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Longitudinal Assessment of Cognition and T2-Hyperintensities in NF1: An 18-Year Study

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The developmental course of cognitive deficits in individuals with neurofibromatosis type 1 (NF1) is unclear. The objectives of this study were to determine the natural history of cognitive function and MRI T2-hyperintesities (T2H) from childhood to adulthood and to examine whether the presence of discrete T2H in childhood can predict cognitive performance in adulthood. We present cognitive and structural neuroimaging data from 18 patients with NF1 and five sibling controls assessed prospectively across an 18-year period. Longitudinal analyses revealed a significant increase in general cognitive function in patients with NF1 over the study period. Improvements were limited to individuals with discrete T2H in childhood. Patients without lesions in childhood exhibited a stable profile. The number of T2H decreased over time, particularly discrete lesions. Lesions located within the cerebral hemispheres and deep white matter were primarily stable, whereas those located in the basal ganglia, thalamus and brainstem tended to resolve. Our results support the hypothesis that resolution of T2H is accompanied by an improvement in general cognitive performance, possibly as a result of increased efficiency within white matter tracts.

Key words: neurofibromatosis type 1; longitudinal studies; magnetic resonance imaging; cognition

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INTRODUCTION

Neurofibromatosis type 1 (NF1) is one of the most common single-gene disorders to affect the human nervous system, with a birth incidence of at least 1 in 2,700 [Evans et al., 2010]. Although characterized by skin lesions, cutaneous and plexiform neurofibromas, and multisystem complications including optic pathway tumors, scoliosis, and increased risk of malignancy [Williams et al., 2009], the most common consequences of the condition in childhood are cognitive impairment and learning disability [Hyman et al., 2005]. Although the neurocognitive phenotype of NF1 is quite variable, approximately 80% of children with NF1 experience moderate to severe impairment in one or more areas of cognitive functioning, including attention, executive function, visuoperception, and language [Hyman et al., 2005; Lehtonen et al., 2012]. Cognitive and behavioral deficits manifest in a variety of ways, including academic failure due to intellectual impairment, specific and generalized learning disabilities, attention deficit-hyperactivity disorder as well as psychosocial maladjustment and poor social skills [Hyman et al., 2006; Noll et al., 2007; Lehtonen et al., 2012]. Very little is known about the natural history of cognitive function from childhood to adulthood in patients with NF1, with cross-sectional studies proving inconclusive. While some indicate an increase in cognitive functioning in children compared to adults with the condition [Riccardi and Eichner, 1986], others do not [Ferner et al., 1996]. To date, only two longitudinal studies have

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examined the natural history of cognitive deficits in individuals with NF1; one explored the growth curves of specific cognitive abilities in 19 individuals with NF1 up to adolescence [Cutting et al., 2002], while the other examined cognitive development up to late adolescence/early adulthood in 32 patients with NF1 over an eight year period [Hyman et al., 2003]. Longitudinal designs avoid some methodological limitations of cross-sectional studies, such as cohort effects, which can be misinterpreted as a change in cognitive function over time. Both studies suggested that the pattern and level of deficit remained stable over time from childhood into at least adolescence. Considering full brain maturation does not occur until early adulthood [Giedd et al., 1999], it is important to longitudinally examine the natural history of cognitive function in individuals with NF1 from child to adulthood.

NF1 is also associated with focal areas of high intensity on T2-weighted MRI (T2H); lesions that typically occur in 60–80% of children with NF1 [Gill et al., 2006; Payne et al., 2010]. T2H commonly occur in the basal ganglia, cerebellum, brainstem, thalamus, and subcortical white matter and are thought to represent areas of dysmyelination or increased fluid within the myelin sheath. While the number, size, and intensity of T2H decrease with age, this is limited to those occurring within the basal ganglia, thalamus, and brainstem [Hyman et al., 2003; Gill et al., 2006]. Although studies have not reached consensus regarding the relationship between the presence or number of T2H and cognitive impairment, there is evidence to suggest that T2H, particularly in the thalamus, represent a significant risk for cognitive impairment [Denckla et al., 1996; Moore et al., 1996; Goh et al., 2004; Hyman et al., 2007; Chabernaud et al., 2009].

