NEUROFIBROMATOSIS TYPE 2 AND RELATED DISORDERS

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Introduction

Neurofibromatosis 1 (NF1), neurofibromatosis 2 (NF2), and schwannomatosis comprise the neurofibromatoses. NF2 (MIM 101000) is an autosomal dominant neurogenetic disorder characterized by the presence of schwannomas, meningiomas, ependymomas, and ocular abnormalities. For many years, NF2 was confounded with the more common syndrome NF1 from which it derives its name. In the 1980's, these two disorders were finally differentiated when tumor studies and linkage analysis localized the genes to different chromosomes. The introduction of gadolinium contrast for MRI scanning in June, 1988, significantly improved detection of small tumors, particularly near the skull base. The cloning of the NF2 gene in 1993 ushered in a period of intense research activity in which mutational analysis was used to establish genotype-phenotype correlations and to study the role of *NF2* inactivation in NF2-associated tumors. More recently, a consortium of hospitals completed the Natural History of Neurofibromatosis Type 2 Study, which prospectively tracked the growth of tumors in patients with NF2. Looking forward, the primary goal of the research community is to identify an effective treatments for patients with NF2.

Historical perspective and terminology

Initial clinical description

The first clinical description of NF2 dates to 1822 when the Scottish surgeon J. H. Wishart presented an unusual case to the Royal College of Surgeons of Edinburgh. He described a 21-year-old man with amblyopia and macrocephaly who became deaf at age 19 (Wishart 1822). The patient subsequently developed seizures and was found to have a tumor that protruded from the occipital eminence. An attempt to resect the lesion was unsuccessful and the patient died from a wound infection. At autopsy, multiple tumors arising from the skull base were identified. His description of a severely affected patient led to the denomination of Wishart subtype for NF2 with an early and severe clinical course.

Delineation of NF2 from NF1

In 1882, von Recklinghausen published his landmark monograph on the disease that would later become known as NF1 (Crump 1981). In the following years, patients with skin and spinal cord tumors were diagnosed with neurofibromatosis. As early as 1903, clinicians began to distinguish NF2 from NF1. In that year, Henneberg and Koch described a distinct form of neurofibromatosis that involved the eighth cranial nerves bilaterally but spared the skin. They introduced the term "central" neurofibromatosis to distinguish these patients from those with the more common "peripheral" neurofibromatosis described by von Recklinhausen. The distinction between central and peripheral neurofibromatosis was further confounded after publication of *Tumors of the nervus acusticus and the syndrome of the cerebellopontile angle* by Harvey Cushing in 1917. In it, he writes "when the acoustic tumors are bilateral they are very apt to be merely a local expression of a more widespread process (central or general neurofibromatosis) of the von Recklinghausen type". (Cushing 1917). Subsequently, NF2 was seen as manifestation of von Recklinghausen's disease rather than as an independent entity. Given Cushing's lofty

reputation, it took almost seven decades for the two diseases to be fully separated again. The unique identity of these conditions was confirmed in the 1980's when linkage analysis localized NF1 to chromosome 17 and NF2 to chromosome 22.

Genetic inheritance

The heritability of neurofibromatosis was established around 1900 but detailed information about the transmission of NF2 was not available for many years. In 1930, Gardner and Frazier described a family with 38 affected family members over five generations. They noted that affected members had early onset deafness and balance problems and often died prematurely (Gardner and Frazier 1930). Autopsy was performed on two affected family members and revealed bilateral cerebellopontine angle (CPA) tumors. They observed that the condition was transmitted with an autosomal dominant pattern with 50% of individuals at risk developing the condition. No evidence of incomplete penetrance or sex specificity was noted (Gardner and Frazier 1930). Ultimately, Gardner published on 97 members of the index family and noted that the majority of patients had a relatively mild clinical course (Young et al. 1970). His description of a mildly affected family led to the denomination of Gardner subtype for NF2 with a mild clinical course.

Incidence and prevalence

The present knowledge about the prevalence and incidence of NF2 comes from large population-based studies in the United Kingdom (UK) and Finland. In a recent study from the UK, the annual incidence of NF2 was estimated at 1 in 1,312,000, the birth incidence at 1 in 24,844, and the prevalence at 1.14 per 100,000 persons (Evans et al. 2005). In the Finnish study, the annual age-adjusted incidence of NF2 was estimated at 1 per 2,004,000 and the birth incidence at 1 in 87,410 (Antinheimo et al. 2000). The differences in estimates between the two studies may be explained by differences in ascertainment of subjects. For example, in the UK study, subjects were ascertained through practitioners and through a tumor registry, and asymptomatic relatives were screened by cranial CT or MRI scans. In the Finnish study, subjects were identified only by pathology reports in medical records and in a cancer registry.

Clinical manifestations

Presentation of NF2

Several large studies have documented the clinical and radiographic findings of patients with NF2. The results are summarized in Table 1 and will be discussed further below. In patients with NF2, the average age of onset of symptoms is between 17 and 21 and typically precedes a formal diagnosis by 5–8 years. Deafness, tinnitus, or imbalance are the most common presenting symptoms, occurring in up to 50% of patients, and reflect dysfunction of the eighth cranial nerve. Less commonly, patients present with symptoms related to other CNS tumors (20%), painful or growing skin lesions (up to 25%), or visual changes (13%) (Evans et al. 1992, Parry et al. 1994, LoRusso et al. 1995). About 10% of patients are asymptomatic at diagnosis and are detected through screening of first-degree relatives of known cases.

Pediatric presentation of NF2

Pediatric patients comprise about 16–18% of cases in large databases in Europe and the U.S. (Evans et al. 1999a, Nunes and MacCollin 2003, Ruggieri et al. 2005). In these patients, dysfunction of the eighth cranial nerve (hearing loss, tinnitus, or imbalance) is less frequent than in adults and occurs in 8–40% of children diagnosed with NF2 (Mautner et al. 1993, Evans et al. 1999a, Nunes and MacCollin 2003, Ruggieri et al. 2005) (Figs. 1–6). Other presenting symptoms include cranial (Fig. 2A) or peripheral nerve dysfunction (Figs. 2B–C), myelopathy (Figs. 3A–C), seizures, skin tumors (Fig. 4A), café-au-lait macules, and juvenile cataracts (Fig. 4B) (Mautner et al. 1993, Evans et al. 1999a, Nunes and MacCollin 2003, Ruggieri et al. 2005, Bosch et al. 2006b). Stroke has also been reported (Ng et al.

Table 1. Clinical findings in individuals with NF2

Reference	All subjects			Pediatric subjects		
	Evans et al. (1992)	Parry et al. (1994)	Mautner et al. (1996)	Mautner et al. (1993)	Nunes et al. (2003)	Ruggieri et al. (2005)
Number cases	120	63	48	9	12	24
Number families	75	32				5
Sporadic cases	45	17				19
Mean age at onset (years)	21.2	20.3	17	5.9	6.5	5.5
Mean age deafness (years)	24.3					
Cranial nerve schwannoma (%)		24	48	33	83	90
Intracranial meningiomas (%)	45	49	58	22	83	60
Spinal tumors (%)	26	67	90	78	75	88
Skin tumors (%)	68	68	64	56	67	92
>10 skin tumors (%)	10	14.5				0
Optic sheath meningioma (%)	4.1	4.8	8	0		0
Lens opacities (%)	38	81	63	44	75	36
Retinal hamartoma		9		0	42	24
Astrocytoma (%)	4.1	1.6	14.6	0	0	24
Ependymoma (%)	2.5	3.2	6.3	11	25	12
Peripheral neuropathy (%)	6	2		0	0	42
Any CAL macules (%)	43	47.5	42	0		100
Lisch nodules (%)	4	3		22	0	

2008). Due to this variable presentation of NF2 in children, a high index of suspicion is required for diagnosis of a patient without a known family history.

Skin abnormalities

Skin abnormalitites are a common feature of NF2. Skin tumors occur in 60–70% of patients with NF2 and is the presenting sign in 12% of pediatric patients and 27% of adult patients (Mautner et al. 1993, 1997; Evans et al. 1999a; Nunes and MacCollin 2003; Ruggieri et al. 2005). Two presentations are most common: a well-circumscribed, raised area that is slightly hyperpigmented and may contain hair follicles, or a subcutaneous, spherical mass that occur along peripheral nerves (Fig. 4A) (Mautner et al. 1997). Histologically, the vast majority of these tumors are schwannomas although a minority are neurofibromas (Mautner et al. 1997). Up to 20% of patients have greater than 10 skin tumors on presentation; these patients are more likely to have a severe clinical course of their disease (Mautner et al. 1997). Skin tumors are more likely to be a cause for evaluation in children than in adults (Evans et al. 1999a, Nunes and MacCollin 2003).

Café-au-lait (CAL) macules are hyperpigmented skin lesions with well-demarcated borders. CAL macules are found in genetically normal individuals as well as in patients with genetic conditions such as NF1. Increased numbers (>6) of CAL macules are a diagnostic criterion for NF1 and are found in >90% of patients with NF1. CAL macules are present in up to 40% of adult patients with NF2, although fewer than 5% of patients have more than 4 CAL macules on close inspection (Mautner et al. 1997). Interestingly, in one series, CAL macules were reported in 100% of pediatric patients, with 8% having greater than four macules (Ruggieri et al. 2005). The reason for this discrepancy is not known but may reflect decreased visibility of CAL macules in adults or particular attention to skin examination in these subjects.

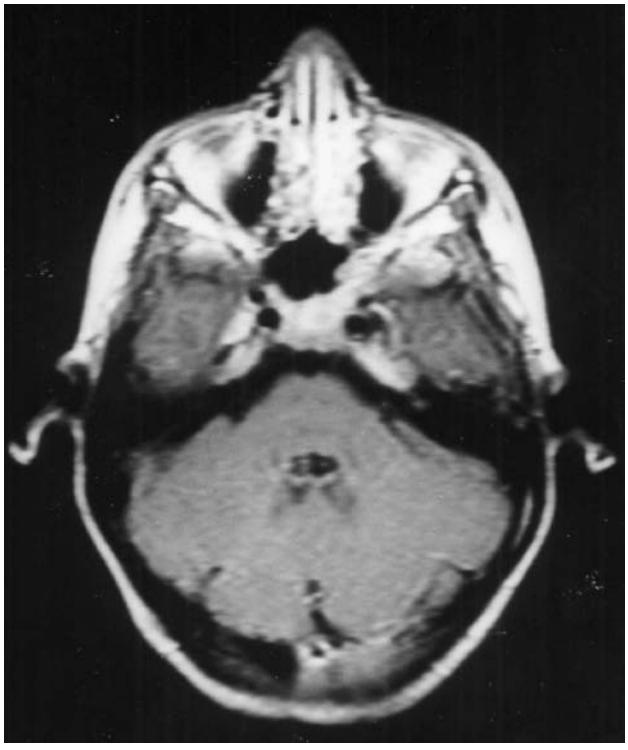


Fig. 1. Axial T1-weighted brain MR image in a child with NF2 showing no intracranial lesion [reprinted with permission from Ruggieri et al. 2005].

Ophthalmic abnormalities

The association between posterior lens opacities (ie, cataracts) and NF2 was first reported in 1969 and later confirmed in the 1980's (Lee and Abbott 1969, Kaiser-Kupfer et al. 1989). Lens opacities occur in 70–90% of patients with NF2 (Bouzas et al. 1993a, b; Ragge et al. 1995). Less than 40% of opacities are cortical in location; the remainder involves the posterior capsular (involving the posterior capsule) region, the posterior subcapsular (anterior to and not involving the posterior capsule) region, or a combination of these regions (Fig. 4B). Only a minority of patients experience diminished visual acuity (20/40 or less) or increased sensitivity to glare. Surgical intervention for lens opacities is rarely necessary. Genotype-phenotype correlations suggest that patients with mosaic disease and those with large deletions have a significantly reduced risk of developing cataracts compared to patients with classic NF2 (Baser et al. 2003).

