Nijmegen breakage syndrome

The International Nijmegen Breakage Syndrome Study Group

Abstract

***Background*—Nijmegen breakage syndrome (NBS) is a rare autosomal recessive disorder. NBS-1, the gene defective in NBS, is located on chromosome 8q21 and has recently been cloned. The gene product, nibrin, is a novel protein, which is member of the hMre11/hRad50 protein complex, suggesting that the gene is involved in DNA double strand break repair.**

***Aims*—To study the clinical and laboratory features of NBS as well as the genotype–phenotype relation.**

***Methods*—Fifty five patients with NBS, included in the NBS registry in Nijmegen were evaluated. The majority of the patients were of eastern European ancestry. Most of them had shown a truncating 5 bp deletion 657–661 delACAAA. Four further truncating mutations have been identified in patients with other distinct haplotypes.**

***Results and conclusions*—Essential features found in NBS were microcephaly, usually without severe retardation, typical facial appearance, immunodeficiency, chromosomal instability, *x* ray hypersensitivity, and predisposition to malignancy. In 40% of the patients cancer was noted before the age of 21 years. Important additional features were skin abnormalities, particularly café au lait spots and vitiligo, and congenital malformations, particularly clinodactyly and syndactyly. Congenital malformations, immunodeficiency, radiation hypersensitivity, and cancer predispostion were comprehensible in case of dysfunctioning of DNA repair mechanisms. No specific genotype–phenotype relation could be found. Patients with the same genotype may show different phenotypes and patients with different genotypes may express the same phenotype. Specific mutations did not lead to specific clinical features.**

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Keywords: NBS; NBS registry; clinical features; laboratory features; genotype; phenotype

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Nijmegen breakage syndrome (NBS) is a rare autosomal recessive condition, which belongs to the so called DNA repair disorders, which also include Bloom syndrome, xeroderma pigmentosa, Fanconi anaemia, and ataxia telangiectasia. These disorders show overlapping clinical and cell biological features, but are genetically heterogeneous.[1–29] Spontaneous chromosomal instability, predisposition to cancer, and immunodeficiency are characteristic features of NBS, Bloom syndrome, and ataxia telangiectasia.[1–29]

The gene responsible for NBS, NBS-1, is located on chromosome 8q21 and has recently been identified.[26 27] The encoding protein has been named nibrin. The domains found in nibrin and the NBS phenotype suggest that NBS is caused by defective responses to DNA double strand breaks.[27 28]

In this report we provide an extended follow up of the first recognised NBS patient described in 1981 and evaluate the clinical and laboratory features of 55 NBS patients included in our NBS registry in Nijmegen.

Case report

This boy (fig 1) is the sixth child of consanguineous healthy parents (second cousins). He was born in 1969 after a pregnancy of 38 weeks duration. Pregnancy was complicated by pyelonephritis at 24 weeks. Birth weight was 2500 g (P10) (data concerning length and head circumference at birth not available). The neonatal period was normal. When he was 6 weeks old his head circumference was 33 cm (<P3). Development of language skills was delayed. During infancy he suffered from recurrent upper respiratory tract infections, chickenpox, and measles. Special education was necessary because of learning difficulties and hyperactivity. We examined him aged 9, when we noted a small microcephalic boy with head circumference 45 cm (<P3), height 124 cm (<P3), and weight 21 kg (<P3). He had a typical face with a receding forehead, prominent midface with long nose, and a receding mandible. Sun sensitive erythema of the face and many freckles were noted as well as café au lait spots and patches of vitiligo. TIQ was 67. Neurological examination was otherwise unremarkable. EEG revealed no abnormalities.

Routine blood tests were normal, as were endocrinological studies. Immunological studies showed IgA and IgE deficiency with normal IgG and IgM (IgA <0.05 g/l, IgE <1 IU/ml, IgG 11.30 g/l, IgM 0.69 g/l); cellular immunity was normal. Cytogenetic studies revealed multiple rearrangements of chromosomes 7 and 14. We proposed a provisional name of Nijmegen breakage syndrome (NBS).[1] At 13 years of age mild thoracolumbar scoliosis was noted. At 14 years of age he experienced repeated skin infections and suffered a severe bronchopneumonia. Head circumference remained below P3 (fig 2). At the age of 17, repeat immunological studies showed undetectable serum IgA and serum IgE concentrations, and disturbances in synthesis of specific antibodies as well as some disturbances in cellular immunity. At the age of 19 he was admitted with malaise and fever. An *x* ray of the chest

