the diagnosis of NHL.

Serious infectious side effects may develop during treatment in cancer patients with DNA repair abnormalities like NBS, making clinical management and diagnosis difficult. In addition to available treatment options, there is also growing evidence in recent years on successful treatment of NBS with hematopoietic stem cell transplantation (HSCT) before life-threatening complications or secondary malignancies occur [1].

Despite all efforts, the outlook for NBS and NHL remains dismal. According to one of the biggest sequence of Polish NBS patients of NHL, some patients could be healed and their chances of survival were better if they had B-cell NHL as opposed to T-cell lymphoma [9]. Therefore, it is crucial to diagnose the illness as early as possible. Furthermore, it has been shown that NBS is associated with reduced tolerance to chemotherapy and toxic deaths mainly from sepsis [1, 6-8]. Similarly, our both patients died from toxicity-related sepsis, despite low dose regimen.

CONCLUSION

In conclusion, this case report is the first to present NBS cases who synchronously developed NHL

in fraternal twins which highlights the importance of recognizing underlying immunodeficiencies or NBS in patients who develop NHL at an uncommonly early age or who experience unusually severe chemotherapy toxicity. Therefore, interdisciplinary clinical diagnosis and long-term actually follow should be encouraged, and clinicians should be aware of these issues and the disease's natural course. However, more prospective multicenter studies are required to determine the effectiveness of NHL treatment in NBS patients.

Authors' contributions

Study Conception: EGK, HG, FGİ, AE, CV,; Study Design: EGK, HG, FGİ, AE, CV,; Supervision: DG,; Materials: EGK, HG, SA,; Data Collection and/or Processing: DG,; Statistical Analysis and/or Data Interpretation: DG,; Literature Review: EGK,; Manuscript Preparation: EGK, DG and Critical Review: EGK, HG, FGİ, AE, CV.

Conflict of interests

No potential conflicts of interests relevant to this article were reported.

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