ACTA NEUROBIOLOGIAE EXPERIMENTALIS

Acta Neurobiol Exp 2004, 64: 503-509

Magnetic resonance imaging of brain abnormalities in patients with the Nijmegen breakage syndrome

Monika Bekiesińska-Figatowska[1], Krystyna H. Chrzanowska[2], Elżbieta Jurkiewicz[3], Anna Wakulińska[4], Henryk Rysiewski[5], Małgorzata Gładkowska-Dura[6] and **Jerzy Walecki[7]**

[1]Department of Diagnostic Imaging, Central Railway Hospital, Bursztynowa 2, 04-749 Warsaw; [2]Department of Medical Genetics; [3]Department of Diagnostic Imaging; [4]Department of Oncology; [5]Department of Pediatrics (Anthropology Unit); [6]Department of Pathology, The Children's Memorial Health Institute, Al. Dzieci Polskich 20, 04-736 Warsaw; [7]Department of Diagnostic Imaging, Medical Centre for Postgraduate Education, Wołoska 137, 02-507 Warsaw, Poland

Short communication

Abstract. The results of brain MRI are presented in 22 patients with documented Nijmegen breakage syndrome (NBS), aged from 1 and 9/12 to 20 years. T1-, PD or FLAIR and T2-weighted SE/TSE images in three planes were obtained. Twenty-one patients showed microcephaly. Decreased size of frontal lobes and narrow frontal horns of the lateral ventricles was observed in all cases. In 6 patients agenesis of the posterior part of the corpus callosum was found as well as colpocephaly and temporal horn dilatation. In 2 patients callosal hypoplasia was accompanied by other anomalies: abnormal cerebrospinal fluid spaces. Sinusitis was present in all patients as a result of primary immunodeficiency. As in ataxia teleangiectasia and other breakage syndromes, NBS patients show inherited malignancy susceptibility and hypersensitivity to X and γ radiation. Because of that computed tomography is contraindicated in these patients and MRI should be the method of choice in diagnostic imaging.

The correspondence should be adressed to
M. Bekiesińska-Figatowska,
Email: m.figatowska@mp.pl

Key words: Nijmegen breakage syndrome (NBS), brain anomalies, magnetic resonance imaging (MRI)

Nijmegen breakage syndrome (NBS) is a rare genetic condition, inherited as an autosomal recessive trait (MIM *251 260). Based on immunological, cytogenetic and cell-biological similarities it is classified as an ataxia telangiectasia (AT) related disorder. These similarities include genomic instability, immunodeficiency, radiosensitivity and malignancy predisposition. The major clinical manifestations of NBS include progressive microcephaly, distinct facial appearance and early retardation of statural growth (Chrzanowska et al. 1995, van der Burgt 1996, Weemaes et al. 1981). Although at a young age intelligence is usually normal or border-line, by adolescence patients are usually mildly or moderately retarded (Wegner et al. 1999). Proneness to infections is observed in the majority of cases. Both humoral and cellular immune deficiency is well documented in these individuals, and together with chromosomal instability may predispose to cancer development, predominantly of lymphoid origin, at a young age (Chrzanowska et al. 1995, van der Burgt 1996, Wegner et al. 1999).

The NBS gene has been mapped to chromosome 8q21 (Saar et al. 1997), and subsequently cloned (Varon et al. 1998). A protein encoded by the *NBS1* gene, nibrin, is involved in the processing of DNA double-strand breaks caused by ionizing radiation (Carney et al. 1998, Varon et al. 1998).

The disease appears to be prevalent among the central European population, in whom the presence of a common founder mutation in NBS1 gene, presumably of Slavic origin, has been found (Varon et al. 1998). Since the first report on 11 Polish NBS patients (Chrzanowska et al. 1995), a further 68 cases have been identified at the Children's Memorial Health Institute in Warsaw or referred to the Polish NBS Registry, which accounts for over a half of all known cases. Detailed clinical, cytogenetic, immunological and biochemical investigations were performed to make an accurate diagnosis, as described earlier (Chrzanowska et al. 1995). Clinical diagnosis was confirmed in each case by molecular analysis of the *NBS1* gene; all our patients were homozygous for the 657del5 mutation in exon 6, which is the most frequent mutation in NBS (over 90% of cases) (Varon et al. 1998).

