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Structural anomalies revealed by neuroimaging studies in the brains of patients with neurofibromatosis type 1 and large deletions

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Purpose: The basis for cognitive problems in patients with neurofibromatosis type 1 (NF1) is unknown. A subset of NF1 patients with deletion of the entire NF1 gene has severe learning problems or mental retardation. We have reviewed neuroimaging studies (CT and MRI) in five such patients to determine whether structural anomalies in the brain are present and might explain the impaired cognitive function. **Methods:** Five patients with NF1 and deletion of the entire gene were identified by FISH studies. A retrospective review was conducted of CT and MRI images, as well as of data from developmental assessments. **Results:** All five patients had severe developmental impairment. None had been exposed to chemotherapy or radiation therapy. All had multiple regions of bright T2 signal intensity. Structural anomalies were seen in three of the five patients and included callosal dysgenesis in one, septum cavum vergae and pellucidum in two, mega cisterna magna in one, and Chiari I malformation with severe hydrocephalus in one patient. **Conclusion:** Individuals with NF1 and large gene deletions have an increased frequency of structural anomalies of the brain not usually seen in NF1 patients. This suggests that the mental retardation in these individuals is due, at least in part, to abnormal brain development rather than a defect in brain function due to haplosufficiency of the NF1 gene product. ***Genetics in Medicine* 1999:1(4):136–140.**

Learning disabilities occur commonly in association with neurofibromatosis type 1 (NF1),[1–5] but mental retardation occurs in fewer than 10% of affected individuals.[6,7] The mechanisms that underlie cognitive impairment in persons with NF1 are unknown. Structural anomalies, including cortical dysplasias and heterotopias, have been described in some individuals with NF1.[8] The NF1 gene is expressed in neurons,[9,10] raising the possibility of a functional defect in cortical function. Neuroimaging studies usually reveal grossly normal structures. Regions of bright T2 signal intensity are commonly seen,[11–15] but the relationship of these changes to learning disabilities is uncertain.[2,16,17]

Recently a group of NF1 patients has been described in which the NF1 gene mutation consists of a deletion of the entire NF1 gene along with unknown amounts of flanking DNA.[18–23] Individuals with such large deletions may have a distinctive phenotype, including facial dysmorphism, a large number of neurofibromas, and severe cognitive impairment. The frequency of large deletions in the NF1 population may be as high as 2–5%,[23] suggesting that they account for a high proportion of NF1 patients with mental retardation. We report here an analysis of cognitive function and neuroimaging findings in a group of NF1 patients with complete gene deletion. These patients have a high frequency of structural brain anomalies, suggesting a mechanism for mental retardation that may differ from that of the more prevalent learning disabilities in NF1.

METHODS

We retrospectively analyzed the medical records and neuroimaging examinations of six pediatric patients who were identified with deletion of the entire NF1 gene. Clinical features of patients 1, 2, and 3 (Table 1) have been described previously.[21,22] All five fulfilled diagnostic criteria for NF1, including multiple neurofibromas. The initial imaging studies included computed tomography (CT) in one patient and magnetic resonance (MR) in four patients. Subsequent follow-up MR imaging studies were obtained in all patients using a 1.5T General Electric Signa system in five patients and 1.5T Magnetom system in one patient (Siemens Medical Systems, Erlangen, Germany). Imaging parameters evaluated included assessment of abnormal structures and location, size, extent, density, intensity, and enhancement of areas of abnormal signal. Developmental assessments were obtained in the course of routine clinical care and were ascertained from chart review.

RESULTS

Results of neuroimaging studies and cognitive function are shown in Table 1. All of the patients have severe cognitive impairment. Full scale IQ scores were available for three patients and were less than 70 in each case. One other patient had a

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Table 1
Summary of clinical and neuroimaging data in NF1 patients with large deletions

Patient	Sex	Age at Initial Imaging Exam	Last Followup Imaging (years)	Hyperintense T2 Foci	Other MR and/or CT Findings	Age at Developmental Assessment (years)	Developmental Assessment	Other Clinical Information	Reference
1	male	10	18	rt cerebellum, rt basal ganglia, lt frontal white matter	none	10	PIQ 60, VIQ 75, FSIQ 66	seizure disorder treated with carbamazepine	21
2	male	7	16	lt cerebellum	callosal dysgenesis; mega cisterna magna; septum cavum pellucidum and vergae; moderate dilation of lateral ventricles	10	VIQ 77; borderline mental retardation	seizure disorder treated with carbamazepine and gabapentin	22
3	female	15	15	rt cerebellum	chiari I malformation with severe hydrocephalus	12	PIQ 45, VIQ 49		21
4	male	2	16	bilateral basal ganglia (disappeared on follow-up scan)	septum cavum pellucidum and vergae; left frontal white matter and left vertex hyperintense T2 foci ?tumor	11	PIQ 64, VIQ 73, FSIQ 66	partial complex seizures treated with carbamazepine	
5	female	2	8	bilateral cerebellar hemispheres, basal ganglia, thalami	none	6	PIQ 58, VIQ 61, FSIQ 56	Treated with ACTH for infantile spasms	