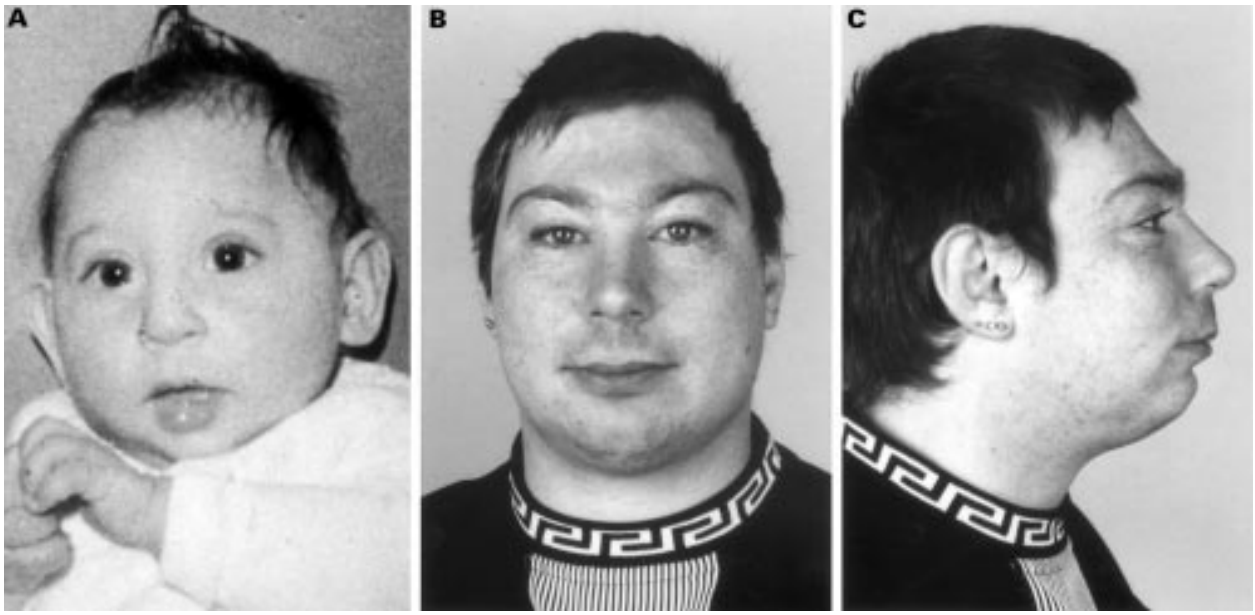

Figure 1 Photograph at young age (A) and at adult age (B, C).

revealed a pathological mediastinal mass, which proved to be non-Hodgkin lymphoma. He received chemotherapy with prednisone and vincristine followed by maintenance with methotrexate. The latter had to be discontinued after a year because of vomiting and loss of weight. The disease remitted. At the age of 24, human immunoglobulin substitution was started subcutaneously because of agammaglobulinaemia (IgG 1.37 g/l, IgM 0.22 g/l). At 27 years of age he had repeated fits with lowered consciousness. Neurological examination was unremarkable. EEG showed low voltage activity, no epileptic discharges. A hyperventilation provocation test was strongly positive. Breathing control manoeuvres were beneficial. He is currently 30 and has no specific complaints.

Clinical and laboratory features of NBS

PATIENTS AND METHODS

We conducted a computer aided literature search to obtain data on patients with NBS syndrome.[1–11] Supplementary information was obtained from questionnaires completed by the patients' attending physicians. We now report on the available clinical and laboratory features of the 55 patients included in the NBS registry to date.