Information on neuropathology in NBS individuals is very scanty. Hydrocephaly, occipital cyst and schizencephaly were each reported once after CT imaging (der Kaloustian et al. 1996, Stoppa-Lyonnet et al. 1992, Taalman et al. 1989).

The results of magnetic resonance imaging of the central nervous system have not been known until year

Table I

Clinical, laboratory and MRI data in NBS patients

Patient no.	1	2	3	4	5	6	7	8	9	10	11
Age at the moment of MRI (years)	16	10	11	1/09	12	9	20	19	12	2	17
Sex	M	F	M	M	M	F	F	F	F	F	M
Laboratory tests radioresistant DNA synthesis *in vitro**	**+**	**+**	**+**	**nd**	**+**	**+**	**+**	**+**	**nd**	**nd**	**+**
Clinical data microcephaly (SDS)**	-4.2	-6.71	-5.6	-2.5	-4.93	-6.64	-6.67	-2.92	-7.53	-7.79	-4.00
Mental retardation	+	+	+	+/-	+	+	++	+	+	+	+
Seizures	-	-	-	-	-	+	-	+	-	+	-
Respiratory tract disorders	-	-	+	-	+	+	+	-	+	+	-
MRI features decreased size of frontal lobes with narrow frontal horns	+	+	+	+	+	+	+	+	+	+	+
Callosal hypoplasia	-	-	-	+	-	+	-	+	-	+	-
Colpocephaly	-	-	-	+	-	+	-	+	-	+	-
Temporal horns dilatation	-	-	-	+	-	+	-	+	-	+	-
Abnormal CSF spaces	-	-	-	-	-	-	-	+	-	-	-

(**+**) present; (**-**) absent; (**nd**) not done; *tested at the Department of Clinical Genetics, Erasmus University, Rotterdam (Dr W.J. Kleijer); **head circumference deficiency expressed in standard deviation scores (compared with age-matched controls). Mental retardation: (+/-) border line intelligence or developmental quotient; (+) mild MR; (++) moderate MR.

