NIJMEGEN BREAKAGE SYNDROME CLINICO-CYTOGENETIC PATTERN

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Abstract

Here we report an 8 years old girl who had post natal growth deficiency, microcephaly, facial dysmorphism, partial syndactyly of the second and third toes, susceptibility to infections, leukocytosis, immunodeficiency, adenopathy, but now sign of telangiectasia, ataxia and in evolution developed malignancy. Chromosomal analysis showed anomalies. By combining clinical manifestations and laboratory findings including cytogenetic findings and taking in account the evolution of the patient, we sustain the diagnosis of Nijmegen Breakage Syndrome.

Key words: Nijmegen breakage syndrome, chromosome aberrations, Burkitt lymphoma

Introduction

Nijmegen breakage syndrome (NBS) is a rare genetic disease with an estimated incidence of 1:100,000 live births. This condition is characterized by chromosomal instability and it is considered to be related with Fanconi anemia (Schroeder et al., 1964), ataxia-telangiectasia (A-T) (Hecht et al., 1966) and Bloom syndrome (Bloom, 1966). NBS has an autosomal recessive inheritance pattern. Heterozygotes are usually asymptomatic. The cardinal symptoms of NBS are: microcephaly, growth retardation and immunodeficiency.

NBS was just recently accepted as a distinct clinical entity, Weemaes et al. in 1981 described this syndrome in 2 patients. In 1985, Seemanova et al. found the chromosomal instability sensitivity to ionizing radiation, and radioresistant DNA synthesis in a group of patients. These manifestations were similar to the characteristic chromosomal anomalies observed in ataxia-telangiectasia (A-T) but the clinical manifestations did not fit the pattern of A-T. NBS was considered a variant of A-T at that time. Two independent groups, one coordinated by Matsuura et al. and the other one by Varon et al, identified the mutation of NBS1 gene in 1998. NBS1 gene is located on chromosome 8q21 and is encoding a protein called nibrin. This protein is a member of the hMre11/hRAD50 protein complex, and has an important role in DNA repair.

Nijmegen Syndrome is characterized by microcephaly, bird-like facies, growth retardation, IQ scores normal or borderline intelligence to mild mental retardation, despite severe microcephaly, irregular skin pigmentation as hyperpigmentation or hypopigmentation, congenital manifestations including clinodactyly, syndactyly, recurrent infections, chromosomal instability, immunodeficiency, predisposition to malignancies as non-Hodgkin lymphomas, leukemia, solid tumors like glioma, rhabdomyosarcoma, and medulloblastoma. The risk of developing malignancies is 60-150 times higher in patients with NBS, due to the chromosomal rearrangements encoding T-cell receptor (Bridges and Harnden, 1982; Gatti and Swift, 1985, Lehmann et al., 1989).

In Poland, Czech Republic, Slovakia, Germany and Ukraine there have been reported an increased number of patients with Nijmegen Syndrome. They seem to have a Slavic origin and carry a major founder mutation, 657del5, in the NBS1 gene. The heterozygote incidence is approximately 1 in 177 in Eastern European populations predominantly among persons from Poland, the Czech Republic and Ukraine (Varon et al. 2000).

Case report

We report an 8 years old female patient. She is the first-born child of a healthy young couple (mother's age 25, father's age 30) residing from a small Romanian community that is an isolate of people with Slavic origins (Ukraine). Affirmative the parents declared that they are not relatives. Somatic parameters at birth were: weight - 3200 g, length - 50 cm, head circumference - 30 cm (<3rd centile). There was no family history of short stature, congenital malformation and malignancy.

Clinical aspects initial and in evolution

The patient was first admitted to hospital for long lasting fever, microcephaly and was under suspicion for a urinary infection. The somatically parameters were below the normal values for her age: she was 115 cm tall (<3rd centile), 18 kg weight (<3rd centile), had a cephalic circumference of 42 cm (<3rd centile). The phenotypic appearance was suggestive for a genetic syndrome: microcephaly, receding forehead, prominent mid-face, upward slanting palpebral fissures, prominent nose, facial lentigines, micrognathia and large ears (Fig.1, 2). Limb anomalies were also present, shorter second finger phalanx and partial syndactyly of second and third toes of both feet (Fig. 3).