Epiretinal membranes have been detected in 80% of patients undergoing comprehensive ophthalmologic testing and in 100% of eyes examined dur-

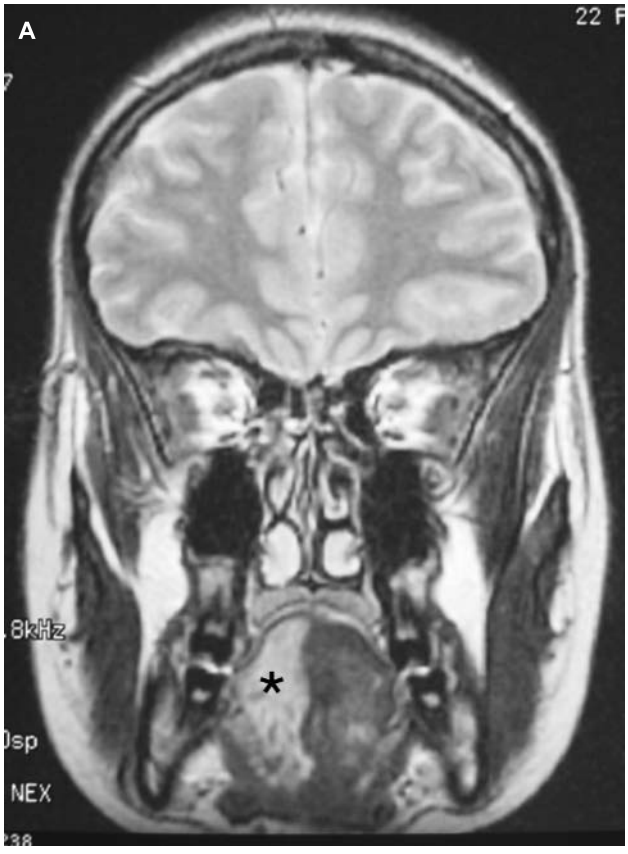
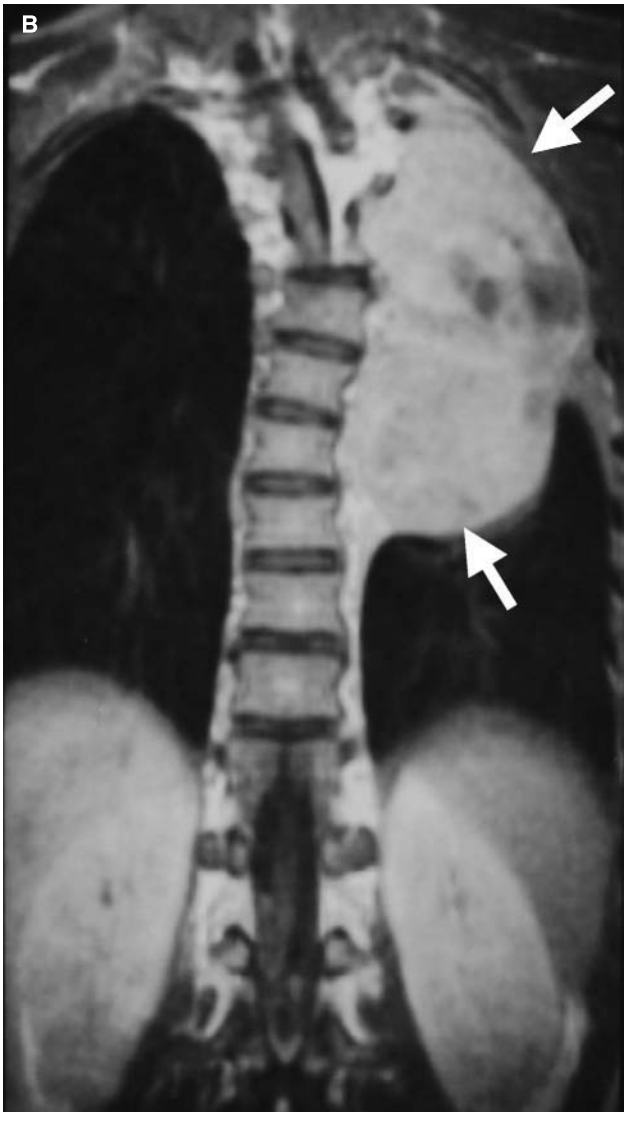


Fig. 2. (**A**) Coronal T1-weighted head MR image demonstrating right tongue atrophy (asterisk) secondary to XII cranial nerve schwannoma – this girl's first NF2 manifestations were two lumps in the right hand misdiagnosed as plexiform neurofibromas the diagnosis being postponed until tongue atrophy and brain MR scanning showed multiple cranial schwannomas and meningiomas; (**B**) coronal T1-weighted spinal MR image of the same child in (Fig. 3B) showing a large paravertebral plexiform schwannoma extending from C1 to T1 which distorts the spine and protrudes in the left thoracic wall (white arrows); (**C**) coronal CT scan images showing two large pelvic masses (white arrows) occupying the entire pelvic region. These masses, which were palpable at physical examination and dislocated the urinary bladder, led the general pediatrician to refer the child to a pediatric oncologist and in turn to the suspicion of "a form of NF" because of café-au-lait spots – the diagnosis of NF2 was then clinically raised because of the presence of typical NF2-plaques and confirmed at MRI because of a bilateral vestibular schwannomas and spinal meningiomas and schwannomas [reprinted with permission from Ruggieri et al. 2005].



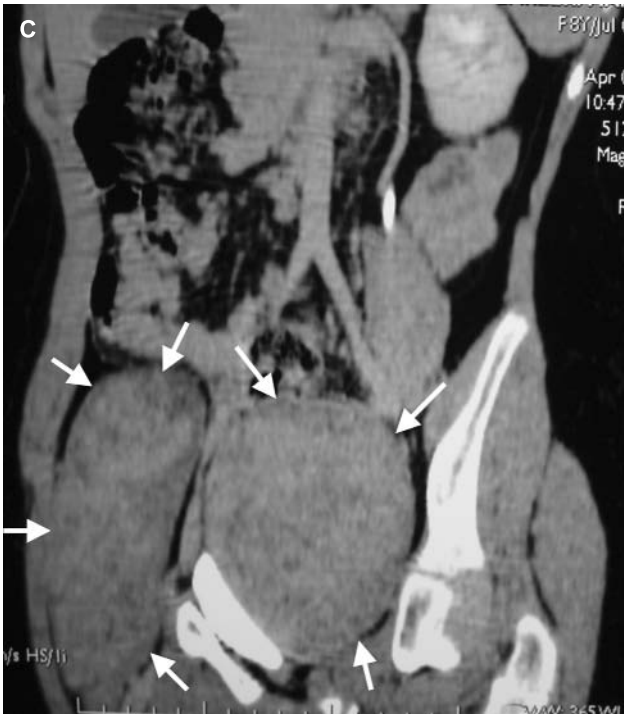


Fig. 2. (Continued)

ing autopsy (Meyers et al. 1995, Chan et al. 2002). Pigment epithelial or retinal hamartomas are benign growths that are located in the peripapillary, macular, or peripheral retinal areas. These hamartomas are derivatives of glial, vascular, and/or melanocytic tissue within the retina and occur in up to 25% of patients with NF2. In a minority of patients, retinal or pigment epithelial hamartomas can cause decreased visual acuity, amblyopia, or strabismus in the affected eye (Bouzas et al. 1993b, Ragge et al. 1995). Epiretinal membranes and pigment epithelial/retinal hamartomas are associated with inactivation of chromosome 22 and loss of expression of merlin (Chan et al. 2002).

Optic sheath meningiomas occur in 4–8% of patients with NF2 and are a disproportionate cause of decreased visual acuity (Evans et al. 1992; Parry et al. 1994; LoRusso et al. 1995; Ragge et al. 1995; Bosch et al. 2006a, b). Compression of the optic nerve can produce optic atrophy. Lisch nodules occur in less than 5% of patients with NF2 and, if present, typically occur as a single nodule (Evans et al. 1992, Parry et al. 1994).

Exposure keratopathy is an important cause of visual impairment in patients with NF2. This condition usually arises after surgery for vestibular schwannomas and is caused by dysfunction of trigeminal (sensory) and facial (motor) nerves. Diligent care can reduce the incidence of exposure keratopathy and close follow-up by an experienced ophthalmologist is recommended.

Nervous system abnormalities

Cranial schwannomas

Vestibular schwannomas (VS) are the hallmark of NF2. A diagnosis of NF2 should be reconsidered in patients who do not have evidence of bilateral VS on a high resolution MRI scan. Unilateral hearing loss, tinnitus, and/or imbalance are common initial presentation for adult patients with NF2. These symptoms typically occur during the third decade of life but can begin as early as the first decade (Fig. 6A, B) or as late as the seventh decade (Evans et al. 1992, Nunes and MacCollin 2003). Vestibular schwannomas typically develop within the internal auditory canal and grow centrally along the nerve. If tumors are not removed surgically, they can indent the pons and lead to compression of the brainstem (Fig. 8). As tumors expand into the cerebellopontine angle, patients may experience other cranial nerve deficits such as facial weakness, dysphagia, pyramidal tract signs (eg, weakness and spasticity), or headache due to obstructive hydrocephalus. The growth rate of vestibular schwannomas is highly variable. In patients with NF2, the growth rate of VS, expressed as a time to tumor doubling, ranges from 11 days to 70 years with a median value of 13.6 years (Mautner et al. 2002, Baser et al. 2002b). In general, the growth rate of VS is greater in younger patients than in older patients (Mautner et al. 2002, Baser et al. 2002b). Growth rates for left- and right-sided tumors are highly correlated even when tumors are different sizes. This finding supports the hypothesis that tumor initiation is a stochastic (ie, random) event (Mautner et al. 2002, Baser et al. 2002b). Intrafamilial variability in growth rates is high even

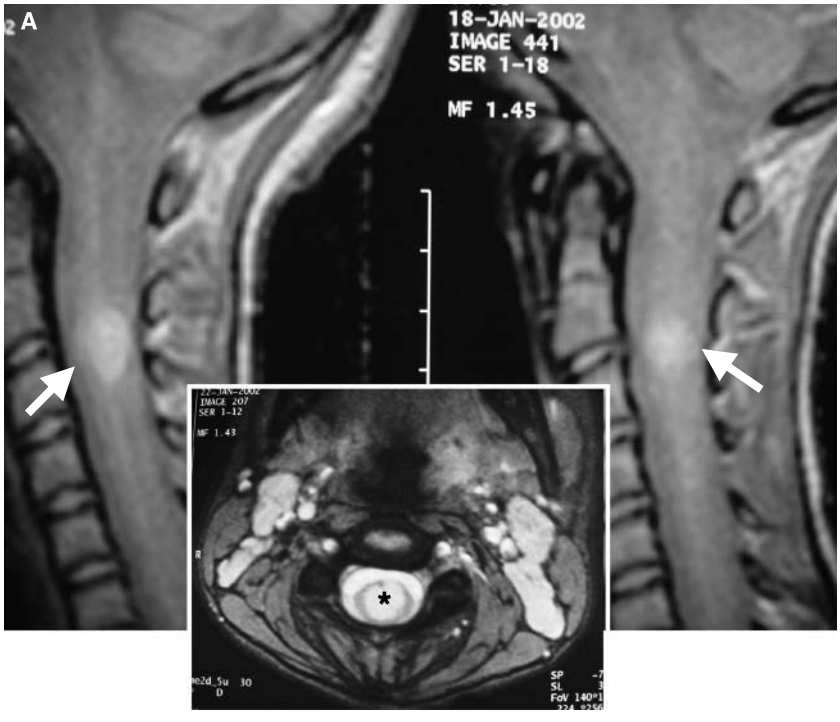
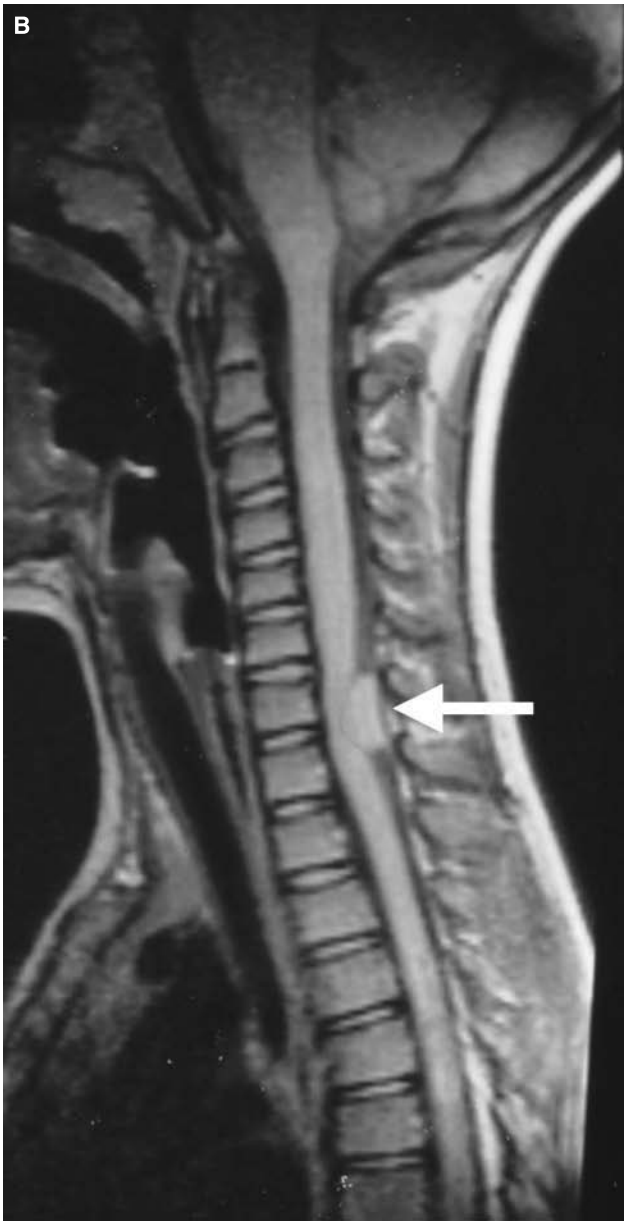