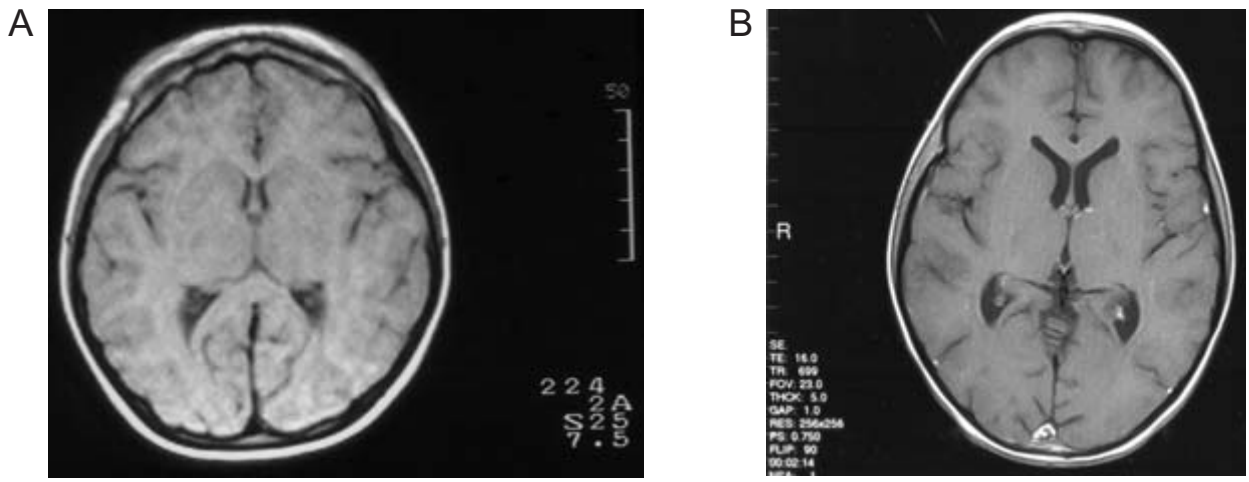

Fig. 1. (A) Patient no. 3. Axial T1-weighted image. Decreased size of the frontal lobes and narrow frontal horns of the lateral ventricles. (B) Axial T1-weighted image of an age-matched healthy individual.

2000 when the first demonstration of brain anomalies in 10 cases of Nijmegen breakage syndrome was published in "Neuroradiology" (Bekiesińska-Figatowska et al. 2000). Now we present clinical and radiological findings in 22 NBS patients.

Twenty-two patients (11 males, 11 females), aged from 1 and 9/12 to 20 years, with confirmed NBS, underwent cranial MRI. They were studied with 0.5 and 1.5 T units. Axial, coronal and sagittal sections were performed, in T1-weighted, PD or FLAIR and T2-weighted images. The clinical and MRI data are shown in Table I.

Decreased size of frontal lobes and narrow frontal horns of the lateral ventricles were observed in all of the patients on MRI (Fig. 1A) as compared to healthy age-matched subjects (Fig. 1B). Six patients (no. 4, 6, 8, 10, 12 and 22) showed partial agenesis of the corpus callosum. Posterior parts of the corpus callosum (splenium and partially trunk) were missing (Fig. 2A). The normal corpus callosum is presented in Fig. 2B. Callosal hypoplasia was accompanied by colpocephaly (Fig. 3A) and

Table I (continued)

Patient no.	12	13	14	15	16	17	18	19	20	21	22
Age at the moment of MRI (years)	7/06	16/06	21	15/06	9	8/06	6/09	8/06	10/06	6	7/03
Sex	F	M	M	M	F	F	F	M	F	M	M
Laboratory tests radioresistant DNA synthesis *in vitro* *	**nd**	**+**	**+**	**+**	**nd**	**nd**	**nd**	**nd**	**-**	**nd**	**nd**
Clinical data microcephaly (SDS)**	-0.09	-5.72	-7.08	-5.35	-7.36	-5.79	-7.31	-7.29	-9.47	-9.00	-7.07
Mental retardation	+/-	+	++	+	+	+	+	+	++	+	N
Seizures	-	-	-	-	-	-	-	-	-	-	-
Respiratory tract disorders	-	-	-	+	+	+	+	-	+	+	+
MRI features decreased size of frontal lobes with narrow frontal horns	+	+	+	+	+	+	+	+	+	+	+
Callosal hypoplasia	+	-	-	-	-	-	-	-	-	-	+
Colpocephaly	+	-	-	-	-	-	-	-	-	-	+
Temporal horns dilatation	+	-	-	-	-	-	-	-	-	-	+
Abnormal CSF spaces	+	-	-	-	-	-	-	-	-	-	-

(**+**) present; (**-**) absent; (**nd**) not done; *tested at the Department of Clinical Genetics, Erasmus University, Rotterdam (Dr W.J. Kleijer); **head circumference deficiency expressed in standard deviation scores (compared with age-matched controls). Mental retardation: (+/-) border line intelligence or developmental quotient; (+) mild MR; (++) moderate MR; (N) normal IQ.