VIQ, verbal IQ; PIQ, performance IQ; FSIQ, full scale IQ.

performance IQ of 45 and a verbal IQ of 49, and the fifth had been designated as "borderline mentally retarded." None of the patients have been exposed to radiation or chemotherapy. Four of the five patients have a history of seizures. Seizures are controlled well using single anti-epileptic medication in three patients and two medications in one patient. All of the patients were found to have foci of hyperintense T2 signal (located in basal ganglia, cerebellum, and thalami). Structural brain anomalies were seen in three patients. Imaging abnormalities found include callosal dysgenesis in one (Fig. 1), septum cavum vergae and pellucidum in two (Figs. 1 and 2), mega cisterna magna in one (Fig. 1), and Chiari I malformation

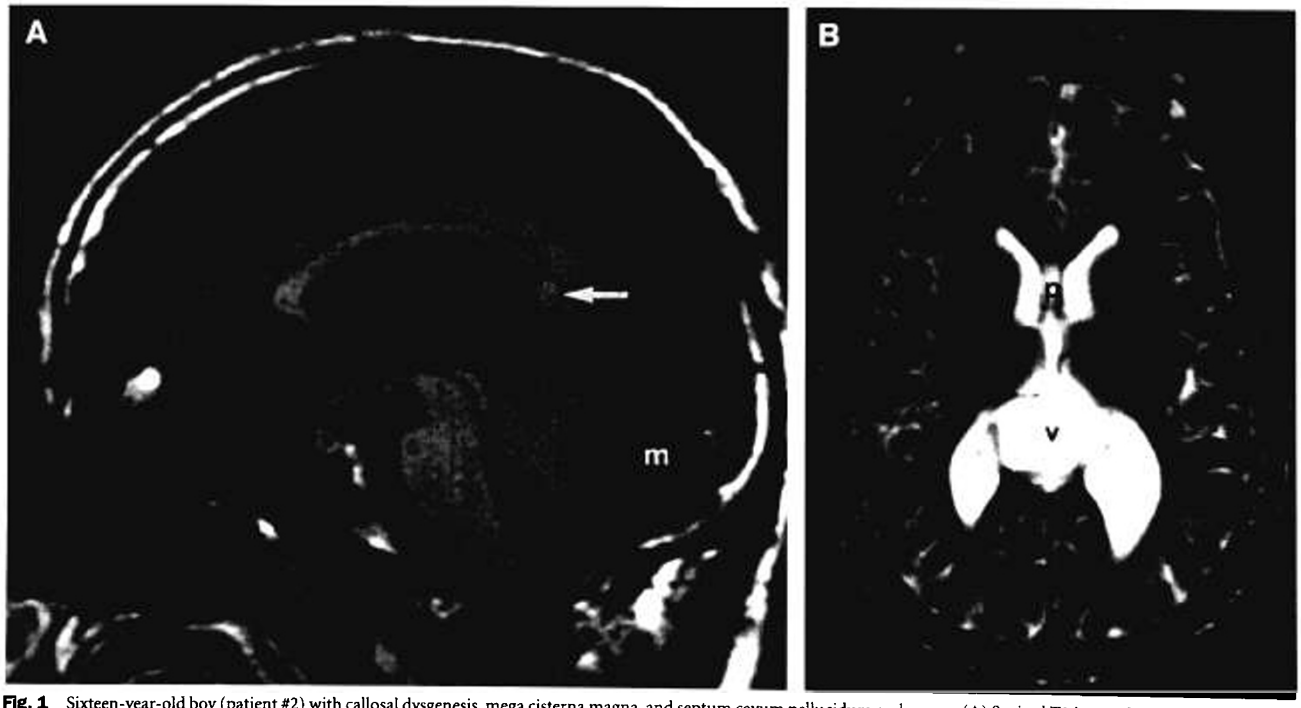

Fig. 1 Sixteen-year-old boy (patient #2) with callosal dysgenesis, mega cisterna magna, and septum cavum pellucidum and vergae. (A) Sagittal T1 image demonstrates hypoplasia of splenium and posterior body of the corpus callosum (*arrow*). In addition, there is a mega cisterna magna (m). (B) Axial T2 image demonstrates septum cavum pellucidum (p) and vergae (v) and moderate enlargement of the lateral ventricles.

