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Diagnosis, Management, and New Therapeutic Options in Childhood Neurofibromatosis Type 2 and Related Forms

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Neurofibromatosis type 2 (*NF2*; MIM # 101000) is an autosomal dominant disorder characterized by the development of vestibular schwannomas (VSs); schwannomas of other cranial, spinal, and cutaneous nerves; cranial and spinal meningiomas or other central nervous system tumors (eg, ependymomas and astrocytomas) or both. Additional features include eye (eg, early onset cataracts, optic nerve sheath meningiomas, retinal or pigment epithelial hamartomas or both, and epithelial retinal membranes) and skin abnormalities (eg, flat dermal [NF2 plaques] or spherical subcutaneous nodular schwannomas or both, and few, atypical café-au-lait spots). Clinically, children with NF2 fall into 2 main groups: (1) *congenital NF2* with bilateral VSs detected as early as the first days to months of life, which can be stable or asymptomatic for 1-2 decades and suddenly progress; and (2) *severe prepubertal (Wishart type) NF2* with multiple (and rapidly progressive) central nervous system tumors other-than-VS, which usually presents first, years before VSs, both associated with more marked skin and eye involvement (vs the classical *mild adult [Gardner type] NF2*, with bilateral VSs presenting in young adulthood, sometimes as the only disease feature). Individuals manifesting unilateral VS associated with ipsilateral meningiomas or multiple schwannomas localized to a part of the peripheral nervous system have *mosaic or segmental NF2*; individuals developing multiple nonVS, nonintradermal cranial, spinal, and peripheral schwannomas (histologically proven) have *schwannomatosis* (*SWNTS*). NF2 is caused by mutations in the *NF2* gene at chromosome 22q12.1, which encodes for a protein called merlin or *schwannomin*, most similar to the exrin-readixin-moesin proteins; mosaic or segmental NF2 is because of mosaic phenomena for the *NF2* gene, whereas SWNTS is caused by germline and possibly mosaic mutations either in the *SMARCB1* gene (*SWNTS1*; MIM # 162091) or the *LZTR1* gene (*SWNTS2*; MIM # 615670), both falling within the 22q region. Data driven from in vitro and animal studies on the *merlin pathway* allowed biologically targeted treatment strategies (employing Lapatinib, Erlotinib, Everolimus, Picropodophyllin, OSU.03012, Imatinib, Sorafenib, and Bevacizumab) aimed at multiple tumor shrinkage or regression or both and tumor arrest of progression with functional improvement.
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Neurofibromatosis 2

Neurofibromatosis type 2 (*NF2*; MIM # 101000),[1-4] previously known as bilateral acoustic neurofibromatosis or central neurofibromatosis,[5-8] is an autosomal dominant disorder caused by mutation in the gene (*NF2*; MIM # 607379),[9,10] encoding *neurofibromin-2* or *schwannomin* (*SCH*), which is also called *merlin* (*moesin-ezrin-radixin-like* protein), on chromosome 22q12.2.[11] Clinically, NF2 is characterized by the development of *vestibular schwannomas* (*VSs*); schwannomas of other cranial, spinal, and cutaneous nerves; and cranial and spinal meningiomas or other central nervous system (*CNS*) tumors including ependymomas and

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astrocytomas or both.[12-15] A variety of ocular abnormalities are also common, such as early onset cataracts (usually asymptomatic), optic nerve sheath meningiomas, retinal or pigment epithelial hamartomas or both, and epithelial retinal membranes.[16] Skin abnormalities include flat dermal (NF2 plaques) and spherical or ovoid subcutaneous nodular schwannomas.[17] Less than 1% of patients with NF2 have ≥6 café-au-lait spots.[1-4,17]

Clinically, affected individuals fall into 2 main groups[1,18,19]: (1) *(Mild) Gardner-type NF2*,[6,7] with bilateral VSs presenting in adulthood (mean age = 22-27 y), often as the only feature[19]; and (2) *(Severe) Wishart-type NF2*,[5] with multiple (and rapidly progressive) CNS tumors other-than-VS, which may present first, years before VSs.[20-33] The latter group also tends to have more marked skin and eye involvement.[1-4,20-33]

A third group, known as *congenital NF2*,[34] has been also recorded with bilateral VSs detected as early as the first days to months of life, which can be stable (and asymptomatic) for 1 to nearly 2 decades and thereafter suddenly progress; this form may be associated with (reversible) NF2 plaques in atypical locations (eg, face, hands, and feet) and other CNS tumors (eg, meningiomas and ependymomas).[34]