Only one longitudinal study examined the natural history of cognitive functioning and T2H from childhood into adulthood [Hyman et al., 2003]. Patients with NF1 (mean age 12.6 years) and 11 unaffected siblings were prospectively followed over 8 years. The current study extends these data by adding a third time-point, 10 years after the second assessment. We had three aims: (1) to determine whether cognitive function is stable in individuals with NF1 over an 18 year period, (2) to track changes in the number and location of T2H over the last ten years, and (3) to determine whether the presence of discrete T2H in childhood predicts cognitive performance in adulthood.

MATERIALS AND METHODS

Study participants were original members of a cohort consisting of 40 NF1 patients and 14 sibling controls recruited in 1992 from the multidisciplinary Neurogenetics Clinic at The Children's Hospital at Westmead, Sydney, Australia. All participants with NF1 had a clinical diagnosis of NF1. The original recruitment procedures and selection criteria are published elsewhere [North et al., 1994; Hyman et al., 2003]. For the current study, eighteen NF1 patients (6 males, 12 females) were successfully recruited from the original cohort [Hyman et al., 2003]. Demographic details are presented in Table I. The presence, number, and type of T2H were analyzed in 17/18 patients. MRI was not undertaken in one patient because she was breastfeeding; a contraindication for use of contrast as prescribed by our standard MRI protocol. Cognitive data were analyzed in 17/18 patients, with data from an additional patient excluded due to identification of a right cerebellar juvenile pilocytic astrocytoma (WHO Grade 1). Of the 22 patients from the original cohort not recruited; 1 had died, 1 developed a left frontal meningioma (removed in 2007), 7 refused to participate (two gave no reason, five lived interstate/overseas) and 13 could not be located. Of the 14 original controls, 5 were successfully recruited (2 males, 3 females); 5 could not be located, 4 refused to participate.

TABLE I. Mean Years of Age and Age Ranges of NF1 (n = 18) and Control Participants (n = 5) at Each Assessment Time-Point (TP)

	NF1	Control
	M (SD); range	M (SD); range
TP1 1992	12.4 (2.5); 8.0–16.8	12.0 (2.3); 8.9–15.2
TP2 2000	20.1 (2.6); 15.1–25.4	19.4 (2.4); 15.8–22.3
TP3 2010	29.4 (2.3); 25.0–33.5	28.8 (1.9); 26.3–30.7

Detailed history and medical examination was performed on all NF1 participants, the results of which are published elsewhere [Oates et al., 2013]. For the current study, participants were individually assessed on the Wechsler adult intelligence scale 3rd edition (WAIS-III) [Wechsler, 1997]. Although full scale IQ (FSIQ), verbal IQ (VIQ) and performance IQ (PIQ) from the WAIS-III are reported, only FSIQ was analyzed to reduce the type I error rate. Participants with NF1 also underwent a cranial MRI on a 1.5 Tesla GE Signa HDxt magnet system. Scanning protocols for this and earlier time-points are reported elsewhere [Hyman et al., 2003].

The location and type (diffuse vs. discrete) of T2H were independently assessed by two experienced pediatric radiologists (KP and NW), who were blinded to the medical and cognitive history. Grading criteria have been described elsewhere [Gill et al., 2006]. KP and NW also re-examined each participants' second time-point scan using the same assessment criteria, enabling direct comparison of T2H across time-points. The study was approved by The Children's Hospital at Westmead Human Research Ethics Committee (08/CHW/74) and written informed consent was obtained from all participants.

RESULTS

Shapiro Wilk and Kolmogorov Smirnov tests were used to assess the normality of the data. Given the cognitive data were not normally distributed, median and interquartile ranges (IQR) have been reported. Median IQ scores across the three time-points are presented in Table II. Friedman test indicated a significant difference between FSIQ scores over time for the NF1 group, indicating IQ improved with age in individuals with NF1 ($P = 0.02$). Mann–Whitney U test indicated that while the FSIQ of the NF1 group was significantly poorer than controls at the first time-point ($P = 0.05$), this difference was no longer significant at time-point 2 ($P = 0.14$) or 3 ($P = 0.45$). FSIQ was stable over time for controls ($P = 0.76$).