Fig. 3. (**A**) Sagittal T1-weighted spinal MR image, obtained at age 7 years in the same child with NF2 in Fig. 1, showing a cervical high signal lesion (histologically an astrocytoma) (white arrows); the window in **A** shows an axial T2-weighted image of the same lesion shown in the sagittal planes (asterisk); (**B**) Sagittal T1-weighted spinal MR images showing a cervical meningioma indenting the spinal cord (white arrow) in a child with NF2; (**C**) Sagittal FLAIR (fluid attenuated inverse recovery) image from an MRI scan of cervical spine demonstrating multiple intramedullary lesions consistent with ependymomas [Figs. 3A, 3B reprinted with permission from Ruggieri et al. 2005].



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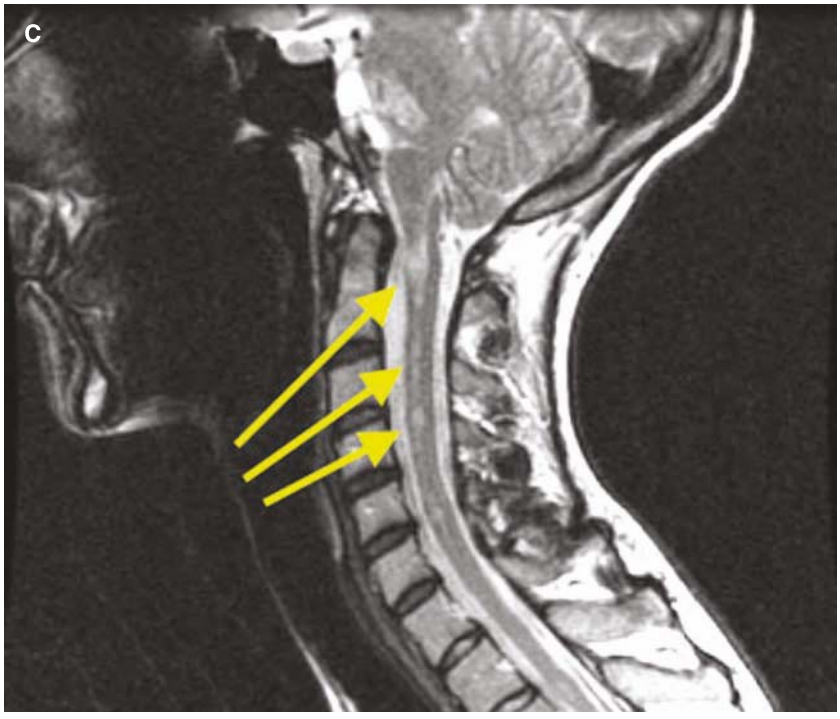
among individuals with similar disease severity. For this reason, caution should be used in extrapolating the clinical behavior of VS even among members of the same family that share a common mutation (Baser et al. 2002b).

Twenty-five to 50% of patients with NF2 have schwannomas of non-vestibular cranial nerves (Parry et al. 1994, LoRusso et al. 1995). The prevalence among pediatric patients is roughly the same as among adults (Mautner et al. 1993, Nunes and MacCollin 2003). The trigeminal nerve is the most commonly involved (about 30% of cases) but almost any nerve can be affected (Fig. 2A) (LoRusso et al. 1995). Neurologic symptoms related to non-vestibular schwannomas are uncommon and the tumors are usually detected incidentally during cranial imaging for vestibular schwannomas or meningiomas.

Schwannomas in patients with NF2 are almost always histologically benign. Compared with unilateral sporadic tumors, NF2-related VS more frequently demonstrate a lobular growth pattern, Verocay bodies, high cellularity, and meningeal cell proliferation or meningioma cells (Sobel 1993). In addition, NF2-related schwannomas are more likely to have embedded nerves than are sporadic schwannomas. Schwannomas typically grow eccentric to the nerve and cause symptoms by compression rather than by direct invasion. For this reason, surgical resection is possible in some cases. Gross and microscopic analysis of autopsy specimens suggests that Schwann cell tumorlets are present in patients with NF2. Histologically, tumorlets are expansions of nerve fibers and for many years, it was unclear whether they represented a benign form of Schwann cell hyperplasia or an initial step in schwannoma formation (Fig. 5A–C). Loss of heterozygosity analysis of tumorlets and schwannomas in a patient with germline frameshift mutation confirms that tumorlets represent an early phase of schwannomagenesis (Stemmer-Rachamimov et al. 1998).

Intracranial meningiomas

About half of all patients with NF2 develop intracranial meningiomas (Evans et al. 1992, Parry et al. 1994, LoRusso et al. 1995). These tumors can arise from any surface lined by dura including the skull base, falx, and convexity (Fig. 8A). Occasionally, they can arise from arachnoid cells located in the choroids plexus of the lateral ventricle (Figs. 8A–B). Meningiomas associated with NF2 are almost universally benign histologically. These tumors are a common cause of death among patients with NF2



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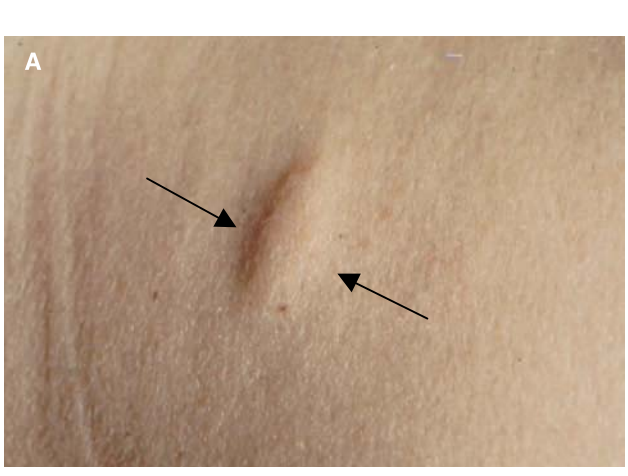


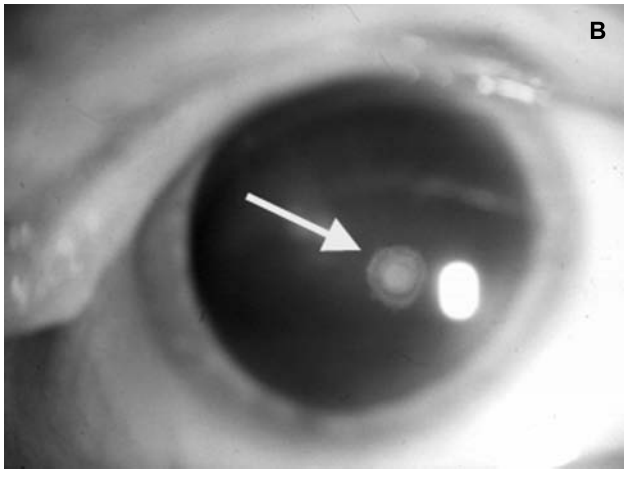


Fig. 4. (**A**) Typical cutaneous NF2 plaque (black arrows); (**B**) Photograph of a subcapsular lenticular opacity (arrow) in a patient with NF2. The reflection from the flash is lateral to the opacity (Courtesy of Dr. Simmons Lessell, Massachusetts Eye and Ear Infirmary, Boston, MA).

as reflected by a 2.5-fold increase in the relative risk of death in these patients compared with those lacking intracranial meningiomas (Baser et al. 2002a). Symptoms from intracranial meningiomas are generally related to local mass effect and include headache, seizures, weakness, sensory abnormalities, and obstructive hydrocephalus.

Spinal cord schwannomas and meningiomas

Spinal cord tumors are common in patients with NF2. If the entire spinal cord is imaged, between 67 and 90% of patients will have evidence of at least one spinal tumor (Figs. 3B–C). Schwannomas and meningiomas typically present as intradural ex-

tramedullary lesions. In general, patients have more than one spinal tumor. For example, in a series of 27 patients, a total of 177 schwannomas (88%) and 24 meningiomas (12%) were identified. The mean number of schwannomas and meningiomas per patient was 6.8 and 2.6, respectively (Patronas et al. 2001). Despite the heavy burden of spine tumors in these patients, slightly less than 50% of patients showed radiographic evidence of cord compression (Patronas et al. 2001). Progression is more likely in tumors >5 mm in size than in those smaller in size.

Spinal cord gliomas: ependymomas and astrocytomas

Spinal ependymomas and astrocytomas in patients with NF2 present as intramedullary spinal cord lesions and occur in up to 53% of patients (Mautner et al. 1995, Patronas et al. 2001). Two-thirds of patients with ependymomas have multiple tumors. The cervicomedullary junction or cervical spine is most commonly involved (Fig. 3C) (63–82%) followed by the thoracic spine (36–44%) (Mautner et al.