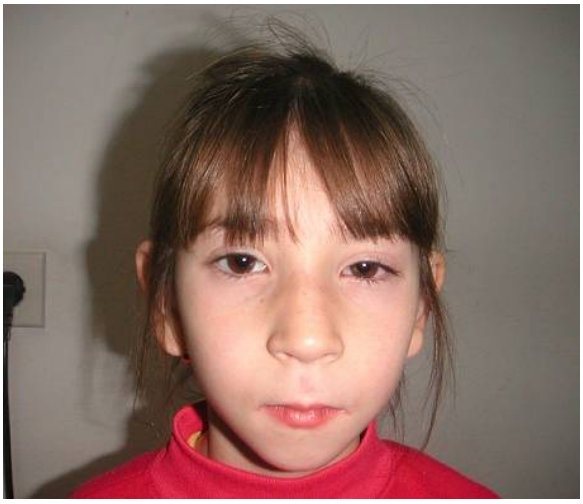

Figure 1. Facial appearance.

Figure 2. Lateral view of patient's face.

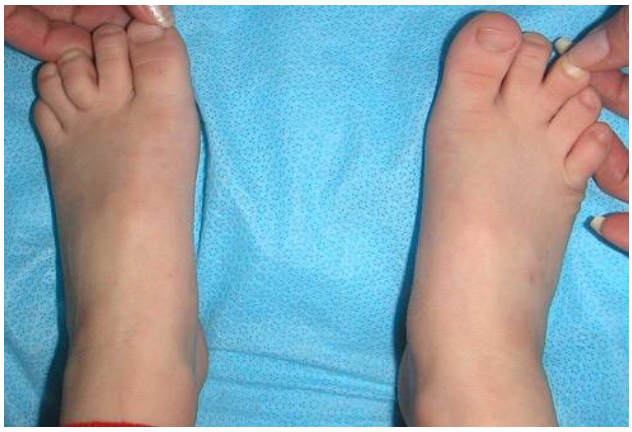

Figure 3. Partial syndactyly of second and third toes of both feet.

The second admitting to hospital was 6 months later when the patient presented with fever, cough, acute abdominal pain and difficulty in breathing. Clinical, imagistic and laboratory investigation were done. Clinical inspection and examination underlined submandibular adenopathy and an area of dullness during percussion of the right lung fields, fine crackles and dimmed vesicular sound.

The patient was admitted again to hospital 10 days after release because the general condition was aggravating although the treatment was continued at home.

Complementary investigations

The first time the patient was evaluated, thoracic X-ray, abdominal ultrasonographies were performed and no worrying signs were noticed. A very detailed neurological evaluation also showed no pathological signs.

At the second admitting the thoracic X-ray revealed right lung pneumonia, but the there was no sign of mediastinal lymphadenopathy. Laboratory analyses were done. Complete blood count was performed and white blood cells (WBC) were high (32.000/mm^3), hemoglobin and hematocrit values were low. C-reactive protein was found to have high values 15.7 mg/L (normal values: 0-3 mg/L). Immunoglobulins levels were tested and IgA was low (0.224 g/l) (normal range: 0.7-4 g/l), but IgE, IgG, IgM had normal values.

When readmitted, the patient was reevaluated and pulmonary CT was performed showing pneumonia Abdominal and pelvic CT were done and the findings rouse the suspicion of malignancy. The abdominal CT (Fig. 4) showed an abdominal mass with dimensions of 5/4 cm that was suppressing inferior vena cava, and was extended upwards to inferior duodenal flexure and downwards to aortic bifurcation, retroperitoneal adenopathy at renal hilum in celiac ganglion group. Pelvic CT revealed adenopathy masses with dimensions between 1 and 4 cm at internal and external iliac lymph nodes on both sides (Fig. 5).