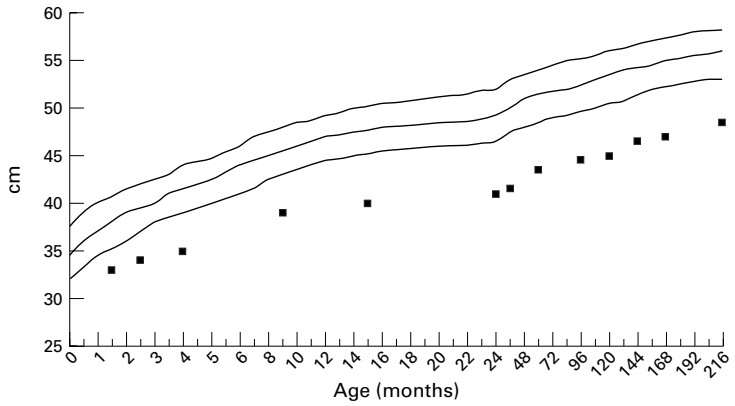

Figure 2 Patient 1: head circumference values in relation to age (lines represent 90th, 50th, and 10th centile values).

CLINICAL FEATURES

Tables 1 and 2 summarise the clinical features of the patients.

Demography

The disease appears prevalent among those of eastern and central European origin, particularly among Polish people. The 55 patients comprise 31 men and 24 women. Of the 55 patients, 36 are still alive; the oldest is now 30 years old (table 1).

Growth and development

All patient are microcephalic. Head circumference at birth varied between 26.5 and 36 cm. About 75% of patients had a birth head circumference below the 3rd centile, so not all were microcephalic at birth. However, all developed progressive and severe microcephaly during the first months of life. They have early growth retardation, height falling below the 10th centile in all. The growth retardation is proportionate and weight corresponds to height. Feeding difficulties are often reported in infancy, probably as a result of abnormal development of the mandible (see below).

Developmental milestones were generally reached at normal times during the first year of life. Hyperactivity was common. Mental development is normal in 40%, 50% have borderline to mild retardation, while 10% are moderately retarded. Severe mental retardation has not been reported. We found no correlation between head circumference at birth and mental development.

Few data are available about the sexual maturation of patients with NBS.[3 12] Offspring have never been reported. Five patients have ovarian dysgenesis (patients 8, 9, 20, 26, 53).

Craniofacial findings
All patients have a typical distinctive facial appearance, characterised by a receding forehead, prominent mid face with long nose and long philtrum, receding mandible, upward slanting palpebral fissures usually accompanied by epicanthic folds, freckles on the cheeks and nose, large ears with dysplastic helices, and sparse hair (fig 1). These characteristics become more obvious with age. Subtle scleral telangiectasia is seen in some.

Cutaneous manifestations
Café au lait spots, vitiligo, sun sensitivity of the eyelids, and pigment deposits in the fundus of the eye are comon. Cutaneous telangiectasia is seen ocassionally.

Congenital malformations
The most common malformations are clinodactyly and/or syndactyly, noted in about 50% of the patients. Less common are anal atresia/stenosis (patients 9, 10, 31, 45), ovarian dysgenesis (patients 8, 9, 20, 26, 53), hydronephrosis (patients 2, 7, 11), and hip dysplasia (patients 11, 28, 49, 53). Other malformations reported are hypoplastic trachea (patient 50), cavernous angioma (patient 46), agenesis of phalanges (patient 34), hypospadias (patient 37), left renal hypoplasia (patient 45), and single kidney (patient 41). Cerebral malformations reported are schizencephaly (patient 37), occipital cyst (patient 17), and hydrocephalus (patients 11 and 46).

Infections
Infections are common, most frequently of the respiratory tract followed by urinary tract infections. Gastrointestinal infections are reported relatively infrequently. The infections are typically community acquired infections rather than opportunistic infections.

Malignancies
To date 22 patients, varying in age from 1 to 22 years have developed a malignancy. Of these, 16 developed a lymphoma (patients 1, 3, 4, 5,