Some individuals may also have NF2-related tumors localized to a part of the nervous system—eg, a unilateral VS with ipsilateral meningiomas or multiple schwannomas in a part of the peripheral nervous system (*mosaic or segmental NF2*)—these phenotypes are caused by true somatic mutations of the *NF2* gene.[35-48]

Some other individuals develop multiple nonvestibular, nonintradermal cranial, spinal, and peripheral (histologically proven) schwannomas and they are usually referred as having *schwannomatosis* (*SWNTS*)[49-56]: 2 major clinical or molecular forms have been characterized so far, caused by mutation either in the *SMARCB1* gene (*SWNTS1*: MIM # 162091) located at 22q11.23[57-59] or in the *LTRZ1* gene (*SWNTS2*: MIM # 615670) located at 22q11.21.[60-62]

Clinically overlapping features, between classical NF2 and alternate forms of NF2 (ie, mosaic NF2 and SWNTS), are increasingly recorded[36,38,41-45,48,55] and only sometimes sorted out by means of molecular analysis.[63] Unilateral VSs (without NF2-related features) are relatively common in the general population (7% of all primary CNS tumors) as well as the occurrence of multiple meningiomas (including familial multiple meningiomas). For all the above reasons and considerations, multiple sets of diagnostic criteria have been developed over the years for NF2 and for its alternate or related forms.[42,44,52,54-56,64-69]

Clinical Manifestations and Natural History in the Pediatric Age

Patterns of Initial Presentations

The pattern(s) of presentation (and the natural history) of NF2 in childhood are very protean and differ from adulthood in many respects.[19-33] In addition, children with NF2 whose onset is at or before puberty usually present differently from adolescents.[28,32,34] The most common initial symptoms in adult-onset NF2 are usually attributed to cranial nerve VIII dysfunction and include hearing loss, tinnitus, or balance dysfunction.[1-4,12-14] Conversely, in the *prepubertal NF2* age group subtle skin tumors, small posterior capsular or cortical-edge cataracts, or neurological signs (discussed later) secondary to other-than-VSs' cranial nerve(s) involvement or brainstem or spinal cord compression or both, are more common and manifest long before dysfunction of cranial nerve VIII.[19-34] A reversal pattern is encountered in the *congenital form* of NF2 (discussed later),[34] whose first nervous system manifestation of the disease is the presence of small (ie, less than 1 cm) bilateral VS, recorded (incidentally) as early as the first months or days (Zampino G., personal observation) of life.

Skin Manifestations

The initial clinical presentation of some children with NF2 is when they manifest with few *café-au-lait spots* (larger than in NF1, with more irregular margins and paler color [Fig. 1] or *peripheral nerve tumors* [Fig. 2] or both) and are initially diagnosed as having either NF1 or sporadic benign neurofibromas or schwannomas, the revision of the diagnosis only occurring when the tumors are removed for histology

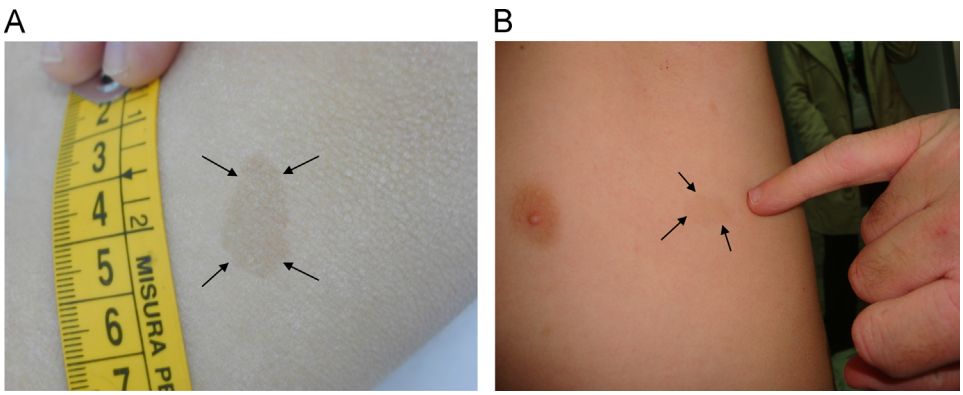

Figure 1 (A and B) Close-up view of the skin of 2 children with NF2, showing 2 café-au-lait spots (black arrows): note the paler brownish color and the irregular size and margins. (Color version of figure is available online.)