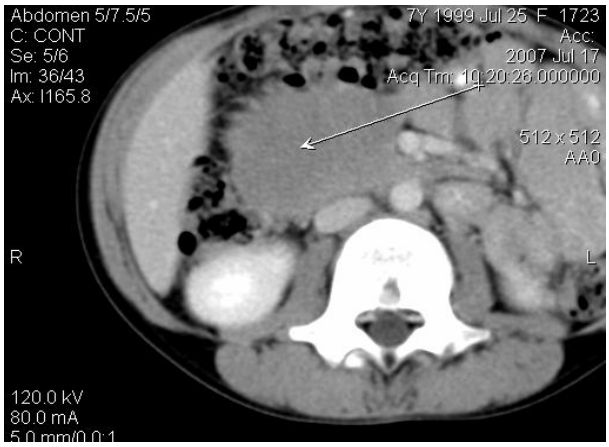

Figure 4. Abdominal CT Abdominal mass suppressing inferior vena cava.

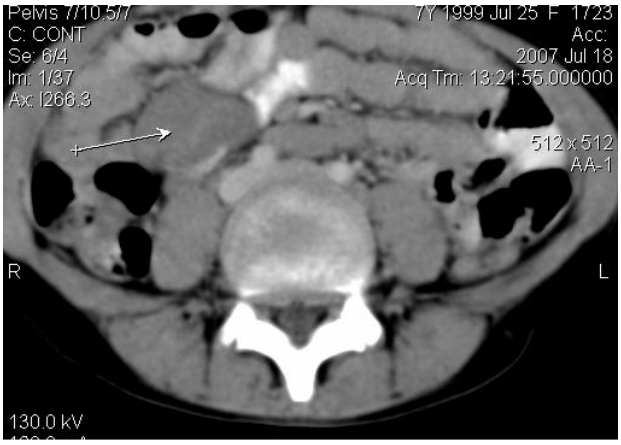

Figure 5. Pelvic CT - adenopathy masses.

Laboratory analyses were repeated and leukocytosis was found, and also C-reactive protein was elevated, serum α-fetoprotein being in normal range. Biopsy samples were taken from abdominal mass, appendix and retroperitoneal ganglion. Pathologic examination of the biopsy pieces established the diagnosis of Burkitt lymphoma and the patient was referred to an Oncology Clinic for chemotherapy.

Cytogenetic analysis

The first attempt to reveal the patient karyotype failed. Cytogenetic analysis was difficult to perform due to the poor proliferation capacity of lymphocytes that was encountered.

A second chromosomal analysis was done at the second admission to hospital. Two PHA stimulated peripheral blood lymphocytes cultures from the patient were performed. In the first culture, 9 mitosis could be analyzed, 6 metaphases had a normal 46,XX karyotype, while 3 revealed chromosomal anomalies. The second culture was supplemented with 2mmol/l L-glutamine and 26 mitoses were obtained, including 19 abnormal metaphases. The slides that were made were examined in Department of Genetics at Ulleval as well as in Timisoara. Cytogenetic findings included preferentially aberrations of chromosomes 7 and 14, as other cases of NBS reported in the literature (t(7;14)(q22;q32)). Other chromosomal anomalies found were translocations (t(2;6)(q33;q27), isochromosomes (11q) and aneuploidies such as monosomies, trisomies of chromosome 19 and 8, marker chromosomes and also chromosomal breakages, del(22)(q11) (Fig. 6, Fig. 7).