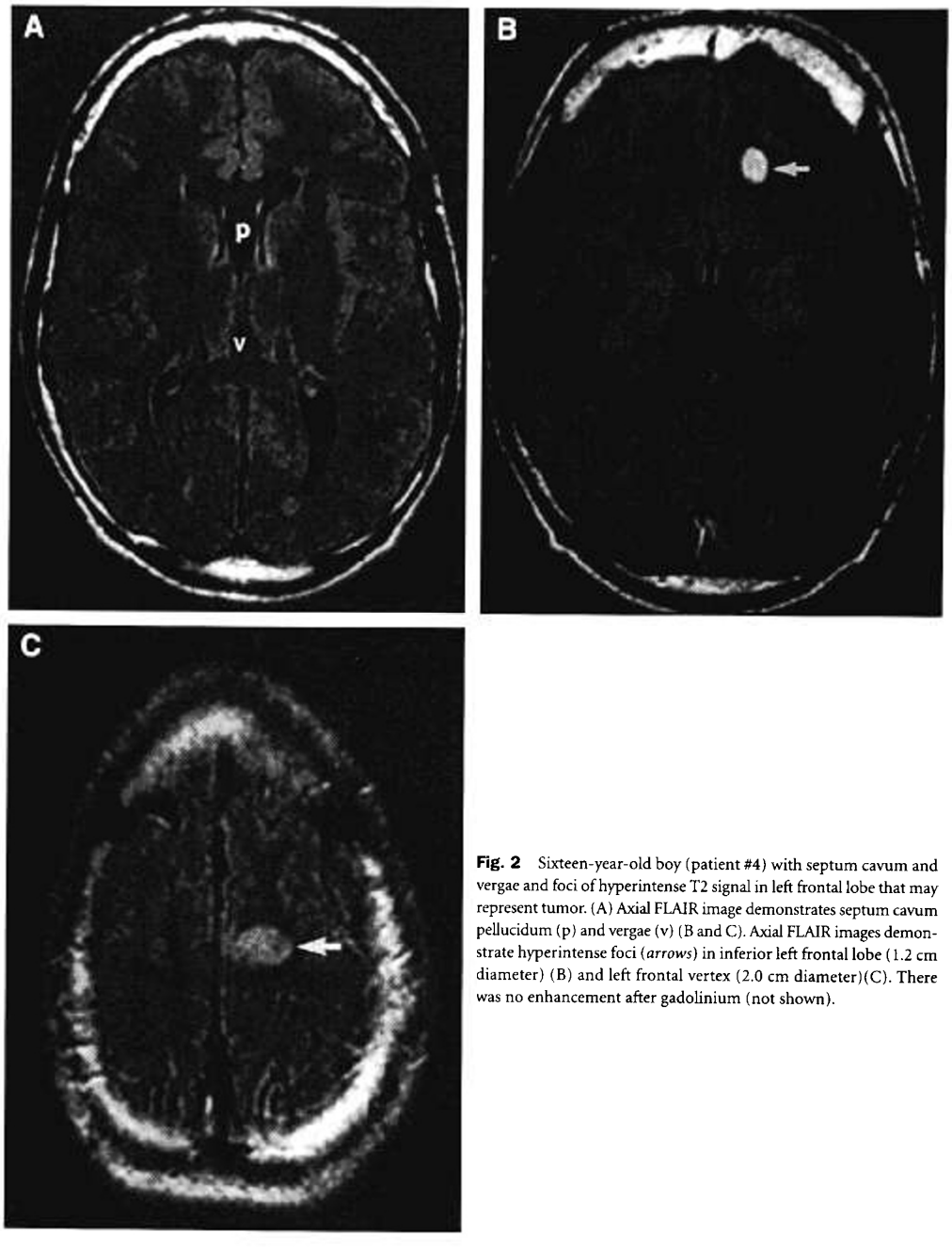

Fig. 2 Sixteen-year-old boy (patient #4) with septum cavum and vergae and foci of hyperintense T2 signal in left frontal lobe that may represent tumor. (A) Axial FLAIR image demonstrates septum cavum pellucidum (p) and vergae (v) (B and C). Axial FLAIR images demonstrate hyperintense foci (*arrows*) in inferior left frontal lobe (1.2 cm diameter) (B) and left frontal vertex (2.0 cm diameter)(C). There was no enhancement after gadolinium (not shown).

with severe hydrocephalus in one patient (Fig. 3). In one patient (#4, Fig. 2), on follow-up scanning, foci of T2 hyperintensity in the left frontal vertex and left inferior frontal lobe developed, which may represent tumor.