In order to understand the impact T2H in childhood may have on the natural history of FSIQ, the NF1 group was split into those with (T2H+; n = 10) or without (T2H−; n = 6) discrete T2H in 1992 (see Table III). While FSIQ of the T2H+ group significantly improved over time ($P = 0.01$), the T2H− group remained stable

TABLE II. Median IQ Scores (Interquartile Range) Across All Time Points for NF1 and Control Participants

	NF1			Control		
Year	1992	2000	2010	1992	2000	2010
FSIQ	98 (13)	100 (18)	107 (17)	108 (19)	110 (18)	110 (17)
VIQ	96 (13)	101 (17)	105 (18)	103 (18)	112 (16)	107 (19)
PIQ	100 (16)	98 (18)	107 (17)	114 (20)	111 (20)	109 (18)

($P = 0.89$). FSIQ of the T2H+ group was significantly poorer than the T2H− group at the first time-point ($P = 0.02$) but there were no group differences at time-point 2 ($P = 0.16$) or 3 ($P = 0.22$). Reliable change statistics indicated that FSIQ of 6/10 (60%) individuals in the T2H+ group significantly improved over the 18-year study period and 4/10 remained stable [Jacobson and Truax, 1991]. Of the individuals in the T2H− group, the FSIQ of 5/6 remained stable (83%) while 1/6 (17%) significantly reduced.

Examples of discrete and diffuse T2H and their change over time can be seen in Figure 1. Figure 2 shows the number and location of T2H in 2000 and 2010. The total number of T2H decreased over the past 10 years from 76 to 49. Greatest reductions were observed in subcortical regions, such as the basal ganglia, brainstem, and thalamus. At least one discrete T2H was present in 62% of participants with NF1 at time-point 2; this had reduced to 37% of the NF1 sample by time-point 3. There was a marked reduction in the prevalence of discrete lesions between time-points 2 and 3. While 14% became diffuse, 49% completely resolved (Fig. 3a). Lesions identified as diffuse at time-point 2 tended to persist over time, with only 21% completely resolved by time-point 3 (Fig. 3b). T2H that remained in 2010 were mostly located within temporal lobe white matter. The vast majority of these were diffuse; only two were discrete. Previously identified lesions within the temporal lobe white matter persisted over time in all but one patient, in whom all three diffuse lesions resolved. There were three new discrete lesions in two patients identified in 2010; one in the splenium and two in right temporal lobe white matter.

DISCUSSION

The objective of this study was to extend our previous longitudinal research into the natural history of cognition and T2H in individuals with NF1 by adding a third time-point. Over the 18-year study period, we found a significant increase in the cognitive function of patients with NF1. Improvements were limited to individuals with T2H in childhood; patients without childhood lesions exhibited a stable profile. These data suggest that while the presence of T2H may predict reduced cognitive performance in childhood, their presence in childhood does not predict cognitive function in adulthood. These results provide the first direct evidence of a relationship between T2H status in childhood and cognitive changes in later life. That is, as the number of discrete T2H decrease, there is an accompanied improvement in general cognitive performance. This relationship is intriguing and given that T2H are hypothesized to represent abnormalities of myelination [Sevick et al., 1992], our data suggests that resolution (or partial resolution) of these lesions may result in increased white matter efficiency, significant enough to produce a functional improvement in IQ. Patients without T2H in childhood exhibited stable cognitive performance, presumably because they had no lesions to resolve.

These findings are in keeping with cross-sectional evidence of an improvement in cognition between childhood and adulthood [Riccardi and Eichner, 1986]. They are also somewhat consistent with previously published longitudinal data on this cohort. Hyman et al. [2003] reported that while this cohort, as a whole, did not demonstrate a significant increase in cognitive performance at the second time-point (2000), when the NF1 group was split into three subgroups based on age (average ages of 9, 12, and 15 years in 1992), there was a significant increase among older patients in the sample (who were an average age of 23 years in 2000). Despite the number of T2H decreasing for the younger groups, there was no corresponding cognitive improvement at the second time-point. A possible explanation of this pattern is a lag between the resolution of T2H as observed on MRI and lesion resolution at the microstructural level; both of which are necessary for improvement in cognition. It may not be until patients reach their early 20s that microstructural/histological resolution occurs to the degree allowing observable improvement in cognitive function. This hypothesis is strengthened by evidence that abnormal microstructural white matter changes persist in regions that once contained T2H which have since resolved [Ferraz-Filho et al., 2012]. It is important to note that our data appear to argue against a critical time period after which T2H resolution cannot result in cognitive improvement.