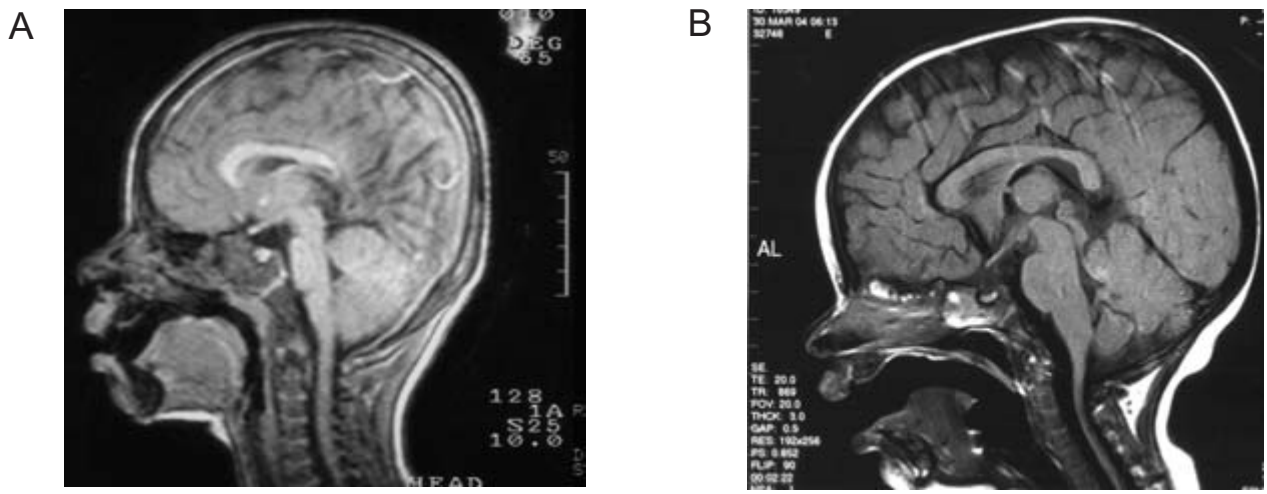

Fig. 2. (A) Patient no. 4. Sagittal T1-weighted image. Partial callosal agenesis: absence of splenium of the corpus callosum. (B) Sagittal T1-weighted image of a normal corpus callosum.

dilatation of temporal horns of the lateral ventricles (Fig. 3B). In two cases (no. 8 and 12) abnormal cerebrospinal fluid spaces communicating with the ventricular system were present (Fig. 4). In three patients lesions suspicious for malignancy were found. Of those in patient no. 10, a big enhancing lesion with edema and mass effect was found in the left occipital lobe (Fig. 5). This lesion seems to most likely represent neoplasm or abscess – no biopsy or operation has been performed. In one child (no. 21) medulloblastoma was diagnosed; the patient died. In case no. 19 enlarged lymph nodes were shown behind the mandibular ramus on the left side. Sinusitis was present in all 22 cases. In 6 patients older than 9 years we found lack of pneumatization of the sphenoid sinuses. Abnormal signal intensity within the mastoid processes and petrous pyramids, corresponding with inner ear inflammation, was observed in 12 cases.

Twenty-one patients presented with microcephaly, all but one with mental retardation. Most of them suffered from recurrent respiratory tract infections. Epilepsy was noted in three children. Twelve patients were diagnosed with malignancy, one of them with medulloblastoma. Nine patients died, and of those seven died due to a malignancy or cancer therapy complications.

There are only few reports in the literature where other brain abnormalities, apart from microcephaly, are noted in NBS patients, like hydrocephaly, occipital cyst and schizencephaly (der Kaloustian et al. 1996, Stoppa-Lyonnet et al. 1992, Taalman et al. 1989). In ad-