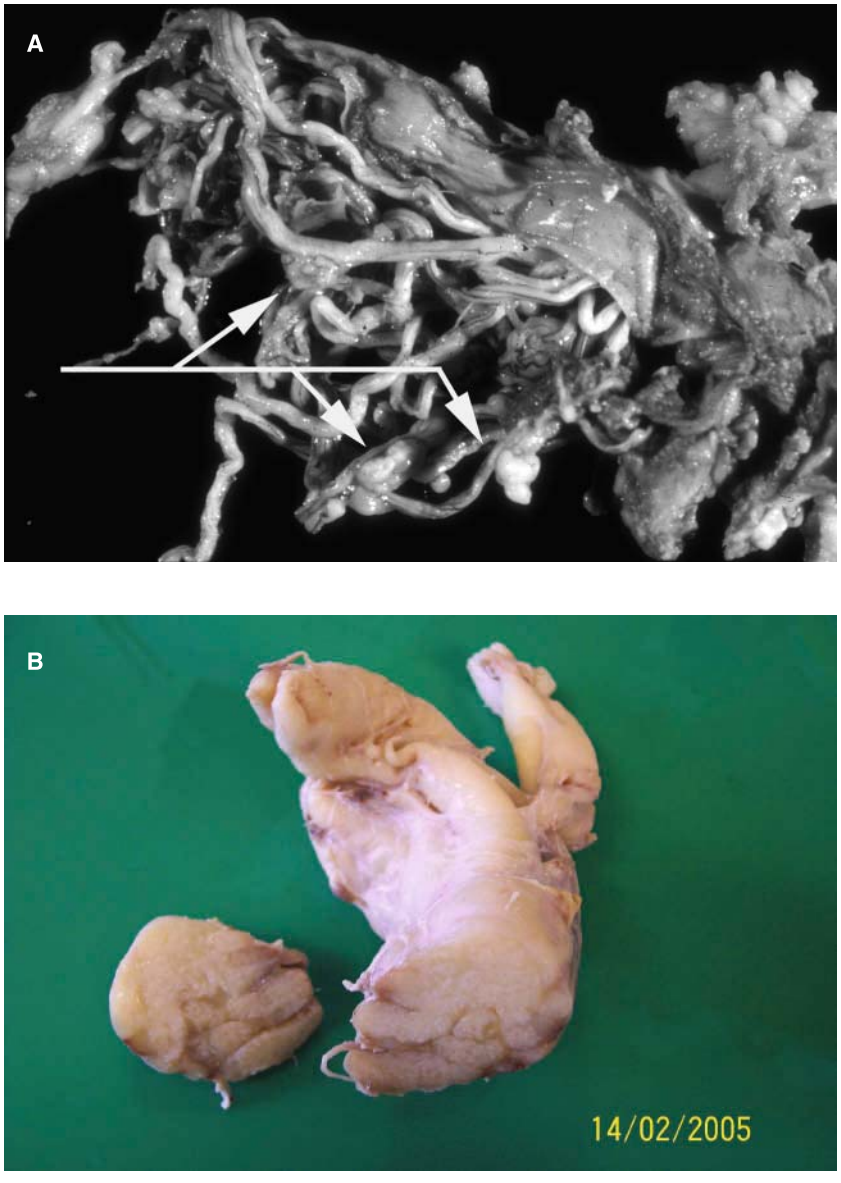
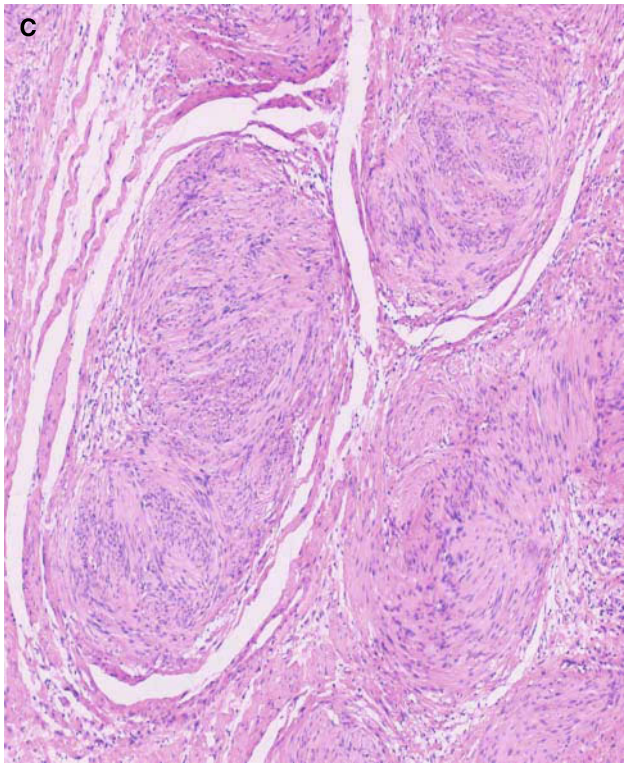


Fig. 5. (**A**) Gross pathologic specimen of a cauda equima from a patient with NF2. Arrows denote schwannoma tumorlets (Courtesy of Dr. Anat Stemmer-Rachamimov, Massachusetts General Hospital, Boston, MA); (**B**) Gross pathologic specimen of a plexiform schwannoma removed in the NF2 girl shown in Fig. 3C; (**C**) histological appearance of the plexiform schwannoma in Fig. 5B (see text for explanation) (courtesy of G. Magro, Institute of Anatomic pathology, University of Caternia).



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1995, Patronas et al. 2001). The brain and lumbar spine are rarely involved. Radiographic evidence of tumor progression occurs in less than 10% of patients and progressive neurologic dysfunction requiring surgical intervention occurs in 12–20% of patients (Patronas et al. 2001) (F. Nunes, personal communication).

Since surgery is rarely necessary for intramedullary spinal cord tumors, little pathologic data is available. In three small series comprising 13 patients, ependymomas were most common (69%), followed by astrocytomas (15%) and intramedullary schwannomas (15%) (Mautner et al. 1995, Lee et al. 1996, Patronas et al. 2001).

Neuromuscular abnormalities

Peripheral neuropathy and monomelic atrophy have been reported in patients with NF2. In a clinical study of 100 patients with NF2 in the UK, 3% of patients demonstrated clinical findings consistent with a symmetric sensorimotor neuropathy which was confirmed by electrodiagnostic testing, and an additional 3% had clinical evidence of asymmetric sensorimotor neuropathy (Evans et al. 1992). In a similar study performed in the US, 1 in 63 patients (1.6%) with NF2 had clinical and EMG findings consistent with a peripheral neuropathy (Parry et al. 1994). A dedicated study of peripheral neuropathy in patients with NF2 suggests that this condition may be underrecognized. Fifteen patients with NF2 (mean age at evaluation 37.9 years) were investigated by clinical exam, electrophysiology, and sural biopsy (Sperfeld et al. 2002). Seven of 15 patients (47%) showed evidence for a motor and/or sensory distal periphal neuropathy. Neuropathy was mild in four, moderate in two, and severe in one. Ten of 15 patients had evidence of symmetric polyneuropathy by nerve conduction and EMG of which seven were axonal, one demyelinating, and two mixed axonal-demyelinating (Sperfeld et al. 2002). MRI scans revealed no evidence of tumors that could explain the clinical or electrophyiological findings.

More recently, focal amyotrophy has been documented in patients with NF2. Although the prevalence of this finding has not been firmly established, wasting of a single limb was noted in 4% of patients in a registry of NF2 patients in the UK (Evans et al. 1992). Detailed examination of four different patients by MRI and electrodiagnostic studies excluded compression of proximal nerves or roots by tumors as a cause (Trivedi et al. 2000). The etiology of focal amyotrophy in NF2 is not known but is thought to arise from neurofibromatous changes in peripheral nerves (Trivedi et al. 2000).

Other intracranial lesions

Intracranial calcifications on CT scans not due to tumors and somewhat similar to those seen in tuberous sclerosis have been reported in a number of NF2 patients (Fig. 9A) (reviewed in Friedman et al. 1999, Short et al. 1994). In addition, either periventricular (Fig. 9B) or cortical (Fig. 9C) high signal lesions resembling **cortical dysplasia** can be recorded. The latter finding has been reported in association to NF2

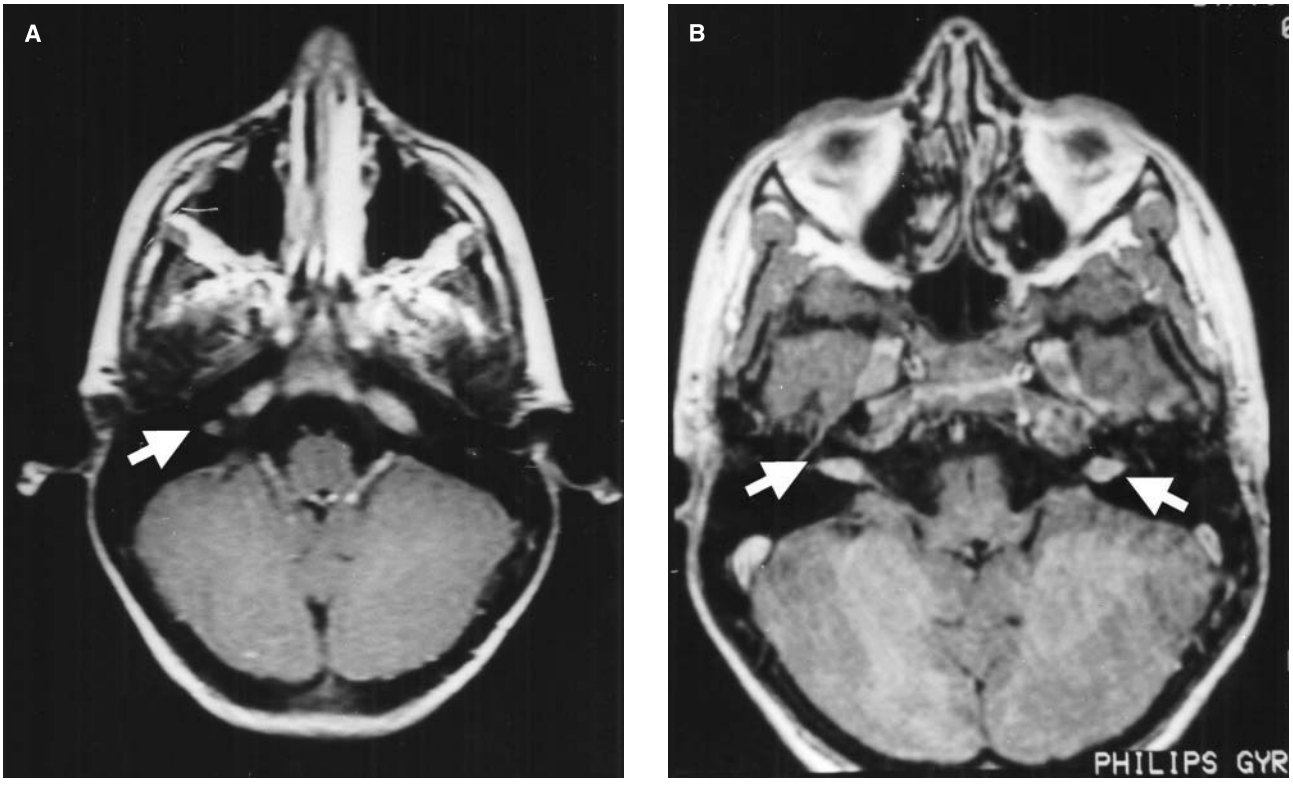

Fig. 6. (**A–B**) axial T2-weighted brain MR images showing the progression of a vestibular schwannoma from a single (right) lesion (**A**, white arrow) to a bilateral middle sized lesions (**B**, white arrows).

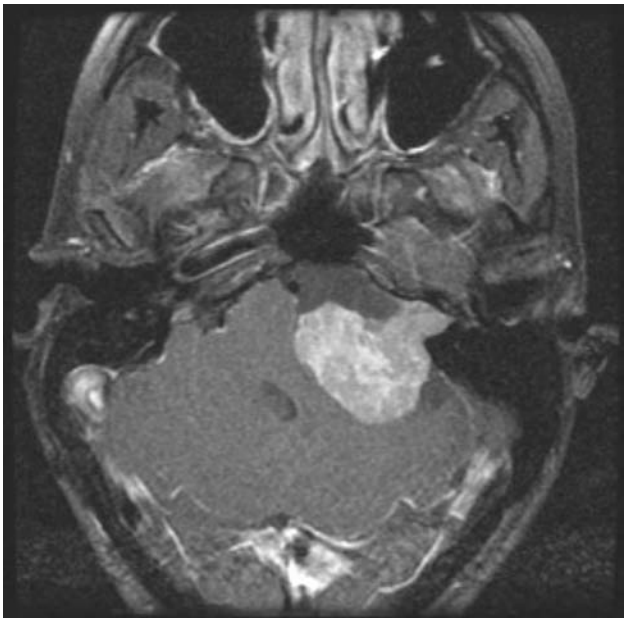

Fig. 7. Gadolinium-enhanced cranial MRI scan of a vestibular schwannoma in a patient with NF2. Note significant compression of the brainstem with effacement of the fourth ventricle.

and attributed either to meningoangiomatosis or to hamartomatous lesions. Of interest, the high signal lesions recorded in one series (Ruggieri et al. 2005) were asymptomatic as reported in four of 11 NF2 cases who had meningoangiomatosis (Huson and Hughes 1994).