TABLE III. Median IQ Scores (Interquartile Range) Across All Time Points for Individuals With NF1 With or Without Discrete T2H in 1992

	NF1 T2H+			NF1 T2H−		
Year	1992	2000	2010	1992	2000	2010
FSIQ	93 (16)	100 (20)	106 (16)	103 (14)	105 (19)	106 (18)
VIQ	94 (11)	102 (16)	105 (17)	103 (18)	109 (21)	106 (15)
PIQ	98 (19)	100 (14)	105 (13)	102 (11)	107 (17)	109 (21)

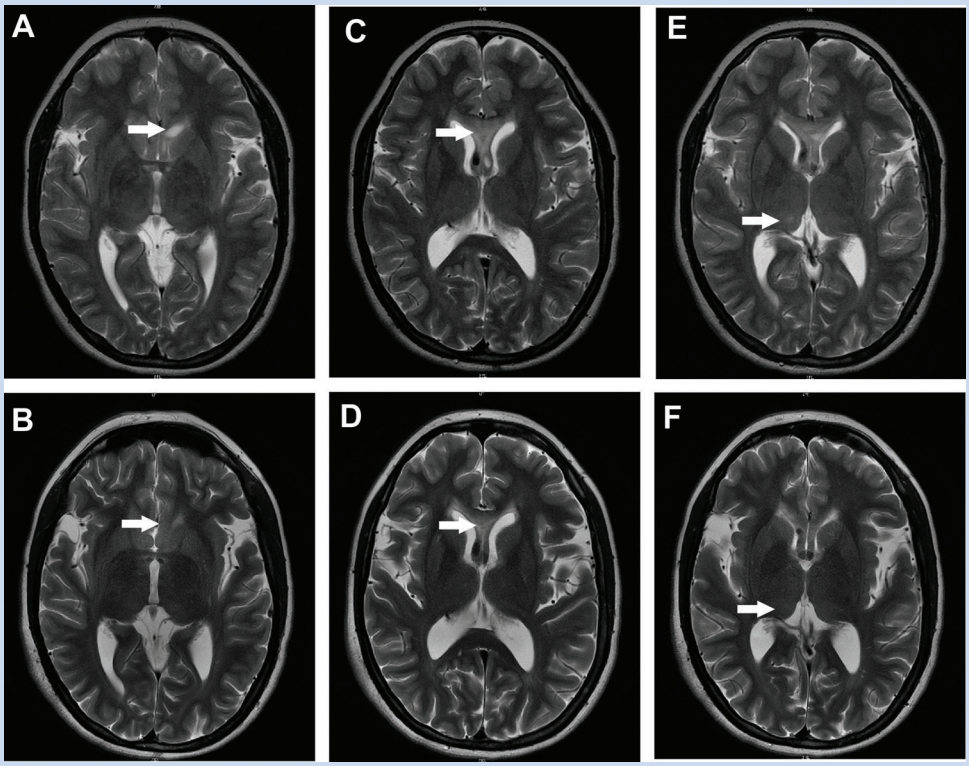

FIG. 1. A series of T2 weighted MRI images from the same individual from 1999 (A, C, E), and 2009 (B, D, F). A: Discrete T2H in the left frontal region (indicated by white arrow), which had completely resolved by 2009 (B). C: Diffuse triangle-shaped region of hyperintensity in the genu of the corpus callosum (white arrow), which was much less extensive and less prominent in the 2009 image (D). E: Diffuse lesion in the right thalamus (white arrow), which had resolved by 2009 (F).

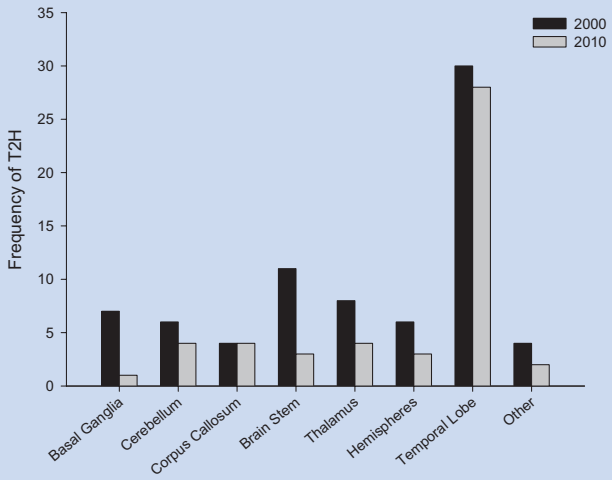

FIG. 2. Changes in prevalence of T2H from 2000 to 2010 by location.