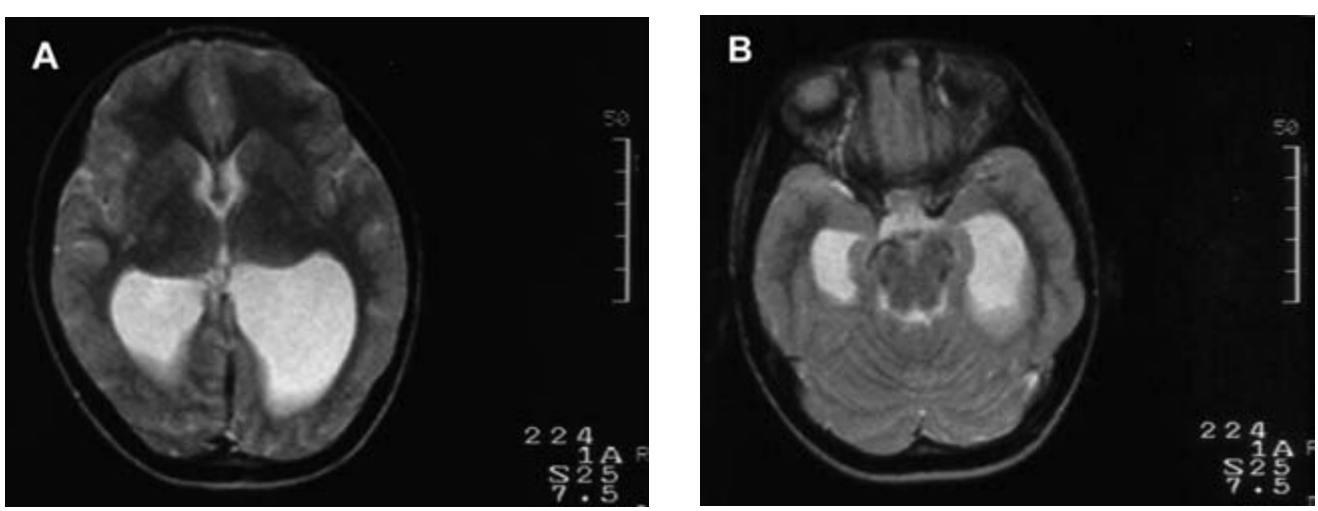

Fig. 3. Patient no. 6. Axial T2-weighted image. (A) Colpocephaly. (B) dilated temporal horns of the lateral ventricles.

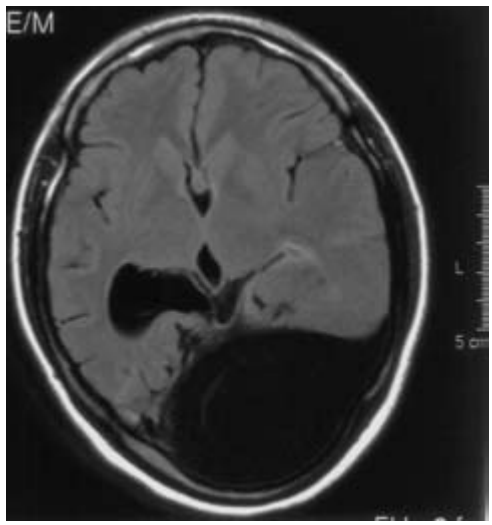

Fig. 4. Patient no. 8. Axial FLAIR image. Big cyst in the left cerebral hemisphere.

dition, autopsies performed on several patients showed brain weights less than a half in relation to age, and normal size of the cerebellum (van de Kaa et al. 1994). The available information is nonetheless very scanty, so our results cannot be related to those of other authors.

In our material, magnetic resonance imaging confirmed the clinical finding of microcephaly in twenty one patients and showed characteristic decreased size of frontal lobes of both cerebral hemispheres with very narrow frontal horns of the lateral ventricles in all twenty two cases. It seems that these findings are due to underdevelopment of the brain, of the frontal lobes in particular, followed by premature ossification of fontanels and sutures