Molecular genetics and Pathogenesis

Molecular biology

In 1987, the *NF2* gene was mapped to chromosome 22 by tumor studies of vestibular schwannomas (Seizinger et al. 1986) and by linkage analysis in patients with NF2 (Rouleau et al. 1987, Wertelecki et al. 1988). In 1993, two groups independently published the identity of the *NF2* gene. One group named the protein "merlin" (moezin, ezrin, radixin-like protein) to emphasize its relationship to various cytoskeletal proteins (Trofatter et al. 1993). The other

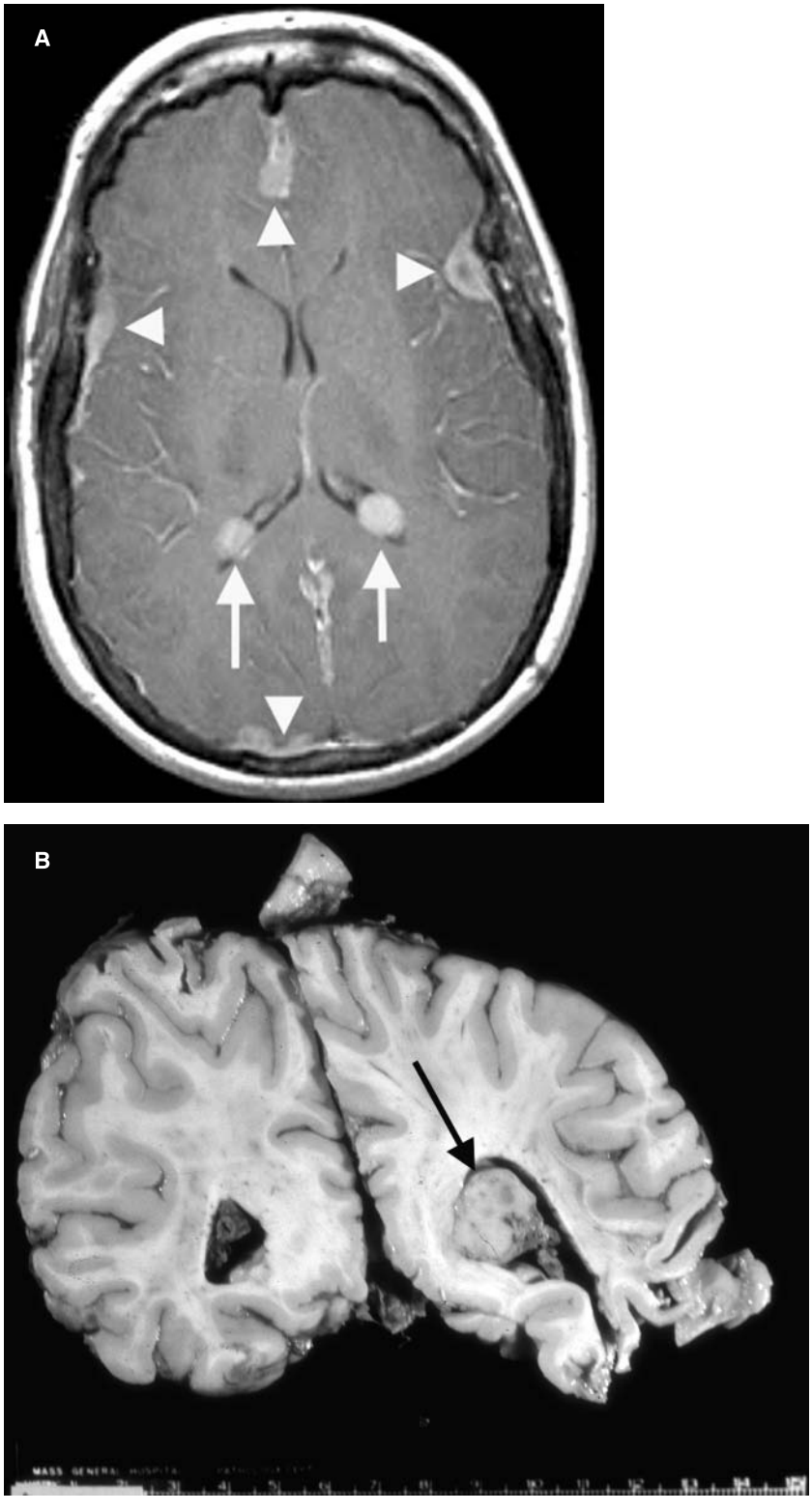

Fig. 8. (**A**) Axial T1-weighted image from a gadolinium-enhanced cranial MRI scan demonstrating bilateral intraventricular meningiomas (arrows) and multiple dural-based meningiomas (arrowheads). (**B**) Gross pathologic specimen of brain from a patient with NF2 demonstrating an intraventricular meningioma.

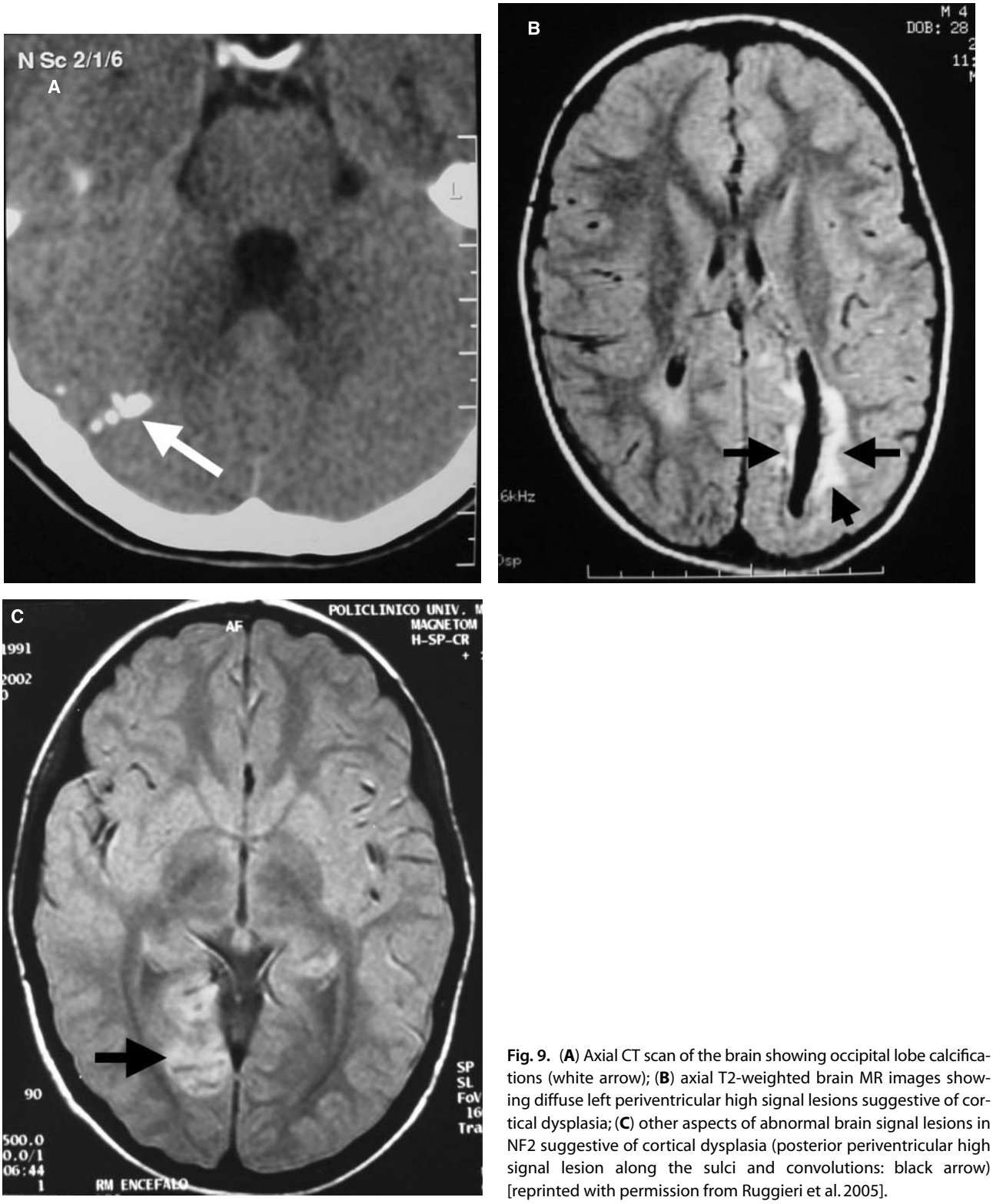

Fig. 9. (**A**) Axial CT scan of the brain showing occipital lobe calcifications (white arrow); (**B**) axial T2-weighted brain MR images showing diffuse left periventricular high signal lesions suggestive of cortical dysplasia; (**C**) other aspects of abnormal brain signal lesions in NF2 suggestive of cortical dysplasia (posterior periventricular high signal lesion along the sulci and convolutions: black arrow) [reprinted with permission from Ruggieri et al. 2005].

group named the protein "schwannomin" to emphasize its role in suppression of schwannoma formation (Rouleau et al. 1993). The *NF2* gene is composed of 17 exons spanning 110 kb. There are three alternative messenger RNA species (7 kb, 4.4 kb, and 2.6 kb) due to variable length of the 3'untranslated region. The predominant *NF2* gene product is a 595 amino-acid protein and is a member of the 4.1 family of cytoskeletal proteins. The protein links membrane-associated proteins and the actin cytoskeleton, thereby acting as an interface with the extracellular environment (McClatchey and Giovannini 2005).

The *NF2* protein acts as a true tumor suppressor: loss of both copies of the gene results in tumor growth. Inactivation of the *NF2* gene can be detected in the vast majority of sporadic schwannoma (Jacoby et al. 1996) and in about 50–60% of sporadic meningiomas. *NF2* mutations have been found in unrelated tumors such as melanoma and malignant mesothelioma (Bianchi et al. 1994). In NF2, loss of the first copy occurs in the egg or sperm and usually involves a coding sequence mutation or deletion. Loss of the second copy occurs as a somatic event, often as loss of part or all of the trans chromosome. Molecularly, this event can be visualized as loss of heterozygosity of nearby polymorphic markers. Despite significant progress in understanding the role of the *NF2* gene product, the molecular mechanism by which loss of the NF2 protein leads to tumorgenesis has not been fully elucidated. Recent data suggests that the protein has an important role in the regulation of receptor tyrosine kinases and in maintenance of contact-dependent inhibition of proliferation (McClatchey and Giovannini 2005).

All families with affected members in more than one generation show linkage to the *NF2* gene and there is no evidence for locus heterogeneity (Evans et al. 1998a). Using exon scanning and single strand conformation polymorphism (SSCP), detection rates for germline mutation in patients with vestibular schwannomas varies between 40 and 66% (Parry et al. 1996, Evans et al. 1998a). The presence of large deletions, mutations in promoter or intronic regions, and somatic mosaicism may explain the difficulty in identifying a causative mutation in all patients. More recently, use of multiplex ligation-dependent probe amplification (MLPA) assays has improved the ability to detect deletions of one to a few exons (Diebold et al. 2005, Kluwe et al. 2005). The most common type of gene alteration identified in NF2 patients are frameshift and nonsense mutations, although point mutations, deletions, and insertions have also been found (MacCollin et al. 1994). The majority of these mutations lead to truncation of the gene product which are predicted not to function either due to loss of the C-terminus of the protein or to instability of the protein product.

Genotype/phenotype correlations

Genotype/phenotype correlations have been published by multiple groups. All studies are limited by the small number of patients with mutations identified. In a German study using number of tumors identified by MRI scan as a measure of disease severity, frameshift and nonsense mutations were associated with severe disease while missense mutations were associated with mild disease (Kluwe et al. 1996a). Splice site mutations were associated with both mild and severe phenotype, suggesting the possible importance of additional determinants such as stochastic, epigenetic, or environmental factors (Kluwe et al. 1996a). In a US study, frameshift or nonsense mutations were associated with a younger age at onset and diagnosis and with a larger mean number of tumors than were splice-site mutations (MacCollin et al. 1994). Interestingly, an association between nonsense mutations and retinal hamartomas and/or epiretinal membranes has been found (Parry et al. 1996). Finally, in UK series, truncating mutations, as compared with other mutations, were associated with an early age at onset and diagnosis, with symptomatic CNS tumors besides vestibular schwannomas, and with spinal tumors (Evans et al. 1998a). Point mutations are rare in patients with NF2 and have been associated with mild, moderate, and severe disease (Kluwe and Mautner 1996b).