Table 1 NBS patients included in the NBS registry in Nijmegen

Patient no.	Sex	Origin	Born	Age at death (y)	Cause of death		Gene mutation
1	M	Dutch	1969			Sib of 2	657-661 del ACAAA
2	M	Dutch	1964	6	Infection	Sib of 1	657–661 del ACAAA
3	F	Czech	1971	21	Malignancy	Sib of 4	657–661 del ACAAA
4	M	Czech	1977	2	Malignancy	Sib of 3	657–661 del ACAAA
5	M	Czech	1981	9	Malignancy	Sib of 6	657–661 del ACAAA
6	F	Czech	1980	0.5	Infection	Sib of 5	657–661 del ACAAA
7	F	Czech	1979				657–661 del ACAAA
8	F	American	1965	24	Infection		657–661 del ACAAA
9	F	German	1971			Sib of 10	657–661 del ACAAA
10	F	German	1975	7	Infection	Sib of 9	657–661 del ACAAA
11	M	Dutch	1984	4	Lymphoma		C>T at 976
12	F	German	1985				
13	F	Czech	1983	6	Lymphoma		
14	F	Czech	1986				657–661 del ACAAA
15	M	Polish	1980			Sib of 16	
16	F	Polish	1982	7	Lymphoma	Sib of 15	
17	M	French–east Europe	1978				
18	M	Polish	1989			Sib of 19	657–661 del ACAAA
19	F	Polish	1991			Sib of 18	657–661 del ACAAA
20	F	Polish	1979	15	B cell lymphoma	Sib of 21	657–661 del ACAAA
21	M	Polish	1981			Sib of 20	657–661 del ACAAA
22	M	Polish	1977			Sib of 23	657–661 del ACAAA
23	M	Polish	1981			Sib of 22	657–661 del ACAAA
24	F	Polish	1987				657–661 del ACAAA
25	M	Polish	1993				657–661 del ACAAA
26	F	Polish	1978				657–661 del ACAAA
27	M	Polish	1986			Sib of 46	657–661 del ACAAA
28	M	Polish	1991	4	B cell lymphoma		657–661 del ACAAA
29	M	Polish	1982				657–661 del ACAAA
30	M	Polish	1992				657–661 del ACAAA
31	M	Polish	1989	8	Infection		657–661 del ACAAA
32	F	English	1991				657–661 del ACAAA/698–701 del AACA
33	M	English	1993				657–661 del ACAAA/698–701 del AACA
34	F	Polish	1985	9	Medulloblastoma		
35	M	Polish	1980				657–661 del ACAAA
36	M	Polish	1985				657–661 del ACAAA
37	M	Canadian	1990	7	Rhabdomyosarcoma		657–661 del ACAAA/1142delC
38	F	Polish	1987	9	Lymphoma		657–661 del ACAAA
39	M	Polish	1989	5	Lymphoma		
40	M	Polish	1993				657–661 del ACAAA
41	F	Polish	1993				657–661 del ACAAA
42	M	Italian	1985	11	B cell lymphoma		835–838 delCAGA
43	M	Kroatian	1991				657–661 del ACAAA
44	M	Kroatian	1996				657–661 del ACAAA
45	M	German	1987				
46	M	Polish	1996			Sib of 27	657–661 del ACAAA
47	F	Polish	1988				657–661 del ACAAA
48	F	Polish	1993				657–661 del ACAAA
49	F	Polish	1978	20	Lymphoma		657–661 del ACAAA
50	F	Polish	1993				657–661 del ACAAA
51	F	Polish	1989				657–661 del ACAAA
52	M	Polish	1995				657–661 del ACAAA
53	F	Polish	1978				657–661 del ACAAA
54	M	New Zealand	1983				
55	M	Spanish–English	1995				657–661 del ACAAA

Table 2 Clinical features reported in NBS

Features	*No. affected*
Growth and development	
Microcephaly	55/55
Growth retardation	55/55
Craniofacial features	
Receding forehead	52/52
Prominent mid face with long nose and philtrum	47/47
Receding mandible	47/47
Epicanthic folds	36/51
Sparse hair	26/35
Large ears	24/29
Subtle scleral telangiectasia	8/25
Intelligence	
Normal intelligence	22/55
Borderline to mild retardation	28/55
Moderate retardation	5/55
Skin abnormalities	
Café au lait spots	18/21
Vitiligo spots	14/21
Sun sensitivity of eyelids	10/19
Pigment deposits in eye fundus	8/17
Cutaneous telangiectasia	3/32
Congenital malformations	
Clinodactyly	22/34
Syndactyly	12/36
Anal atresia	4/55
Hydronephrosis	3/55
Hip dysplasia	3/55
Others	10/55
Infections	
Bronchopneumonia	38/50
Otitis	17/33
Urinary tract infections	13/20
Sinusitis	9/30
Gastrointestinal tract infections	3/3
Malignancies	
Lymphoma	16/55
Leukaemia	1/55
Lymphoblastic lymphoma/leukaemia	2/55
Medulloblastoma	1/55
Rhabdomyosarcoma	1/55
Glioma	1/55

9, 11, 13, 16, 20, 27, 28, 35, 38, 39, 42, 49), the majority B cell. The remaining six have leukaemia (patient 54), precursor T cell lymphoblastic lymphoma/leukaemia (TLBL/ALL) (patients 29 and 51), glioma (patient 7), medulloblastoma (patient 34), or rhabdomyosarcoma.[37] Eight of the 22 patients with malignancy are still alive, including the patient described in this case report.