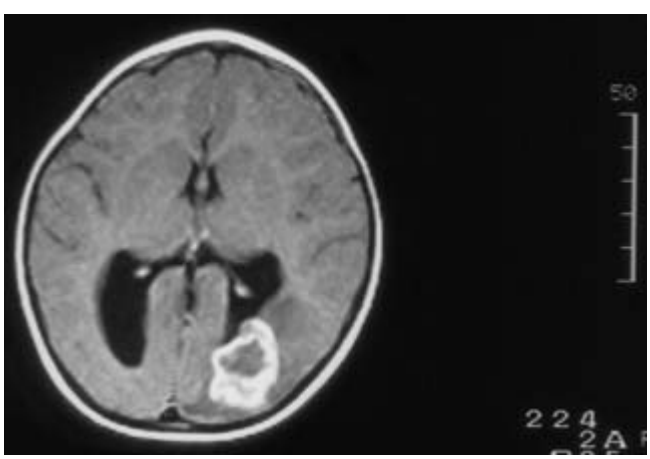

Fig. 5. Patient no. 10. Axial T1-weighted image after contrast medium administration. Pathological, contrast-enhancing mass in the left occipital lobe, with edema and mass effect – most likely representing neoplastic lesion. Colpocephaly.

since no signs of increased intracranial pressure were found.

Sinusitis was present in all of the patients as well. This finding is compatible with recurrent respiratory tract infections as a result of primary immunodeficiency. In twelve patients we found an abnormal signal in the petrous pyramids and mastoid processes indicating middle ear inflammation. NBS is similar to ataxia teleangiectasia (AT), another breakage syndrome, in which MRI finding of sinusitis and clinical observation of proneness to infections are reported (Sardanelli et al 1995). In eight patients we observed the absence of sphenoid sinus pneumatization. Only two of them were under the age of 9 years when sphenoid sinuses should be fully developed (Kossowska 1986).

In six patients with NBS, partial agenesis of the corpus callosum was found. Posterior parts of the corpus callosum (splenium and partially trunk) were missing. Partial defect always concerns the posterior part of the corpus callosum (Bull 1967) which is consistent with its normal embryologic development. This defect is also responsible for medial widening of the lateral ventricles (colpocephaly) that was present in all of the children in our material with callosal hypoplasia as well as the dilated temporal horns of the lateral ventricles. Dilatation of the temporal horns reflects maldevelopment of the limbic system that frequently accompanies callosal agenesis (Zimmerman et al. 1992). In our material, four patients (no. 4, 6, 10 and 22) seem to represent type II callosal anomaly according to Jinkins and coauthors (Jinkins et al. 1989). In two patients (no. 8 and 12) partial callosal agenesis was accompanied by abnormal cerebrospinal fluid spaces communicating with the ventricular system. In these patients callosal anomalies most likely represent type III (Barkovich and Norman 1988, Byrd et al. 1978, Parrish et al. 1979). In patient no. 8 microcephaly was much less prominent than in the remaining group. Patient no. 12 presented an atypical clinical picture with the absence of microcephaly, a hallmark of NBS (Chrzanowska et al. 2001, 2002). The presence of large intracranial fluid collections explains the lack and smaller degree of microcephaly in these patients.

Both callosal defects and limbic system anomalies do not manifest clinically in most cases, unless specific psychological tests are performed (Sperry 1968). Radiological diagnosis of callosal anomalies is usually made incidentally in patients examined because of developmental retardation or epilepsy (Wegner et al.

1999). In all but one of the presented patients mental retardation of various degree was observed. Three of six children with partial callosal agenesis suffered from epilepsy.

Like AT, Nijmegen syndrome is a disease with inherited cancer susceptibility (Meyn 1997, Shiloh 1997). Among the reported patients, malignancy was diagnosed in twelve cases; intracranial tumour (medulloblastoma) was found in the patient no. 21. In the patient no. 10, suffering from recurring severe middle ear infections, MRI revealed a pathological, contrast-enhancing lesion in the left occipital lobe. This lesion seems to represent an abscess, however, because there was no continuity of the brain lesion with the left ear, and because of the lack of meningeal enhancement after Gd-DTPA administration and of clinical manifestations of CNS infection (normal cerebrospinal fluid) a neoplastic condition should be taken into account. The diagnosis could not be verified, because the parents did not agree to surgery.