DISCUSSION

Most studies of the pathology of NF1 have focused on the neoplasms associated with the disorder, especially neurofibromas. Although learning disabilities and developmental delay are among the most common manifestations of the condition, there is little known about the cause of these problems. Rosman and Pearce[8] examined the brains of 10 NF1 patients, five of whom had severe cognitive impairment. They found areas of disorganized cortex and heterotopias, with more abnormalities seen in the cognitively impaired subjects. The relationship of such changes to learning disabilities or mental retardation in patients with NF1 is uncertain, however, given the relatively small number of patients studied and the lack of clear documentation of their cognitive function.

Magnetic resonance imaging studies have revealed a distinctive finding in children with NF1, consisting of foci of hyperintense T2 signal intensity.[11–15] These are not space-occupying and are typically located in the basal ganglia, internal capsule, brainstem, and cerebellum. These foci appear at age 3 years and increase in number and size until age 10 to 12 years, followed

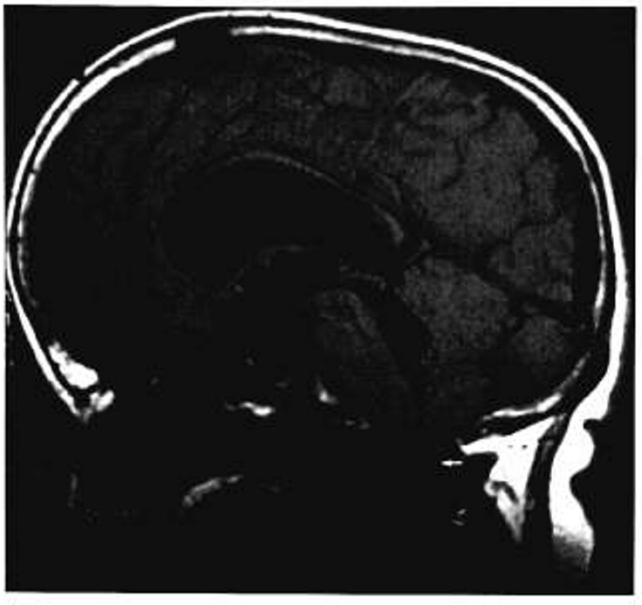

Fig. 3 Fifteen-year-old girl (patient #3) with Chiari I malformation. Sagittal T1 image demonstrates severe hydrocephalus and Chiari I malformation with cerebellar tonsils (*arrow*) 1.2 cm below the foramen magnum.

by a subsequent decrease in size.[24] There is little information regarding the neuropathological basis for these foci. One study has revealed vacuolar changes at the site of these foci, suggesting increased fluid content that may be transient.[25] The foci do not correlate with distinctive abnormalities of neurological examination, but two studies have shown that children with learning disabilities and NF1 tend to have a larger number of foci.[2,16] Other studies have failed to confirm this,[17] and in one study there was a suggestion that the presence of foci in the thalamus correlates with cognitive function.[26]

Although learning disabilities occur commonly in individuals with NF1, mental retardation affects a much smaller proportion of patients. Some of these patients appear to have deletions of the entire NF1 gene, leading to a distinctive phenotype that includes, in addition to mental retardation, the development of a large number of neurofibromas and dysmorphic facial appearance.[18–23] The reason for this severe presentation is unknown. Haploinsufficiency for the NF1 gene may play a role, or there may be deletion of contiguous genes that contribute to this phenotype. Because deletion studies have mostly been performed in the more severely affected individuals, there remains the possibility of ascertainment bias.