LABORATORY FEATURES

α Fetoprotein concentrations

In contrast to the situation with ataxia telangiectasia, all NBS patients had normal serum α fetoprotein concentrations.

Immunological disturbances

Figure 3 shows concentrations of IgG, IgA, and IgM, measured in 48 patients. The most commonly reported defects in humoral immunity were IgG and IgA deficiency, as well as IgG2 and IgG4 deficiency. IgM deficiency was very rare.

Agammaglobulinaemia was found in 16 patients (pateints 2, 3, 5, 8, 17, 18, 27, 29, 31, 36, 40, 41, 43, 46, 48, 55). Selective IgA deficiency was seen in five patients (patients 1, 9, 10, 14, 54). IgA deficiency as well as IgG2 deficiency, with or without IgG4 deficiency was noted in seven patients (patients 13, 25, 28, 34, 38, 42, 47). IgG2 deficiency with or without IgG4 deficiency was seen in 11 patients (patients 7, 11, 19, 20, 21, 22, 23, 24, 35, 52, 53). Selective IgG4 deficiency was noted in three patients (patients 32, 45, 51). Only six patients had normal immunoglobulins (patients 12, 26, 30, 37, 49, 50). For some patients not all data were available: in four patients with IgA deficiency, IgG subclasses were not determined; in three patients with normal immunoglobulins, IgG subclasses were not determined. Figure 4 shows the percentages of CD3, CD4, and CD8 cells of about 70% of the patients. The most commonly reported defects in cellular immunity were reduced percentages of total CD3+ cells and CD4+ cells and a decreased CD4+/CD8+ ratio. The frequency of CD8+ cells usually does not appear to be affected. The in vitro response of lymphocytes to mitogenic stimuli such as phytohaemagglutinin (PHA) was decreased in nearly all NBS patients tested (of 51 patients tested, 47 had a greatly reduced response, two patients had a slightly reduced response, and two had a normal response).

Cytogenetic features

Constitutional karyotypes of NBS patients are normal. Cultured T cells often show a poor proliferative capacity, making cytogenetic analysis far from easy. In all patients cytogenetic aberrations are present in 10–45% of metaphases from PHA cultured T cells. Most of the rearrangements occur preferentially in chromosomes 7 and 14 and are typically inversions and translocations, with breakpoints at the sites of immunoglobulin or T cell receptor genes. Inv(7)(p13q35) is the most frequently detected aberration in NBS. Other frequent rearrangements are t(7;14)(p13;q11), t(7;14)(q35;q11), t(7;7)(p13;q35), and t(14;14)(q11;q32).[5 7 11 15 16] Chromosomal rearrangements typically are not increased in cultured fibroblasts from NBS patients and, in cases where increased rearrangements in fibroblasts are reported, no bias in the sites of rearrangement analogous to that in lymphocytes is observed.

Radiation hypersensitivity and radioresistant DNA synthesis

Primary cells (fibroblasts and lymphocytes) cultured from NBS patients typically display poor growth in culture, a feature they share with cells from ataxia telangiectasia patients. In addition, primary cells and transformed cells have aberrant responses to ionising radiation. In colony forming assays, NBS cells are 3–5 times more sensitive to ionising radiation or radiomimetic drugs than normal cells. Radiation induced chromosome aberrations occur with increased frequency in NBS cells. *x* Ray hypersensitivity was present in 26 of 27 patients tested (patients 1, 3, 5, 7–12, 14, 18, 20–24, 27–29, 32, 33, 36, 37, 45, 47, 53). One patient showed intermediate sensitivity (patient 42). NBS cells also display radioresistant DNA synthesis (RDS), the inability to halt or slow S phase progression after exposure to high doses of *x* rays. The inhibition of DNA synthesis after *x* or γ irradiation is two to three