It may be speculated whether the decreased size of forebrain leading to microcephaly, as well as the other developmental abnormalities seen in NBS homozygotes are the consequence of reduced cell proliferation and increased apoptosis due to the accumulation of DNA damage. Evaluation of the nibrin knockout animals could probably help to clarify at least some functions of the defective protein.

Long term prognosis of children with Nijmegen breakage syndrome is not favourable. Premature death occurs due to either malignancy or infection. Over 50% of the registered Polish NBS patients developed malignancy, all except three of lymphoid origin.

Enhanced predisposition to malignancy in NBS patients is connected with genomic instability, as in other known chromosome instability syndromes, like ataxia-telangiectasia, Fanconi anemia and Bloom syndrome (Meyn 1997). It should be stressed that two of these diseases, AT and NBS, although clinically and genetically distinct, share cell-biological characteristics, in particular hypersensitivity to X and γ irradiation or the radiomimetic agent bleomycine (Shiloh 1997). For this reason, ionizing radiation (x-ray and computed tomography) is contraindicated in both and should be avoided as much as possible, both for therapeutic and for diagnostic reasons (van der Burgt et al. 1996, Wegner et al. 1999). When diagnostic imaging is necessary, MRI should be the method of choice in patients with Nijmegen breakage syndrome, as well as with ataxia-telangiectasia.

ACKNOWLEDGMENT

This work was supported in part by grants from the State Committee for Scientific Research of the Republic of Poland to M. Bekiesińska-Figatowska (4P05B01311) and to K.H. Chrzanowska (4P05E07314).

Barkovich AJ, Norman D (1988) Anomalies of the corpus callosum: correlation with further anomalies of the brain. ASNR 9: 493-501.

Bekiesinska-Figatowska M, Chrzanowska KH, Sikorska J, Walecki J, Krajewska-Walasek M, Jóźwiak S, Kleijer WJ (2000) Cranial MRI in the Nijmegen breakage syndrome. Neuroradiology 42: 43-47.

Bull J (1967) The corpus callosum. Clin Radiol 18: 2.

Byrd S, Harwood-Nash D, Fitz CR (1978) Computed tomography in the evaluation of encephaloceles in infants and children. J Comput Assist Tomogr 2: 81.

Carney JP, Maser RS, Olivares H, Davis EM, Le Beau M, Yates JR III, Hays L, Morgan WF, Petrini JHJ (1998) The hMre11/hRad50 protein complex and Nijmegen breakage syndrome: linkage of double-strand break repair to the cellular DNA damage response. Cell 93: 477-486.

Chrzanowska KH, Kleijer WJ, Krajewska-Walasek M, Białecka M, Gutkowska A, Goryluk-Kozakiewicz B, Michałkiewicz J, Stachowski J, Gregorek H, Łysoń-Wojciechowska G, Janowicz W, Jóźwiak S (1995) Eleven Polish patients with microcephaly, immunodeficiency, and chromosomal instability: the Nijmegen breakage syndrome. Am J Med Genet 57: 462-471.

Chrzanowska KH, Stumm M, Bekiesińska-Figatowska M, Varon R, Białecka M, Gregorek H, Michałkiewicz J, Krajewska-Walasek M, Jóźwiak S, Reis A (2001) Atypical clinical picture of the Nijmegen breakage syndrome associated with developmental abnormalities of the brain. J Med Genet 38: e3.

Chrzanowska KH, Bekiesińska-Figatowska M, Jóźwiak S (2002) Corpus callosum hypoplasia and associated brain anomalies in Nijmegen breakage syndrome. J Med Genet 39: e25.

Der Kaloustian VM, Kleijer W, Booth A, Auerbach AD, Mazer B, Elliot AM, Abish S, Usher R, Watters G, Vekemans M, Eydoux P (1996) Possible new variant of Nijmegen syndrome. Am J Med Genet 65: 21-26.