Significant reductions in the number and intensity of T2H continued from 2000 to 2010, consistent with the hypothesis that these NF1 lesions tend to resolve over time [Gill et al., 2006]. The total number of lesions reduced by 35%. While there were equal numbers of discrete and diffuse lesions in 2000, over 60% of discrete lesions had resolved or transformed into diffuse lesions by 2010. Diffuse lesions were more likely to be stable, with only 21% resolving. Apart from one patient, lesions within the cerebral cortex were stable over the study period. The three new lesions were located within temporal lobe white matter or deep white matter. Our data continue to differentiate the developmental trajectory of lesions found within the cerebral hemispheres and deep white matter (stable) to those in the basal ganglia, thalamus and brainstem (resolve) [Hyman et al., 2003]. This suggests that the underlying pathology of cerebral lesions may differ from those in subcortical tissue.

It is important to consider that the findings of the current study are limited by the sample size and should be considered preliminary. The reduced power of our sample restricted the analyses that could be performed, particularly with regard to examining relationships between T2H location and cognitive performance. The current study provides a platform for future research into the progression of cognitive functioning in NF1. A large prospective

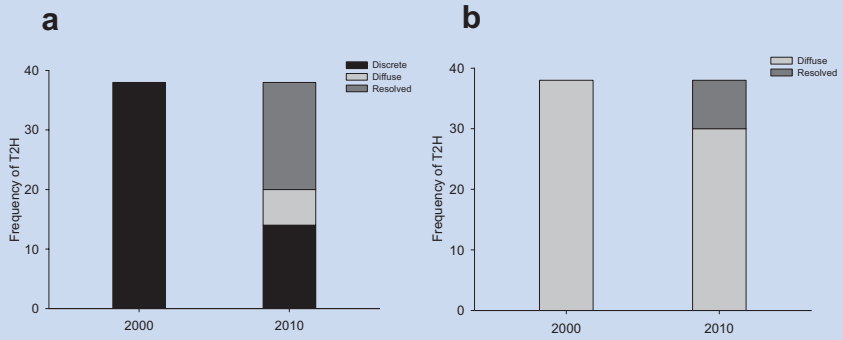

FIG. 3. Evolution of lesions that were identified as (a) Discrete and (b) Diffuse at the 2000 assessment. Note that 3a does not include the three new discrete lesions identified in 2010.

longitudinal study is now required, spanning childhood to adulthood, utilizing structural neuroimaging (including diffusion tensor sequences) and a comprehensive neurocognitive battery at each time-point to confirm and extend these findings.

REFERENCES

Chabernaud C, Sirinelli D, Barbier C, Cottier J-P, Sembely C, Giraudeau B, Deseille-Turlotte G, Lorette G, Barthez M-A, Castelnau P. 2009. Thalamo-striatal T2-weighted hyperintensities (unidentified bright objects) correlate with cognitive impairments in neurofibromatosis type 1. Dev Neuropsychol 34:736–748.

Cutting LE, Huang GH, Zeger S, Koth CW, Thompson RE, Denckla MB. 2002. Growth curve analyses of neuropsychological profiles in children with neurofibromatosis type 1: Specific cognitive tests remain "spared" and "impaired" over time. J Int Neuropsych Soc 8:838–846.

Denckla MB, Hofman KJ, Mazzocco MM, Melhem E, Reiss AL, Bryan RN, Harris EL, Cox CS, Schuerholz LJ. 1996. Relationship between T2-weighted hyperintensities (unidentified bright objects) and lower IQs in children with neurofibromatosis-1. Am J Med Genet 67:98–102.

Evans DG, Howard E, Giblin C, Clancy T, Spencer H, Huson SM, Lalloo F. 2010. Birth incidence and prevalence of tumor-prone syndromes: Estimates from a UK family genetic register service. Am J Med Genet Part A 152A:327–332.