In the present study of five patients with NF1 deletions and severe developmental impairment, we have found a high frequency of structural abnormalities of the brain. One of our patients was found to have severe hydrocephalus, presumably due to Chiari I malformation. Hydrocephalus in individuals with NF1 may occur in association with aqueductal stenosis,[11,15,27,28] and Chiari I malformation has been reported in patients with NF1.[15] Of the other four patients, two had structural brain anomalies, including one with dysgenesis of the corpus callosum and mega cisterna magna, and septum cavum vergae and pellucidum and one with septum cavum vergae and pellucidum. These features are not commonly reported in MRI studies in patients with NF1, although it is not clear how carefully such findings have been searched for. Careful analysis for structural brain anomalies in NF1 patients with learning disabilities but without large deletions would be warranted. Cavum septum pellucidum and vergae[29–31] and mega cisterna magna[32] have been found with increased frequency in non-NF affected individuals with impaired development. Interestingly, both of our patients with these findings had seizures, as did two other deletion patients without structural anomalies. In our previous studies, seizures have been found to affect only approximately 6% of individuals with NF1[33].

These findings suggest that the mental retardation in NF1 patients with large deletions are due, at least in part, to disordered brain development. This may indicate that the NF1 gene product is necessary for normal brain development. Alternatively, the effect on development may be due to deletion of genes contiguous to NF1. This question may be resolved by MRI examination of NF1 patients with mental retardation who do not have large deletions. There is also a need for further examination of brain structure in individuals with NF1, studied with modern imaging and pathological methods and correlated with detailed assessment of cognitive function.

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References

1. Hofman KJ, Harris EL, Bryan RN, Denckla MB. Neurofibromatosis type 1: The cognitive phenotype. *J Pediatr* 1994;124:S1–S8.
2. North K, Joy P, Yuille D, Cocks N, Mobbs E, Hutchins P, McHugh K, de Silva M. Specific learning disability in children with neurofibromatosis type 1: Significance of MRI abnormalities. *Neurology* 1994;44:878–883.
3. Eldridge R, Denckla MB, Bien E, Myers S, Kaiser-Kupfer MI, Pikus A, Schlesinger SL, Parry DM, Dambrosia JM, Zasloff MA, Mulvihill JJ. Neurofibromatosis type 1 (Recklinghausen's disease). Neurologic and cognitive assessment with sibling controls. *Am J Dis Child* 1989;143:833–837.
4. Legius E, Descheemaeker MJ, Spaepen A, Casaer P, Fryns JP. Neurofibromatosis type 1 in childhood: A study of the neuropsychological profile in 45 children. *Genet Couns* 1994;5:51–60.
5. North KN, Riccardi V, Samango-Sprouse C, Ferner R, Moore B, Legius E, Ratner N, Denckla MB. Cognitive function and academic performance in neurofibromatosis 1: Consensus statement from the NF1 cognitive disorders task force. *Neurology* 1997;48:1121–1127.
6. Huson SM, Harper PS, Compston DAS. Von Recklinghausen neurofibromatosis. A clinical and population study in south-east Wales. *Brain* 1988;111:1355–1381.
7. Carey JC, Laub JM, Hall BD. Penetrance and variability in neurofibromatosis: A genetic study of 60 families. Birth Defects: Original Article Series 1979;15, No. 5B:271–281.
8. Rosman NP, Pearce J. The brain in multiple neurofibromatosis (von Recklinghausen's disease): A suggested neuropathological basis for the associated mental defect. *Brain* 1967;90:829–838.
9. Daston MM, Ratner N. Neurofibromin, a predominantly neuronal GTPase activating protein in the adult, is ubiquitously expressed during development. *Dev Dyn* 1993;195:216–226.
10. Daston MM, Scrable H, Nordlund M, Sturbaum AK, Nissen LM, Ratner N. The protein product of the neurofibromatosis type 1 gene is expressed at highest abundance in neurons, Schwann cells, and oligodendrocytes. *Neuron* 1992;8:415–428.
11. Es SV, North KN, McHugh K, Silva MD. MRI findings in children with neurofibromatosis type 1: A prospective study. *Pediatr Radiol* 1996;26:478–487.