Jinkins JR, Whittemore AR, Bradley WG (1989) MR imaging of callosal and corticocallosal dysgenesis. Am J Neuroradiol 10: 330.

Kossowska E (1986) Diseases of the nose. Anatomical, physiologcal and diagnostic diversity. In: Otorhinolaryngology of the Developmental Age (Ed. E. Kossowska). PZWL, Warsaw, p. 9.

Meyn MS (1997) Chromosome instability syndromes: lessons for carcinogenesis. Curr Top Microbiol Immunol 221: 71-148.

Parrish ML, Roessman U, Levinsohn MW (1979) Agenesis of the corpus callosum: a study of the frequency of associated malformations. Ann Neurol 6: 349.

Saar K, Chrzanowska KH, Stumm M, Jung M, Nürnberg G, Wienker TF, Seemanova E, Wegner RD, Reis A, Sperling K (1997) The gene for the Ataxia-telangiectasia variant, Nijmegen breakage syndrome, maps to a 1-cM interval on chromosome 8q21. Am J Hum Genet 60: 605-610.

Sardanelli F, Parodi RC, Ottonello C, Renzetti P, Saitta S, Lignana E, Mancardi GL (1995) Cranial MRI in ataxia teleangiectasia. Neuroradiology 37: 77-82.

Shiloh Y (1997) Ataxia-telangiectasia and the Nijmegen breakage syndrome: related disorders but genes apart. Ann Rev Genet 31: 665-662.

Sperry RW (1968) Hemispheric disconnection and unity in conscious awareness. Am J Psychol 23: 723.

Stoppa-Lyonnet D, Girault D, LeDeist F, Aurias A (1992) Unusual T cell clones in a patient with Nijmegen breakage syndrome. J Med Genet 29: 136-137.

Taalman RDFM, Hustinx WJ, Weemaes CMR, Seemanova E, Schmidt A, Passarge E, Scheres JMJC (1989) Further delineation of the Nijmegen breakage syndrome. Am J Med Genet 32: 425-431.

Van de Kaa ChA, Weemaes CMR, Wessling P, Schaafsma HE, Haraldsson A, De Weger RA (1994) Postmortem findings in the Nijmegen breakage syndrome. Pediatric Pathol 14: 787-796.

Van der Burgt I, Chrzanowska KH, Smeets D, Weemaes CMR (1996) Nijmegen breakage syndrome. J Med Genet 33: 153-156.

Varon R, Vissinga Ch, Platzer M, Cerosaletti KM, Chrzanowska KH, Saar K, Beckmann G, Seemanova E, Cooper PR, Nowak NJ, Stumm M, Weemaes CMR, Gatti RA, Wilson RK, Digweed M, Rosenthal A, Sperling K, Concannon P, Reis A (1998) Nibrin, a novel DNA double-strand break repair protein, is mutated in Nijmegen breakage syndrome. Cell 93: 467-476.

Weemaes CMR, Hustinx TWJ, Scheres JMJC, van Munster PJJ, Bakkeren JAJM, Taalman RDFM (1981) A new chromosomal instability disorder: the Nijmegen breakage syndrome. Acta Paediatr Scand 70: 557-564.

Wegner RD, Chrzanowska KH, Sperling K, Stumm M (1999) Ataxia-Telangiectasia variants (Nijmegen breakage syndrome). In: Primary Immunodeficiency Diseases, a Molecular and Genetic Approach (Eds. H.D. Ochs, C.I.E. Smith and J.M. Puck). Oxford University Press, New York, Oxford, p. 324-334.

Zimmerman RA, Bilaniuk LT, Gusnard DA (1992) Pediatric cerebral anomalies. In: Magnetic Resonance Imaging (Eds. D.D. Stark and W.G. Bradley). Mosby Year Book, St. Louis, p. 1029-1056.

Received 29 January 2004, accepted 9 June 2004