Detailed clinical studies of patients with NF2 suggest that phenotypic variability is smaller within families than between families. This is in contrast to patients with NF1 where there is significant variability within families. Mathematical modeling of intrafamilial correlation supports these clinical impressions. In a study of 390 patients from 153 families in the UK NF2 registry, age at onset of diagnosis, age at onset of hearing loss, and number of intracranial meningiomas was correlated within families (Zhao et al. 2002). A significant intrafamiliar correlation was noted for age at onset (correlation coefficient, 0.35), age at onset of hearing loss (correlation coefficient, 0.51), and number of meningiomas (correlation coefficient, 0.29) (Zhao et al. 2002). This study supports the notion of familial homogeneity but also demonstrates the importance of other uncharacterized factors.

Mosaic/segmental NF2

Mutations in the *NF2* gene have been detected in up to 70% of affected subjects (MacCollin et al. 1994; Ruttledge et al. 1996; Parry et al. 1996; Kluwe and Mautner 1998, Kluwe et al. 2005). The detection rate for mutations is 20–30% lower for founders (i.e., patients without a family history of NF2) (Kluwe and Mautner 1998, Evans et al. 1998b). In part, the low rate of detection for mutations in sporadic cases is due to somatic mosaicism. Somatic mosaicism develops when a mutation occurs during postzygotic embryonic development. In these patients, only a subpopulation of cells carry the constitutional mutation and analysis of blood leukocytes is often unremarkable.

Indirect evidence suggests that mosaicism exerts a mitigating effect on the NF2 phenotype such that patients may experience a later time of onset and milder course of disease (Evans et al. 1998b, Kluwe et al. 2003) on a unilateral involvement of central nervous system (Fig. 10) (Ruggieri and Huson 2001). Historically, a precise estimate of the rate of mosaicism in these patients has been difficult to establish. The most definitive numbers come from a study of 233 NF2 founders with bilateral vestibular schwannomas. In this study, the authors estimated the rate of mosaicism to be 16.7% to 24.8% (MacCollin et al. 1994, Evans et al. 1998a, Kluwe et al. 2003). Recurrence risk to offspring of mosaic patients is significantly lower than the 50% expected rate for an autosomal dominant disorder (Evans et al. 1998b) and is probably on the order of 5–10%.

Diagnosis, follow-up, and management

Diagnosis

Clinical criteria for the diagnosis of NF2 were first formulated at the National Institutes of Health Consensus Conference on NF1 and NF2 in 1987 (1988) and revised in 1991 (Mulvihill et al. 1990). These criteria emphasize the presence of bilateral vestibular schwannomas in a high percentage of patients with NF2 (Table 2). Alternatively, patients can qualify for a diagnosis of NF2 with a family history of NF2 and either a unilateral vestibular schwannoma or any two other tumors typically associated with NF2 (Table 1). Under NIH criteria, patients without bilateral vestibular schwannomas or a family history of NF2 cannot qualify for a diagnosis of NF2.

Revised criteria were proposed by the Manchester group in 1992 (Evans et al. 1992), and by the National Neurofibromatosis Foundation (NNFF) in 1997 (Gutmann et al. 1997). The goal of these revisions was to improve the sensitivity for patients with features associated with NF2 but who did not reach formal NIH criteria. None of the criteria can distinguish perfectly normal individuals from those with NF2 and each has its strengths and weaknesses. Unfortunately, mutational analysis cannot replace clinical criteria for diagnosis of NF2 since a causative mutation cannot be identified in about 30% of affected patients.

Initial evaluation

Initial evaluation of patients who have or are at risk for NF2 should include testing to confirm a diagnosis and to identify potential problems. A medical

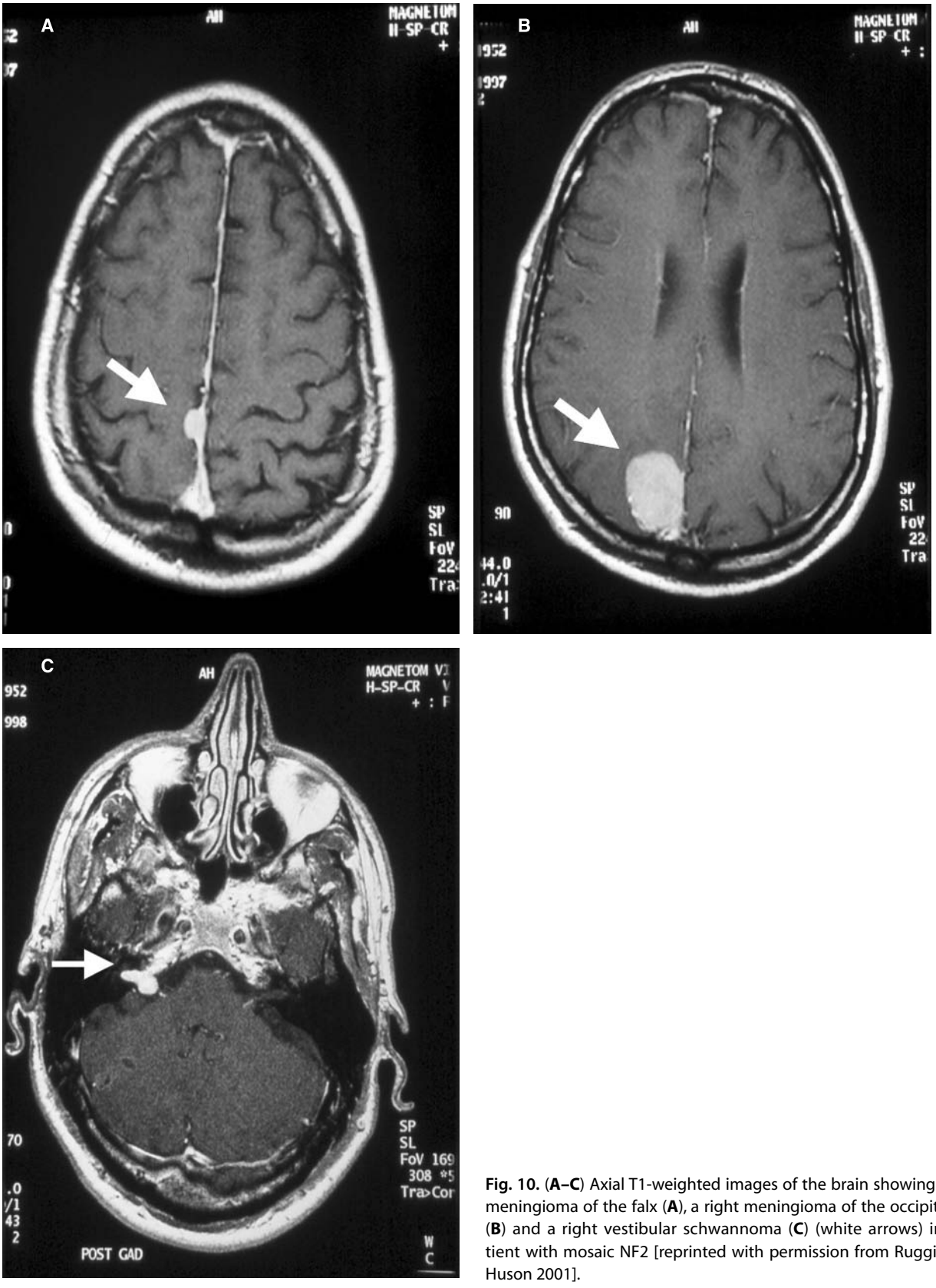

Fig. 10. (**A–C**) Axial T1-weighted images of the brain showing a right meningioma of the falx (**A**), a right meningioma of the occipital lobe (**B**) and a right vestibular schwannoma (**C**) (white arrows) in a patient with mosaic NF2 [reprinted with permission from Ruggieri and Huson 2001].

Table 2. Clinical criteria for diagnosis of NF2

NIH criteria	Manchester criteria	NNFF criteria
	Definite or confirmed NF2	
• Bilateral vestibular schwannoma • 1st degree family relative with NF2 and either unilateral VS or any one of: meningioma, schwannoma, glioma, neurofibroma, juvenile posterior subcapsular lens opacity	• Bilateral vestibular schwannoma • 1st degree family relative with NF2 and either unilateral VS or any two individual manifestations including: meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lens opacity • Unilateral VS and any two individual manifestations including: meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lens opacity • Multiple meningiomas (≥ 2) and either unilateral VS or any two individual manifestations including: schwannoma, glioma, neurofibroma, cataract	• Bilateral vestibular schwannoma • 1st degree family relative with NF2 and either unilateral VS at $<$30 years of age or any two of: meningioma, schwannoma, glioma, juvenile lens opacity
	Presumptive or probable NF2	
		• Unilateral VS $<$ 30 years of age and at least one of: meningioma, schwannoma, glioma, juvenile lens opacity • Multiple meningiomas and either unilateral VS $<$ 30 years of age or at least one of: schwannoma, glioma, juvenile lens opacity

history should include questions about auditory and vestibular function, focal neurologic symptoms, skin tumors, seizures, headache, and visual symptoms. A family history should explore unexplained neurological and audiological symptoms in all first-degree relatives.

MRI scan of the brain should include gadolinium and include axial and coronal thin cuts through the brainstem to identify vestibular schwannomas. MRI scan of the cervical spine should be performed given the predilection of ependymoma for this site. Some clinicans recommend imaging of the thoracic and lumbar spine whereas others reserve these exams for patients with neurologic symptoms referable to these locations. Ophthalmologic examination serves to identify characteristic lesions such as lens opacities, retinal hamartomas, or epiretinal membranes. A complete neurological examination serves as a baseline for future comparison and may assist in the selection of sites within the nervous system that require further imaging studies. Audiology (including pure tone threshold and word recognition) and brainstem evoked responses document eighth cranial nerve dysfunction related to vestibular schwannomas and set a baseline for future comparisons. Abnormalities of pure tone thresholds are present in 90% of patients between 10 and 72 years with NF2. Word recognition serves as a measure of functional hearing. Brainstem auditory evoked responses are a more sensitive measure of auditory function and is abnormal in 100% of patients with symptomatic vestibular schwannomas. In cases where the diagnosis is uncertain, review of any pathologic material may be helpful.

Follow-up

After initial diagnosis, patients should be seen relatively frequently (every 3–6 months) until the growth rate and biologic behavior of tumors are determined. Consultation with an experienced surgeon after initial diagnosis is often helpful for presymptomatic patients (ie, those with adequate hearing) to discuss the feasibility of hearing-sparing surgery. Most patients without acute problems can be followed on an annual basis. Evaluation at these visits should include complete neurological examination, MRI scans of the brain with thin cuts through the brainstem, MRI scans of symptomatic lesions outside the brain if present, audiology, and brainstem evoked responses. Ophthalmologic evaluation should be performed in selected patients with visual impairment or facial weakness. Yearly audiology serves to document changes in pure tone threshold and word recognition. This information can be helpful in planning early surgical intervention for vestibular schwannomas and in counseling patients about possible deafness. Changes in brainstem auditory evoked responses may precede hearing loss. The frequency with which routine spinal imaging is obtained varies among clinics, but is clearly indicated in patients with new or progressive symptoms referable to the spinal cord.

Management

The approach to management of NF2-associated tumors differs from that of sporadic tumors. Because patients with NF2 develop multiple cranial and spinal tumors, surgical removal of every lesion is not possible or advisable. Instead, the primary goal is to preserve function and to maximize quality of life.