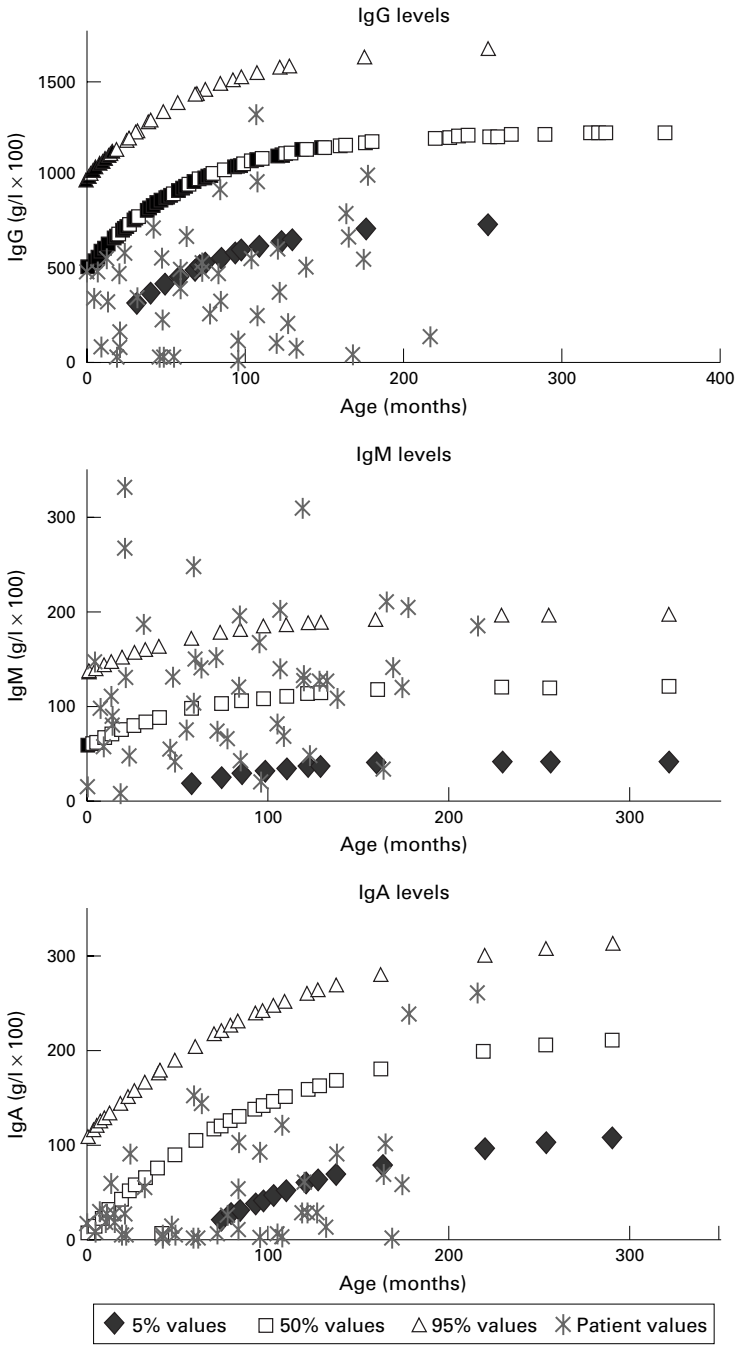

Figure 3 Serum immunoglobulin concentrations.

times less pronounced than in normal cells.[7 11 14 16 18]

Necropsy findings

Nineteen of the patients have died, five from infection, and 14 from malignancy. Limited autopsy findings are available: an extensive postmortem examination has been reported for only one patient, a 4 year old child (patient 12), in whom brain weight was extremely reduced. There was no evidence of cerebellar degeneration. The thymus was small, dysplastic, and relatively devoid of lymphoid cells. Limited necropsy data from other patients confirm small brain, thymus dysplasia, or even thymus aplasia.[2 13]

Genetics

Registered patients come from 44 families, the majority of eastern European ancestry. Recent genetic studies have provided evidence for a common haplotype of markers present in the families with Eastern European origins, suggesting a common founder effect with regard to mutations causing the disorder. After identification of the gene, mutation detection has revealed a truncating 5 bp deletion, 657–661delACAAA, as the disease causing mutation in these patients (see table 1). Five further truncating mutations were identified in patients with other distinct haplotypes. Four of these mutations are listed in table 1. The fifth, a 842–843insT, was identified in a Mexican patient, who has not yet been registered.