12. Itoh T, Magnaldi S, White RM, Denckla MB, Hofman K, Naidu S, Bryan RN. Neurofibromatosis type 1: The evolution of deep gray and white matter MR abnormalities. *Am J Neuroradiol* 1994;15:1513–1519.
13. Terada H, Barkovich AJ, Edwards MS, Ciricillo SM. Evolution of high-intensity basal ganglia lesions on T1-weighted MR in neurofibromatosis type 1. *Am J Neuroradiol* 1996;17:755–760.
14. Duffner PK, Cohen ME, Seidel FG, Shucard DW. The significance of MRI abnormalities in children with neurofibromatosis. *Neurology* 1989;39:373–378.
15. Bognanno JR, Edwards MK, Lee TA, Dunn DW, Roos KL, Klatte EC. Cranial MR imaging in neurofibromatosis. *Am J Roentgenol* 1988;151:381–388.
16. Denckla MB, Hofman K, Mazzocco MM, Melhem E, Reiss AL, Bryan RN, Harris EL, Lee J, Cox CS, Schuerholz LJ. Relationship between T2-weighted hyperintensities (unidentified bright objects) and lower IQs in children with neurofibromatosis-1. *Am J Med Genet* 1996;67:98–102.
17. Ferner RE, Chaudhuri R, Bingham J, Cox T, Hughes RA. MRI in neurofibromatosis 1. The nature and evolution of increased intensity T2 weighted lesions and their relationship to intellectual impairment. *J Neurol Neurosurg Psychiatry* 1993;56:492–495.
18. Kayes LM, Riccardi VM, Burke W, Bennett RL, Stephens K. Sporadic neurofibromatosis 1, mental retardation, and dysmorphism. *J Med Genet* 1992;29:686–687.
19. Leppig KA, Kaplan P, Viskochil D, Weaver M, Ortenberg J, Stephens K. Familial neurofibromatosis 1 microdeletions: Cosegregation with distinct facial phenotype and early onset of cutaneous neurofibromata. *Am J Med Genet* 1997;73:197–204.
20. Leppig KA, Viskochil D, Neil S, Rubenstein A, Johnson VP, Zhu XL, Brothman AR, Stephens K. The detection of contiguous gene deletions at the neurofibromatosis 1 locus with fluorescence in situ hybridization. *Cytogenet Cell Genet* 1996;72:95–98.
21. Wu BL, Austin MA, Schneider GH, Boles RG, Korf BR. Deletion of the entire *NF1* gene detected by FISH: Four deletion patients associated with severe manifestations. *Am J Med Genet* 1995;59:528–535.
22. Wu BL, Schneider GH, Korf BR. Deletion of the entire *NF1* gene causing distinct manifestations in a family. *Am J Med Genet* 1997;69:98–101.
23. Upadhyaya M, Ruggieri M, Maynard J, Osborn M, Hartog C, Mudd S, Penttinen M, Cordeiro I, Ponder M, Ponder BA, Krawczak M, Cooper DN. Gross deletions of the neurofibromatosis type 1 (*NF1*) gene are predominantly of maternal origin and commonly associated with a learning disability, dysmorphic features and developmental delay. *Hum Genet* 1998;102:591–597.
24. Sevick RJ, Barkovich AJ, Edwards MSB, Koch T, Berg B, Lempert T. Evolution of white matter lesions in neurofibromatosis type 1: MR findings. *Am J Roentgenol* 1992;159:171–175.
25. DiPaolo DP, Zimmerman RA, Rorke LB, Zackai EH, Bilaniuk LT, Yachnis AT. Neurofibromatosis type 1: Pathologic substrate of high-signal-intensity foci in the brain. *Radiology* 1995;195:721–724.
26. Moore BD, Slopis JM, Schomer D, Jackson EF, Levy BM. Neuropsychological significance of areas of high signal intensity on brain MRIs of children with neurofibromatosis. *Neurology* 1996;46:1660–1668.
27. Horwich A, Riccardi VM, Franke U. Aqueductal stenosis leading to hydrocephalus: An unusual manifestation of neurofibromatosis. *Am J Med Genet* 1983;14:577–581.
28. Senveli E, Altinörs N, Kars Z, Arda N, Turker A, Cinar N, Yalniz Z. Association of von Recklinghausen's neurofibromatosis and aqueduct stenosis. *Neurosurgery* 1989;24:99–101.
29. Bodensteiner JB, Schaefer GBCJM. Cavum septum pellucidum and cavum vergae in normal and developmentally delayed populations. *J Child Neurol* 1998;13:120–121.
30. Bodensteiner JD, Shaefer GB. Wide cavum septum pellucidum: A marker of disturbed brain development. *Pediatr Neurol* 1990;6:391–394.
31. Miller ME, Kido D, Horner F. Cavum vergae: Association of neurologic abnormality and diagnosis by MRI. *Arch Neurol* 1986;43:821–823.
32. Bodensteiner JB, Gay CT, Marks WA, Hamza M, Schaefer GB. Macro cisterna magna: A marker for maldevelopment of the brain? *Pediatr Neurol* 1988;4:284–286.
33. Korf BR, Carrazana E, Holmes GL. Patterns of seizures observed in association with neurofibromatosis 1. *Epilepsia* 1993;34:616–620.