Ferner R, Hughes RAC, Wenman J. 1996. Intellectual impairment in neurofibromatosis type 1. J Neurol Sci 138:125–133.

Ferraz-Filho JRL, José da Rocha A, Muniz MP, Souza AS, Goloni-Bertollo EM, Pavarino-Bertelli EC. 2012. Unidentified bright objects in neurofibromatosis type 1: Conventional MRI in the follow-up and correlation of microstructural lesions on diffusion tensor images. Eur J Paediatr Neurol 16:42–47.

Giedd JN, Blumenthal J, Jeffries NO, Castellanos FX, Liu H, Zijdenbos A, Paus T, Evans AC, Rapoport JL. 1999. Brain development during childhood and adolescence: A longitudinal MRI study. Nat Neurosci 2:861–863.

Gill DS, Hyman SL, Steinberg A, North KN. 2006. Age-related findings on MRI in neurofibromatosis type 1. Pediatr Radiol 36:1048–1056.

Goh WH, Khong PL, Leung CSY, Wong VCN. 2004. T2-weighted hyperintensities (unidentified bright objects) in children with neurofibromatosis type 1: Their impact on cognitive function. J Child Neurol 19:853–858.

Hyman SL, Gill DS, Shores EA, Steinberg A, Joy P, Gibikote SV, North KN. 2003. Natural history of cognitive deficits and their relationship to MRI T2-hyperintensities in NF1. Neurology 60:1139–1145.

Hyman SL, Gill DS, Shores EA, Steinberg A, North KN. 2007. T2 hyperintensities in children with neurofibromatosis type 1 and their relationship to cognitive functioning. J Neurol Neurosurg Psychiatry 78:1088–1091.

Hyman SL, Shores EA, North KN. 2005. The nature and frequency of cognitive deficits in children with neurofibromatosis type 1. Neurology 65:1037–1044.

Hyman SL, Shores EA, North KN. 2006. Learning disabilities in children with neurofibromatosis type 1: Subtypes, cognitive profile, and attention-deficit-hyperactivity disorder. Dev Med Child Neurol 48:973–977.

Jacobson NS, Truax P. 1991. Clinical significance: A statistical approach to defining meaningful change in psychotherapy-research. J Consult Clin Psychol 59:12–19.

Lehtonen A, Howie E, Trump D, Huson SM. 2012. Behaviour in children with neurofibromatosis type 1: Cognition, executive function, attention, emotion, and social competence. Dev Med Child Neurol 55:111–125.

Moore BD, Slopis JM, Schomer D, Jackson EF, Levy BM. 1996. Neuropsychological significance of areas of high signal intensity on brain MRIs of children with neurofibromatosis. Neurology 46:1660–1668.

Noll RB, Reiter-Purtill J, Moore BD, Schorry EK, Lovell AM, Vannatta K, Gerhardt CA. 2007. Social, emotional, and behavioral functioning of children with NF1. Am J Med Genet Part A 143A:2261–2273.

North K, Joy P, Yuille D, Cocks N, Mobbs E, Hutchins P, McHugh K, de Silva M. 1994. Specific learning disability in children with neurofibromatosis type 1: significance of MRI abnormalities. Neurology 44:878–883.

Oates EC, Payne JM, Foster SL, Clarke NF, North KN. 2013. Young Australian adults with NF1 have poor access to health care, high complication rates, and limited disease knowledge. Am J Med Genet Part A 161:659–666.

Payne JM, Moharir MD, Webster R, North KN. 2010. Brain structure and function in neurofibromatosis type 1: Current concepts and future directions. J Neurol Neurosurg Psychiatry 81:304–309.

Riccardi VM, Eichner J. 1986. Neurofibromatosis. Phenotype, natural history and pathogenesis. Baltimore: John Hopkins University Press.

Sevick RJ, Barkovich AJ, Edwards MCB, Koch T, Berg B, Lempert T. 1992. Evolution of white matter lesions in neurofibromatosis type 1: MR findings. Am J Roentgenol 159:171–175.

Wechsler D. 1997. Wechsler adult intelligence scale. 3rd edition. New York: Psychological Corporation.

Williams VC, Lucas J, Babcock MA, Gutmann D, Korf B, Maria BL. 2009. Neurofibromatosis type 1 revisited. Pediatrics 123:124–133.