Patients with different genotypes may show the same phenotype, as illustrated by patients 2 and 11 both showing hydronephrosis, by patients 7 and 37 both showing severe T cell immunodeficiency, and by patients 11 and 20 both having developed a lymphoma. On the other hand, patients with the same genotype may vary in phenotypic expression, as illustrated clearly by patient 1 who only has an IgA deficiency and is still quite healthy, while his older brother had agammaglobulinaemia and died young from infection. Other examples are: patient 18 has clinodactyly, patient 19 does not; patient 20 developed a glioma, while patient 21 is still free of malignancy.

Discussion

The hallmarks of NBS are microcephaly, a typical facial appearance, growth retardation, immunodeficiency accompanied by recurrent infections, chromosomal instability, *x* ray hypersensitivity, and predisposition to malignancy. Important additional features are skin abnormalities, particularly café au lait spots and vitiligo, and congenital malformations, particularly clinodactyly and syndactyly.

Psychomotor development is usually normal or only mildly to moderately retarded despite severe microcephaly. This is in contrast to the severe mental impairment commonly seen in isolated or autosomal recessive non-syndromal microcephaly. About three quarters of the NBS patients are microcephalic at birth and the remainder become microcephalic within the first year of life. No correlation can be seen between head circumference at birth and mental development. Severe microcephaly at birth may be associated with normal mental development and counterwise.

Life expectancy is reduced because of their tendency to develop malignancies at a relatively young age and sometimes fatal infections.

Remarkably, despite the often severe immunodeficiency, frequently occurring infections rarely lead to severe complications. Moreover, opportunistic infections are very sparse despite the T cell defect, as also experienced in ataxia telangiectasia (AT), which has similar T cell defects.

About 40% of the patients included in the NBS registry have developed a malignancy, predominantly in childhood. Treatment may be difficult, because of hypersensitivity to

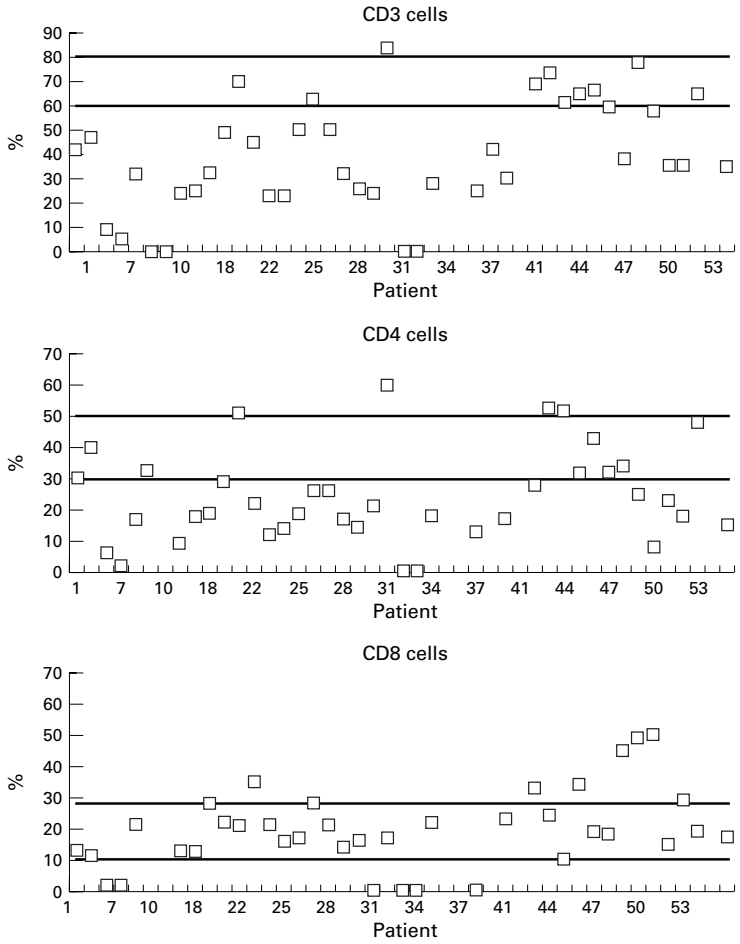

Figure 4 Percentage of T cells (lines represent normal ranges).