Surgery

Surgery is the mainstay for treatment of NF2-related tumors. Patients with NF2 typically have multiple tumors in the brain and spinal cord and surgical extirpation of all lesions is not a practical goal. Surgery is clearly indicated for patients with significant brainstem or spinal cord compression or with obstructive hydrocephalus. In patients with little or no neurologic dysfunction related to their tumors, watchful waiting may allow patients to retain neurologic function for many years (Liu and Fagan 2001). For this reason, timing of intervention is often a difficult decision for patients and physicians. Superior short-term outcomes and shorter length of stay for VS surgery has been associated with higher volume hospitals and surgeons (Barker et al. 2003). For this reason, surgery, if indicated, should be performed at hospitals by surgeons with expertise in management of these patients.

The approach to vestibular schwannomas has been the best studied. Surgical extirpation of vestibular schwannomas can be accomplished using middle cranial fossa, posterior suboccipital, and translabyrinthine approaches. The goal of presymptomatic surgery is retention of hearing with a minimum of post-operative complications such as facial weakness or dysphagia. In patients with a documented change in hearing, bony decompression of the internal auditory canal through a middle cranial fossa can stabilize hearing for a period of time. A middle cranial fossa approach for tumor resection can preserve measurable hearing is in 65–70% of adult patients (Doyle and Shelton 1993, Slattery III et al. 1998, Brackmann et al. 2001). Pre-operative tumor size has been shown to be an important indicator of outcome in some series (Doyle and Shelton 1993), but not in others (Slattery III et al. 1998). In general, patients with vestibular schwannomas related to NF2 have comparable surgical outcomes to patients with sporadic lesions (Slattery III et al. 1997). A suboccipital approach for small tumors can result in hearing preservation although precise numbers using this technique have not been published. Alternatively, a translabyrinthine approach with placement of an auditory brainstem implant (ABI) can provide auditory sensations in some patients (Otto et al. 2002). Patients opting for this approach should be counseled that about 10% of patients do not receive auditory sensations, that ABI's do not provide normal sound quality, that processor optimization requires regular follow-up, and that maximal benefit is often not achieved for many years (Otto et al. 2002). For most patients with ABI's, the primary benefit occurs when the implant is used in conjunction with lip reading. In a recent study on a small NF2 cohort (Vincenti et al. 2008) coclear implant patients performed better than ABI's patients

even if variability in auditory performance was observed with both devices. At the present time, little information is available about the efficacy of hearing sparing surgery in pediatric patients but outcomes appear to be inferior to that for adults (Nunes and MacCollin 2003).

The decision to proceed with hearing-sparing surgery must be individualized for each patient. Options include observation without surgical intervention and hearing-sparing surgery; stereotactic radiation has not yielded comparable results for preservation of hearing (see below). For those with tumors that are multilobulated or greater than 1.5 cm in greatest dimension, the risk of peri-operative complications (including hearing loss and cranial nerve dysfunction) likely outweight the potential benefits. In these patients, tumor resection should be deferred until another indication for surgery such as increased intracranial pressure, impending hydrocephalus, or new neurologic symptoms develops.

Indications for surgical resection of other tumors are less well defined. In general, schwannomas of other cranial nerves are slow growing and produce few symptoms. Surgical resection in these patients should be reserved for those with unacceptable neurologic symptoms or rapid tumor growth. Patients with meningiomas typically have more than one tumor and resection of all lesions is often not advisable. The benefit of surgery must be carefully weighed against potential complications. As a general rule, indications for resection include rapid tumor growth and worsening neurologic symptoms. Spinal cord tumors are present in about 90% of patients with NF2 and have no site of predilection. Intervention is necessary in a minority of patients (Mautner et al. 1995). Surgery is more often required in patients with extramedullary tumors (59%) than for intramedullary tumors (12%) (Patronas et al. 2001). In general, spinal meningiomas behave more aggressively than schwannomas and require surgery more frequently.

Radiation

Radiation is often used as adjuvant therapy for treatment of sporadic brain tumors. Treatment outcomes for patients with NF2-related vestibular schwannomas are worse than for patients with sporadic tumors (Fuss et al. 2000). In early studies of stereotactic radiosurgery, 18–20 Gy were delivered to tumors. Local control was achieved in 90% of patients but no serviceable hearing was preserved in patients with serviceable hearing pre-operatively (Linskey et al. 1992). For this reason, the dose of radiation to the tumor margin was reduced to 12–16 Gy. Using modern regimens, treatment with stereotactic radiosurgery results in tumor control in 98% of patients with NF2 with preservation of useful hearing in 40–67% (Subach et al. 1999, Rowe et al. 2003). Decreased facial and trigeminal function occurs in 5–16% and 10% of patients, respectively (Subach et al. 1999, Rowe et al. 2003). The risk of deafness in patients with serviceable hearing pre-operatively is about 20% (Rowe et al. 2003). More recently, fractionated stereotactic radiotherapy has been advocated to minimize the risk of hearing loss. The actuarial 5-year local control rate using this technique is 93% and the hearing-preservation rate is 64% (Combs et al. 2005).

The role of adjuvant radiation in other tumors such as meningiomas and ependymomas is not established but the majority of these tumors demonstrates benign histology and can be controlled surgically. No case series have been published on treatment of NF2-related meningiomas. In general, treatment of sporadic tumors with stereotactic radiosurgery results in local control in 90–95% of cases (Flickinger et al. 2003, DiBiase et al. 2004). Peritumoral cerebral edema develops in up to 25% of patients, but symptoms referable to cerebral edema develop in less than 10% of patients (Flickinger et al. 2003, Chang et al. 2003).

Most clinicians prefer surgical extirpation of tumors when possible and reserve radiation treatment for tumors that are not surgically accessible. This practice is based on the experience that radiation therapy makes subsequent resection of VS and function of ABI's more difficult (Slattery III and Brackmann 1995). In addition, there are anectodal reports of malignant transformation of NF2-associated schwannomas after radiation treatment and indirect evidence of increased numbers of malignancy in NF2 patients who have received radiation (Baser et al. 2000, Thomsen et al. 2000).

Chemotherapy

At the present time, there is no effective chemotherapy for treatment of NF2-related tumors. Sporadic meningiomas represent the best-studied tumor at the present time. Typically, patients with refractory or non-surgical tumors have been included in chemotherapy trials. Although some initial reports suggested efficacy of hydroxyurea in treating meningiomas (Schrell et al. 1997), more recent reports do not support this view (Loven et al. 2004). Furthermore, there seems to be little role for use of tamoxifen or temozolomide for recurrent tumors (Chamberlain et al. 2004). No trials of chemotherapy for treatment of vestibular schwannomas or ependymomas have been reported. Gene therapy remains a potential option for the future as injection of oncolytic recombinant herpes virus into schwannomas in mice results in significant tumor shrinkage (Messerli et al. 2005).

Mortality in NF2

Patients with NF2 have diminished lifespan compared to non-affected family members. In a study of 74 Japanese patients with bilateral vestibular schwannomas, the overall 5-, 10-, and 20-years survival rates after diagnosis were 85, 67, and 38%, respectively (Otsuka et al. 2003). Younger age at diagnosis was correlated with poor survival (Otsuka et al. 2003). In a UK study, the mean actuarial survival for patients with NF2 was 62 years (Evans et al. 1992). Of 368 people from 261 families registered in the UK NF registry as of February 15, 2002, 74 (20%) died during follow-up (Baser et al. 2002a). The cause of death in these patients was tumor burden (69%), peri-operative complications (19%), malignancy from NF2-related tumor (4%), traffic accident (3%), suicide (3%), falls (1%), and myocardial infarction (1%) (Baser et al. 2002a). Cox proportional hazards models revealed increased relative risk of mortality associated with decreasing age of diagnosis (relative risk, 1.13-fold per year decrease below 27 years of age) and presence of intracranial meningiomas (relative risk, 2.51). A decreased risk of mortality was associated with treatment at a specialty medical center (relative risk, 0.34) and with presence of a missense mutation compared with nonsense or frameshift (relative risk, 0.08) (Baser et al. 2002a).

Differential diagnosis

The diagnosis of NF2 is generally straightforward when a patient has a family history. In sporadic cases, other diagnostic possibilities must be considered.

Bilateral cerebellopontine angle masses

Vestibular schwannomas are the hallmark of NF2. Any disease that presents with bilateral cerebellopontine angles masses can resemble NF2 at initial presentation. Case reports of such mimic syndromes include patients with glioblastoma multiforme, metastases, and petrous apex cholesterol granulomas. A detailed history and examination coupled with a high-quality MRI scan is usually sufficient to differentiate these entities from NF2. Only rarely is a brain biopsy required to confirm a diagnosis in the presence of bilateral vestibular schwannomas.

Unilateral vestibular schwannoma

Vestibular schwannomas are relatively common and represent about 7% of all primary central nervous system tumors. The vast majority of these tumors are unilateral and sporadic in nature. However, between 10 and 20% of patients with NF2 initially present with unilateral VS (Evans et al. 2005). Thus, when evaluating a young patients with unilateral VS, one should consider the possibility of NF2. Using epidemiologic data, the average risk (per decade) of having NF2 has been calculated for patients presenting with a unilateral vestibular schwannoma (Evans et al. 1999b). For a patient who presents in the second decade, the average risk of having NF2 is 6%. This average risk declines to 2.7% in the third decade, to 0.9% in the fourth decade, and to 0.36% in the fifth decade (Evans et al. 1999b). In younger patients with unilateral vestibular schwannomas, particular

attention should be given to identification of other manifestations of NF2 such as meningiomas, ependymomas, skin tumors, and lens opacities.

Patients with unilateral vestibular schwannomas and other NF2-related tumors (e.g., meningioma) represent a unique phenotype (Aghi et al. 2006). These patients tend to present with symptoms later in life than those with classic NF2 and are less likely to have ophthalmologic findings (Fig. 10) (Ruggieri and Huson 2001). Cranial and spinal tumors are common with a mean of 2.9 intracranial nonunilateral schwannomas and 2.3 spinal tumors. Contralateral vestibular schwannoma can develop with an actuarial chance of 2.9% at 17 years, 11% at 24 years and 29% at 40 years. Molecular analysis has confirmed somatic mosaicism in 18% of these patients. Transmission to offspring is rare with only 2 of 63 children of subjects exhibiting NF2-related findings such as unilateral VS or cataracts.

Multiple meningiomas

Multiple meningiomas are found in up to 10% of patients with meningiomas (Davis et al. 1998, Antinheimo et al. 2000). In such patients, diagnostic considerations include NF2, non-contiguous spread of a single meningioma, or familial multiple meningiomas. Analysis of tumor and blood samples from patients with multiple meningiomas without a family history of NF2 usually supports a somatic and clonal origin for these tumors (Stangl et al. 1997). In rare circumstances, multiple meningiomas are familial but the identity of this tumor suppressor gene has not been identified (Heinrich et al. 2003). The initial work-up should include a contrast-enhanced cranial MRI scan with axial and coronal thin cuts through the brainstem to identify any possible VS. The presence of bilateral vestibular schwannomas confirms a diagnosis of NF2 whereas a unilateral vestibular schwannoma ipsilateral to multiple meningiomas suggests a diagnosis of mosaic NF2.

Genetic counseling

Genetic counseling is an essential component of the care of the patient with NF2. All patients and families with NF2 should have access to genetic testing to facilitate presymptomatic diagnosis of individuals at risk. If a causative mutation in the *NF2* gene can be identified, molecular testing with 100% specificity will be available for that family. Mosaicism is a common cause of non-informative testing in sporadic NF2 patients. For these individuals, tumor specimens should be frozen for analysis, if possible. If two genetic alterations (e.g., one mutation and one allele loss of the *NF2* gene) can be identified in a tumor, one is inferred to be the constitutional mutation. Haplotype analysis can then be used to screen at risk individuals for the mutation in constitutional DNA. (Kluwe et al. 2002). In families with two or more affected individuals, linkage analysis using intragenic markers or markers flanking the *NF2* gene can be used for presymptomatic diagnosis with >99% certainty of affected status. As with other genetic diseases, genetic counseling by an experienced provider is essential prior to embarking on prenatal or presymptomatic diagnosis.