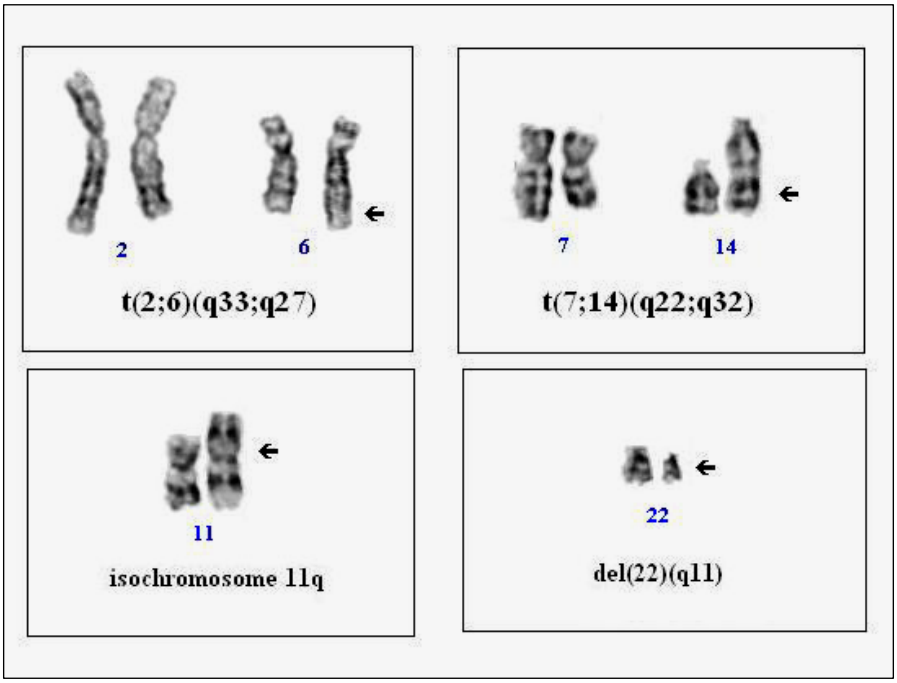

Figure 6. Partial karyotypes with chromosomal anomalies: translocations, isochromosome and deletion. Arrows indicate chromosomal aberrations.

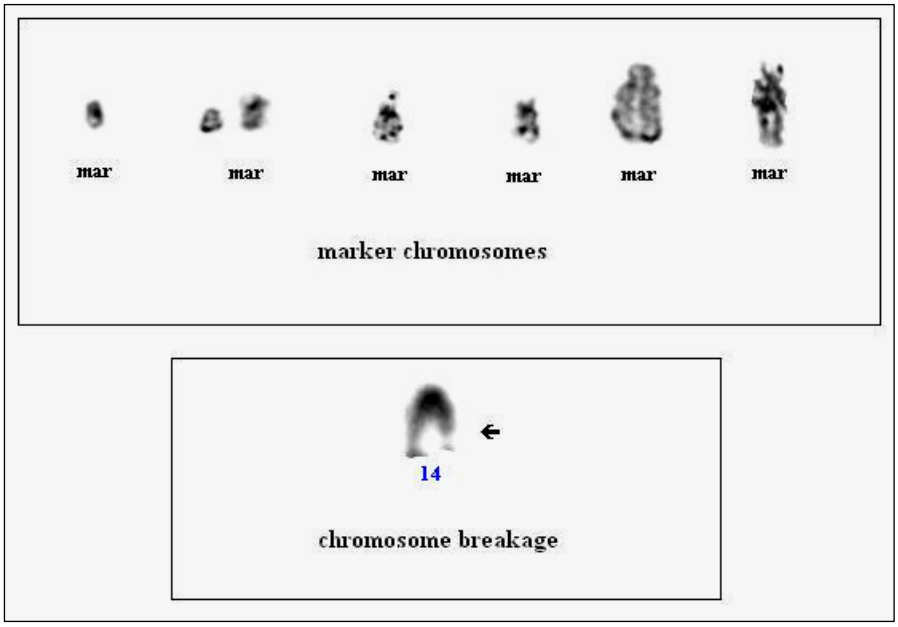

Figure 7. Marker chromosomes from different metaphases and chromosome breakage. Arrow indicates chromosome 14 breakage.

Discussions and conclusions

Associating the hallmark clinical findings, the recurrent respiratory infection, the paraclinical investigations (leukocytosis, fever, low levels of IgA), the imagistic investigations (echography, CT and histological exam), the cytogenetic findings and the evolution to Burkitt lymphoma, we can sustain the diagnosis of Nijmegen Syndrome. From the manifestation more rarely found we identified syndactyly (Table I).