ionising radiation and radiomimetic drugs, which may have to be avoided or used at reduced dosages.[18]

The immunological, cytogenetic, and cell biological findings in NBS closely resemble those in AT (see table 3). Therefore NBS has long been considered as an AT variant.[19–25] Concerning the clinical aspects, however, NBS is more similar to Bloom syndrome (BS), both of which encompass severe microcephaly with relatively preserved mental development. Unlike AT, neurological features are rare. The facial appearance is different, being small and narrow in BS. NBS and BS lack the increased serum α fetoprotein concentrations of AT. BS shows a characteristic cytogenetic feature, the sister chromatid exchanges, which is not seen in NBS and AT.[19–25 29]

The specific pathogenesis of the disorder still has to be elucidated, despite recent identification of the gene.[26–28] This has had immediate implications for diagnosis and family studies. Studies on the gene product, nibrin, have provided a key to new fundamental knowledge on the molecular mechanism of double strand DNA break repair. Comprehensive sequence comparison of nibrin has revealed two domains in the amino terminal region: a forkhead associated domain (FHA) and a breast cancer carboxy terminal domain (BRCT). Both domains have been found separately in DNA damage responsive cell cycle checkpoint proteins. Carney *et al*[28] provided evidence that nibrin can form complexes with two proteins that play a role in double strand break DNA repair. This suggests that deficiency in nibrin disrupts a common pathway that functions to sense or repair double stranded DNA breaks.

Table 3 Comparison of NBS with Bloom syndrome (BS) and ataxia telangiectasia (AT)

	NBS	*BS*	*AT*
Gene locus	8q21	15q26	11q22–23
Gene	NBS1	BLM	ATM
Microcephaly	++	++	−
Growth retardation	++	++	±
Mental retardation	±	−	±
Typical facial appearance	++	−	−
Telangiectasia			
Ocular	±	−	++
Cutaneous	±	+	++
Skin abnormalities			
Hyperpigmentation	+	+	+
Sunlight sensitivity	+	++	−
Cerebellar ataxia	−	−	++
Recurrent infections	++	±	++
Elevated α fetoprotein levels	−	−	++
Immunodeficiency	++	+	+
Cancer predisposition	++	++	+
Chromosomal instability	++	++	++
Radiation hypersensitivity	++	−	++

−, absent; ±, rare; +, usual; ++, frequent.

DNA double strand breaks occur often but seldom lead to aberrations in case of a normal functioning repair mechanism. In the case of dysfunction of repair mechanisms, however, serious aberrations can be expected, particularly in tissues with high proliferative capacity. In that light, congenital deformations, immunodeficiency, radiation hypersensitivity, and cancer predisposition are comprehensible.

In DNA repair disorders immunodeficiency, growth retardation, and predisposition to malignancy are common, both in man and in animals with Ku70 and Ku80 deficiency. In Ku70 and Ku80 deficient mutants an abnormal sensitivity to ionising radiation and a severe combined immunodeficiency caused by abnormal V(D)J recombination exist. Immunoglobulin heavy chain rearrangements in an NBS lymphoblastoid cell line have been analysed by DNA sequencing and found to be normal.[30] However, quantitative analysis in NBS cells is required to address adequately the role of the hMrell/hrad 50 protein complex in this process.[28] As IgM level is nearly always normal in NBS, whereas IgG and IgA concentrations are frequently abnormal, this suggests that the gene may be involved in this process during the isotype switch.

No specific genotype–phenotype relation has been identified. NBS registry patients with the same genotype may display different phenotypes, and patients with different genotypes may express the same phenotype. Defects in sensing and repairing double stranded DNA breaks by nibrin on several specific places of the genome as well as the interplay with other gene products, involved in DNA double strand repair, may be the explanation for this feature.

Finally, specific mutations do not lead to specific clinical features. For example, a specific mutation predisposing to malignancy is not seen.

It is interesting that within the same genotype clinical and laboratory features may

differ. Obviously compensating mechanisms play a role. Insight into these mechanisms may offer new approaches for therapeutic interventions.

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