Schwannomatosis

Schwannomatosis (OMIM 162091) is a recently recognized form of neurofibromatosis. In early clinical reports, these patients were described as having multiple schwannomas, multiple neurilemomas, multiple neurilemmomas, or neurilemmomatosis. Historically, these patients have been difficult to distinguish from those with NF2 due to the overlap in their phenotypes.

No estimate of the prevalence of schwannomatosis has been reported. The annual incidence is estimated to be 0.58 cases per 1,000,000 persons, which is similar to that of NF2 (0.50 cases per 1,000,000) from the same study (Antinheimo et al. 2000). Two percent of patients with schwannomas qualify for a diagnosis of schwannomatosis (Antinheimo et al. 2000). Data from German and US clinics suggest that 15% of cases of schwannomatosis are familial whereas data from the UK suggest that up to 50% of cases may be familial (MacCollin et al. 2005).

Schwannomatosis is characterized by the predisposition to develop multiple schwannomas (Figs. 11, 12). In contrast to patients with NF2, patients with

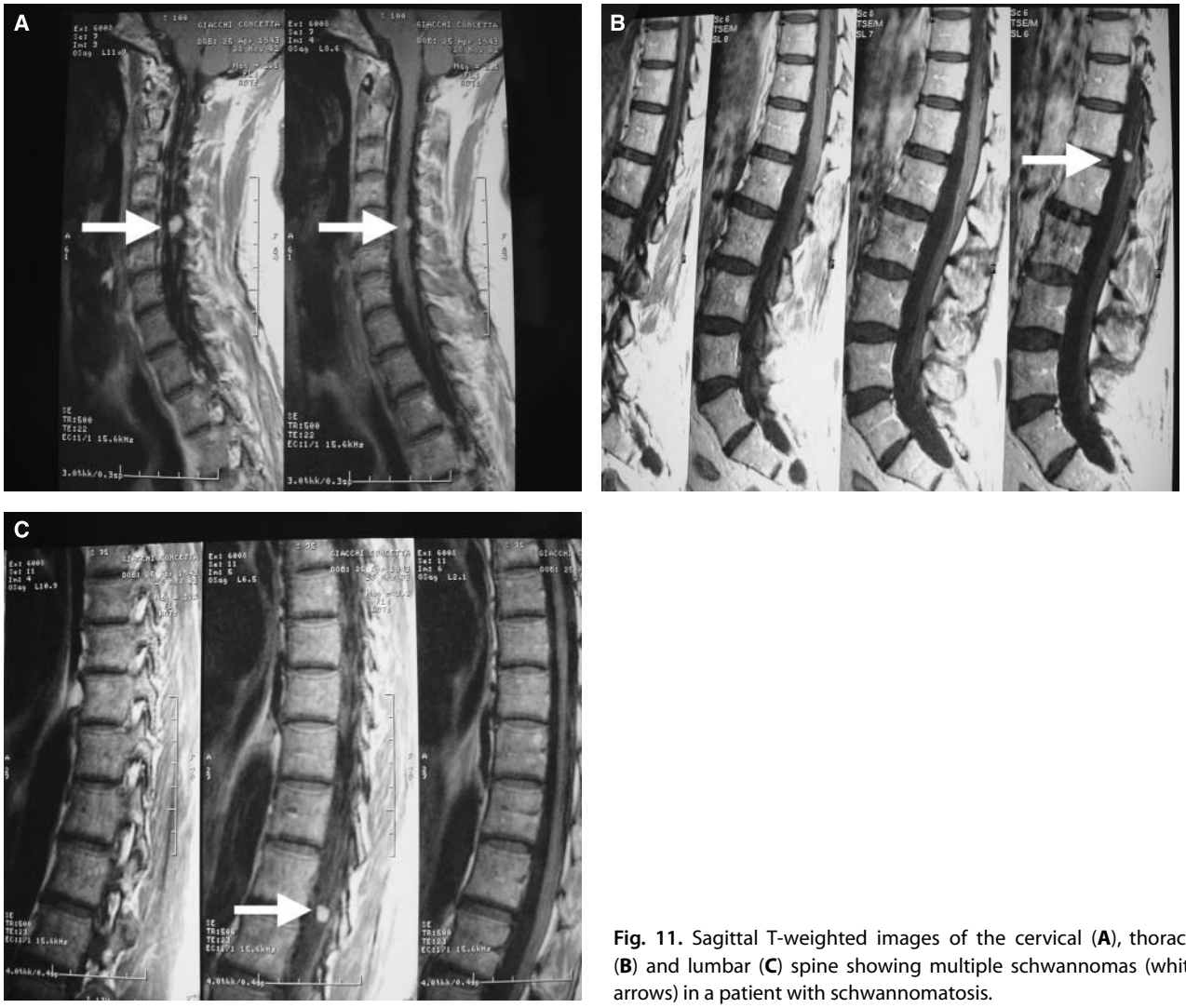

Fig. 11. Sagittal T-weighted images of the cervical (**A**), thoracic (**B**) and lumbar (**C**) spine showing multiple schwannomas (white arrows) in a patient with schwannomatosis.

schwannomatosis do not have vestibular or intradermal schwannomas on other NF2 features (Baser et al. 2006). Patients with schwannomatosis most commonly develop symptoms in the second or third decade of life. Pain is the hallmark of schwannomatosis and is the most common initial complaint. Neurologic dysfunction related to schwannomas is uncommon and, when present, is often a complication of surgery. One-third of patients with schwannomatosis have evidence of anatomically limited disease. The MRI appearance of schwannomatosis is characterized by multiple, discrete lesions along peripheral or spinal nerves. The lesions have low to intermediate signal intensity on T1 sequence and high signal intensity on T2- and short T1 inversion recovery (STIR) sequences (Fig. 12). Pathologically, schwannomas in patients with schwannomatosis resemble those from patients with NF2 and sporadic lesions. Although no single feature can reliably distinguish schwannomatosis-associated schwannomas, they tend to have more peritumoral edema in the adjacent nerve, intratumoral myxoid changes, and intraneural growth patterns than other schwannomas (MacCollin et al. 2005).

The pathogenesis of schwannomatosis is an area of active research. A minority of patients with

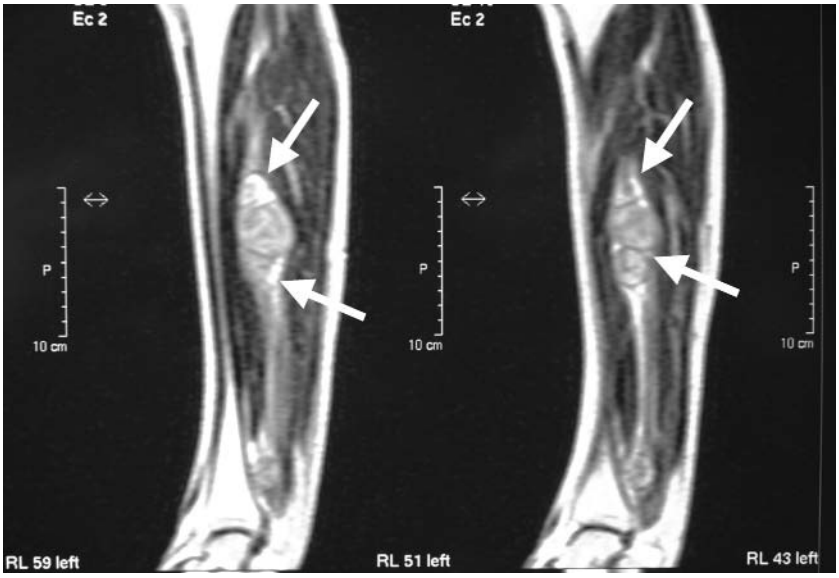

Fig. 12. Coronal T2-weighted image of the leg showing an isolated multilobular schwannoma (white arrow) in a patient with schwannomatosis.

Table 3. Clinical criteria for diagnosis of schwannomatosis

Definite schwannomatosis*	**Possible schwannomatosis***
Presence of all the following criteria	*Presence of all the following criteria*
Age <30 years, 2 or more non intradermal schwannomas of which at least on histologically proven, lack of vestibular tumor after high quality MR study, lack of constitutional mutations of the NF2 gene	Age <30 years, 2 or more non intradermal 2 or more non intradermal histologically proven, lack of vestibular schwannoma after high quality MR study, lack of constitutional mutations of the NF2 gene
or	*or*
1 non-vestibular schwannoma histologically proven, one 1st degree parent satisfying the above criteria	Age >45 years, 2 or more non intradermal 2 or more non intradermal histologically proven, lack of symptoms of eight nerve dysfunction, lack of constitutional mutations of the NF2 gene *or* Radiological evidence of non-vestibular Schwannoma, 1st degree parent satisfying the above criteria

Adapted and modified from MacCollin et al. (2005)
*According to the ***revised criteria*** for schwannomatosis (Baser et al. 2006) all patients with ***definite*** or ***possible*** schwammomatosis must not fulfill any of the existing sets of diagnostic criteria for NF2 (see Table 2) and have no evidence of vestibular schwannoma on high quality MRI scan, no first-degree relative with NF2, and no known constitutional NF2 mutation.

sporadic schwannomatosis have been shown to have mosaic NF2 (Jacoby et al. 1997). Truncating mutations in the *NF2* gene are present in the vast majority of schwannomatosis-associated schwannomas. However, multiple tumors from the same patient do not share a common mutation. The underlying cause for somatic instability in the *NF2* gene in schwannomatosis is not known. Mutational analysis of tumors from affected families has excluded germline inactivation of *NF2* gene as the cause of

schwannomatosis (MacCollin et al. 2003). Hulsebos et al. (2007) identified on inactivating germline mutation in exon 1 of the tumor suppressor gene INI1/SMARCB1 (OMIM 601607) on chromosome 22q12.2 in a father and daughter who both had schwannomatosis. In 2 of 4 investigated schwannomas from these patients, inactivation of the wildtype INI1 allele by a second mutation in exon 5 of the gene on by loss of the gene was found, consistent with the Kondson 2-hit hypothesis and suggesting that INI1 might be the predisposing gene in familial schwonnomatosis (Hulsebos et al. 2007). More recently, two studies (Hadfield et al. 2008, Sestini et al. 2008) identified germline SMARCB1 mutations in patients with schwonnomatosis along with somatic NF2 mutations in the same patients' tumours suggesting a four-hit mechanism involving the SMARCB1 and NF2 genes in schwonnomatosis-related tumorigenesis.

Consensus criteria for diagnosis of schwannomatosis have been published (Table 3) (MacCollin et al. 2005) and, more recently modified (Baser et al. 2006). Initial evaluation of patients who have or are at risk for schwannomatosis should include testing to confirm a diagnosis (usually exclusion of NF1 and NF2) and to identify potential problems. A medical history should include questions about auditory and vestibular function, focal neurologic symptoms, skin tumors or hyperpigmented lesions, seizures, headache, and visual symptoms. A family history should explore unexplained neurological, dermatological, and audiological symptoms in all first-degree relatives. MRI scan of the brain with attention to the internal auditory canals should be performed to exclude vestibular schwannomas on other NF2 features (Baser et al. 2006). MRI scans of other body parts should be obtained based on the history and clinical exam. A combination of MRI scan and pathologic analysis is used to establish a diagnosis of definite or possible schwannomatosis. Management of patients with schwannomatosis is primarily symptom oriented. As noted above, pain is the hallmark of this disorder. Surgery should be reserved for patients with symptomatic tumors or rapidly expanding lesions in the spinal cord. Most patients require pain medication; these patients may benefit from referral to a Pain Clinic with experience in managing neuropathic pain.

The differential diagnosis for schwannomatosis includes other disorders characterized by multiple nerve sheath tumors including NF1, NF2, Carney complex (characterized by skin pigmentation, myxomas, and endocrine tumors), and an unnamed syndrome characterized by the presence of multiple schwannomas, multiple nevi, and multiple vaginal leiomyomas. A combination of history, pathologic diagnosis of tumor tissue, and imaging is usually sufficient to distinguish between these competing diagnoses.

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