Table I. NBS clinical manifestations

Clinical manifestations in NBS:	Present patient	Others clinical manifestations in NBS:	Present patient
Growth retardation	+	Clinodactyly	-
Microcephaly	+	Polydactyly (preaxial)	-
Peculiar face (“bird-like” appearance)	+	Transverse palmar crease	-
Receding forehead	+	Wide gap toes	-
Prominent mid-face	+	Syndactyly of the toes	+
Prominent philtrum	+	Renal abnormality	-
Receding mandible	+	Eye fundus with pigment deposits(“salt and pepper” type)	-
Upward slant of palpebral fissures	+	Recurring infections	+
Epicanthic folds	-	Respiratory tract: pneumonia, bronchitis	+
Large ears with dysplastic helices	+	Respiratory tract: bronchiectasis	-
Areas of hyperpigmentation	-	Urinary tract infections	+
Areas of hypopigmentation	-		
Sun-sensitivity of palpebrae	-		
Skin abnormalities	+		
Telangiectasia (conjunctival)	-		
Freckles (mainly in butterfly distribution in face)	+		

The combination of immunodeficiency and chromosomal instability as seen in the girl we described is present in both ataxia-telangiectasia and Nijmegen breakage syndrome. Ataxia telangiectasia is excluded because the girl did not have progressive cerebellar ataxia, oculo-cutaneous telangiectasia or elevated serum α-fetoprotein typical for the disorder. Differential diagnosis also included: primary microcephaly, Fanconi anemia, Xeroderma pigmentosum, Bloom Syndrome, Immunodeficiency with proportionate short stature, A-T–like disease, X-linked

agammaglobulinemia, Ligase IV (LIG4) syndrome (Ming et al. 1999). The clinical findings and the paraclinical investigations ruled out these syndromes.

The constitutional karyotypes of patients with NBS are usually normal (46,XX or 46,XY). However in literature, the typical cytogenetic anomalies reported are: spontaneous chromatid and/or chromosomal breakage (7p13, 7q35, 14q11, and 14q32), rearrangements involving mainly chromosomes 7 and 14: inv(7)(p13q35), translocations 7/14, 7/7 and 14/14 and acentric fragments. There have also been reported other chromosomal anomalies such as: dup(4)(q28q35.2), t(1;8), t(14;20).

It is important to mention that the first lymphocytes culture from this patient was unsuccessful. This is concordant with the other reports from literature (Vazken M. Der Kaloustian, 1996). It is also known that is difficult to perform cytogenetic analysis due to the poor proliferation capacity of lymphocytes (The International Nijmegen Breakage Syndrome Study Group conduced by J. A. Hiel, C. M. Weemaes and L. P. van den Heuvel). The cytogenetic anomalies found for the patient were in high proportion (62.8%). According to Hiel et al (2001), cytogenetic aberrations are present in all cases varying usually from 10 to 45% of the metaphase, but higher percentages have been reported. Translocations of chromosomes 7 and 14, 2 and 6 were clonal. The frequency of chromosomal breakage was low, possible due to the fact that the cytogenetic analysis was performed at the time the malignant process was identified. A high number of supernumerary marker chromosomes were also found.

Due to the fact that this is an autosomal recessive condition, the parents must be heterozygotes, carriers of a single copy a mutation in the NBS1 gene. It is important to monitories the genitors due to the fact that some reports have suggested an increased risk of malignancy in carriers of the common Slavic mutation, 657del5 (Chrzanowska, 2007). They have a risk of 25% of giving birth to another affected offspring. For prenatal genetic diagnosis might be useful the molecular genetic analysis and there are also available biochemical assay. Unfortunately, in Romania there is not possible to perform prenatal diagnosis for Nijmegen Syndrome.

No specific therapy is yet available for NBS. For this patient it is necessary a therapeutic strategy for Burkitt lymphoma. It also may be useful the antibiotic prophylaxis, vitamin E supplementation and substitution hormone therapy to support the development of secondary sex characteristics when the patient reaches the appropriate age.

The prognosis for the patients with Nijmegen Syndrome is poor; usually the premature death occurs due to the infection complications or the malignancy. Our patient had developed malignancy in a relative short period of time after she was first investigated and the prognosis is estimated to be low.

Although the clinical manifestations and investigations of the patient, and also the evolution of the disease allowed us to establish the diagnosis of Nijmegen Syndrome, for an accurate diagnosis, molecular genetic investigation for the mutations of the NBS1 gene is to be performed.

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