

ELECTRONIC LETTER

Corpus callosum hypoplasia and associated brain anomalies in Nijmegen breakage syndrome

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We read with interest the article by Maraschio *et al*¹ on "A novel mutation and novel features in Nijmegen breakage syndrome". The authors stressed their findings of malformations not previously described in NBS patients, namely agenesis of the corpus callosum, dilatation of the ventricles, and cerebral hypotrophy. However, they seem to have overlooked our earlier report on cranial MRI findings in 10 Polish NBS patients, first presented in 1998 at the 30th Annual ESHG Meeting,² and recently published.³ Four of the 10 Polish patients described showed agenesis of the posterior parts of the corpus callosum (splenium and partial trunk). Callosal hypoplasia was accompanied by colpocephaly (widening of trigones and occipital horns) and dilatation of the temporal horns of the lateral ventricles. These anomalies of the ventricles are associated developmentally with agenesis of the corpus callosum. The enlargement of the trigones and occipital horns reflects maldevelopment of the splenium of the corpus callosum, and the widening of the temporal horns stems from failure of inversion of the hippocampus. To date, seven more of our patients have been studied by MRI, increasing the number to 17, and hypoplasia of the corpus callosum was seen in five cases altogether (~30%). In addition, in two patients from the group with the callosal defect, very large collections of cerebrospinal fluid were found. Arachnoid cysts belong to a group of congenital anomalies that are frequently associated with abnormalities of the corpus callosum. They arise as the result of an abnormal splitting of the arachnoid membrane. The presence of large collections of CSF results naturally in underdevelopment of the adjacent brain structures, owing to permanent compression, but may also change the clinical phenotype, as in the case of our patient lacking microcephaly, a hallmark of NBS.⁴ This latter patient presented unilateral preaxial polydactyly as well. In all 17 patients, a characteristic decreased size of the frontal lobes of both cerebral hemispheres with very narrow frontal horns of the lateral ventricles was observed. Frontal lobe hypoplasia seems to result from the underdevelopment of the brain, which is followed by premature closure of the fontanelles. In effect, microcephaly is observed as the major clinical sign. It is not clear whether similar findings are termed cerebral hypotrophy by Maraschio *et al*.¹

All our patients are homozygous for the 657del5 allele in exon 6,⁵ a truncating mutation of *NBS1*, and the Moroccan patient¹ is homozygous for a different allele, 900del15 in exon 8, both leading to a premature termination of nibrin. Recently Maser *et al*⁶ showed that the common *NBS1* allele (657del5) encodes a partially functional protein, detectable in LCLs but not in fibroblasts, which probably diminishes the severity of

the NBS phenotype, and is responsible for the viability of the patients. If this hypothesis is true, this should also be the case in all mutations identified to date in NBS patients, including that described by Maraschio *et al*.¹ It is suggested that in addition to the role of the *NBS1* gene product as part of a DNA DSB repair complex, it may serve further, hitherto unknown, functions during development, and may explain the pleiotropic effects observed in affected subjects. As has been discussed above, patients with different genotypes may show the same phenotype, and patients with the same phenotype may vary in phenotypic expression, as we observed in two sibs discordant for callosal hypoplasia and hydrocephalus.

We would also like to stress that it appears that the additional brain abnormalities described may be more common than expected in NBS and are probably underdiagnosed, as they are usually not manifest clinically.

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Authors' reply

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We thank Chrzanowska *et al* for their comments on our paper. In fact, their paper³ was published while ours was already in press.

Their observation on the clinical variability in patients carrying the same mutation is relevant and interesting. In support of their observations is our recent finding that the case we reported in 1986 as a "new syndrome"⁷ has now been proven to be a NBS patient, homozygous for the mutation 742ins2 in exon 7 of the *NBS1* gene. This patient is now 49 years old and in good health, while her sister died at the age of 20 as a result of lymphoma. Certainly it is still of great relevance to gather more clinical and molecular information on NBS which will help in diagnosis and genetic counselling.

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