April 2003 Research Newsletter

General Reviews

Hunt et al. (7) review common craniofacial abnormalities including conditions of craniofacial atrophy/hypoplasia and neoplasia. Neurofibromatosis is discussed.

Perilongo et al. (24) review low-grade gliomas and leptomeningeal dissemination.

NF1 Reviews

Abdel-Wanis and Kawahara (1) review bone development in NF1.

Gitler and Epstein (6) review the role of neurofibromin in regulating heart development.

McLaughlin and Jacks (21) review NF1.

NF2 Reviews

Pellet et al. (23) review the relative indications for radiosurgery and microsurgery for acoustic schwannoma.

Neurofibromatosis Type 1 (NF1)

NF1 Clinical

Kollen et al. (12) describe the case report of a 6-year-old boy with diabetes insipidus with a monosomy-7 associated myelodysplastic syndrome and NF1.

Lal et al. (17) describe the case report of a 14-year-old boy with unilateral Lisch nodules without other diagnostic features of NF1. There has been only one previous report of Lisch nodules without other clinical evidence of neurofibromatosis. They speculate that this patient may have a somatic mutation of the NF1 gene with very limited mosaicism, perhaps limited to the affected iris sector only.

Prinzie et al. (28) compared the personality profiles of 44 children and adolescents with NF1 with a group of 220 non-NF1 controls (matched on age and gender). Compared to the controls, the NF1 group were equally agreeable, but less conscientious, less emotionally stable, less open for new experience, with less motor activity, more extroverted, more dependent and more irritable. There was no association with gender, the severity of medical and cosmetic problems, and IQ.

Billingsley et al. (3) describe the cortical morphology associated with language function in NF1. They found that verbal skills in NF1 were related to inferior frontal gyrus morphology, such that individuals with NF1 who showed “typical” gyral patterns in the right hemisphere performed worse across language measures than those showing an extra
“atypical” gyrus. A doubling of Heschl’s gyrus in the left and right hemispheres was also significantly associated with performance on several neuropsychological measures.

Hyman et al. (8) conducted a prospective longitudinal study of a cohort of 32 patients with NF1 to determine the natural history of cognitive deficits and their relationship to MRI T2-hyperintensities. They found no improvement in cognitive ability as the children with NF1 developed into adulthood compared with controls. Despite significant decreases in the number, size, and intensity of the T2-hyperintensities over the 8-year period, these changes were not associated with changes in cognitive ability. The best predictor of cognitive dysfunction in adulthood was the presence of T2-hyperintensities in childhood rather than current lesion status. There is a limited time window (<18 years) in which the presence of T2-hyperintensities can be used as biologic markers of cognitive dysfunction.

Ogle et al. (22) discuss caring for patients with NF1 and plexiform neurofibromas in pediatric oncology centers.

**NF1 Dermatology**

Leplege et al. (19) adapted and validated the Skindex questionnaire, an American tool designed to measure the impact of skin diseases on quality of life, in French in a population of patients with NF1. The final version was named Skindex-France.

Sasaki et al. (29) propose that mast cells may play an important role in the modulation of healing seen with charged beads. If increased mast cell populations are intimately linked to hypertrophic scar and keloid formation, their results suggest that bead therapy of cutaneous wounds may lead to pathologic wound healing in humans. This could impact on the treatment of a number of pathologic skin conditions including neurofibromatosis.

**NF1 Imaging**

Lacour-Petit et al. (16) report on six patients for whom MRI was used to diagnose peripheral nerve lesions of the lower limbs. One patient with known NF1 had an enhancing nodular lesion of the peroneal nerve compatible with a neurofibroma.

**NF1 Vascular Features**

Kusaba et al. (15) describe the case report of a 26-year-old woman with renal artery stenosis and NF1. She was successfully treated with angioplasty.

Prave et al. (27) describe the case report of a patient with NF1 and regional dysmorphism in the superficial femoral vein. Sonography revealed thickening of a short portion of the vein wall with calcification.
NF1 Tumors

Abe et al. (2) describe the case report of a 60-year-old-man with primary pulmonary sarcoma complicated by NF1.

Korones et al. (13) performed a retrospective study of twenty-six patients treated at their institution to determine if children with optic pathway tumors (OPTs) had an increased frequency of other CNS tumors. Of the 17 children who had NF1 and OPTs, 8 (47%) had additional CNS tumors, while none of the 9 children without NF1 had other CNS tumors. Thus, they found a high incidence of second CNS tumors in children with OPTs and NF1. Although they could not document a statistically significant association of these tumors with prior radiation, radiation may be a contributing risk factor.

NF1 Gene and Tumor Biology

Kehrer-Sawatzki and Messiaen (11) reply to a letter to the editor by Gervasini et al. (see April 2002 Research Newsletter). They state that they have ruled out duplication of the NF1 gene at 17q11.2 using Interphase FISH, the structure of reciprocal translocation chromosomes, and physical mapping studies.

Kratz et al. (14) discuss acute myeloid leukemia associated with t(8;21) or trisomy 8 in children with NF1.

Phillips et al. (25) show that neurofibromin and inorganic phosphate (P_i) dissociate from the NF1-Ras-GDP-P_i complex with identical kinetics, which are 3-fold slower than the preceding cleavage step. They present a model in which the P_i release is associated with the change of Ras from “GTP” to “GDP” conformation. In this model, the conformation change on P_i release causes the large change in affinity of neurofibromin, which then dissociates rapidly.

Neurofibromatosis Type 2 (NF2)

NF2 Auditory

Skrivan et al. (30) describe the results of the auditory brainstem implant program in the Czech Republic that started in 1999. 5 patients have received the implant.

NF2 Tumors

Cohen-Gadol et al. (4) discuss their 21-year, retrospective study of spinal meningiomas in patients younger than 50 years of age. 5 (12.5%) of the 40 patients had NF2. They conclude that spinal meningiomas in younger patients have a worse prognosis than similar tumors in older patients.
NF2 Gene and Tumor Biology

Kang et al. (9) report on the crystal structure and functional properties of the PDZ tandem of human syntenin. They show that the functional properties of syntenin are a result of independent interactions with target peptides, and that each domain is able to bind peptides belonging to two different classes: PDZ1 binds peptide from classes I and III, while PDZ2 interacts with classes I and II. The independent binding of merlin by PDZ1 and syndecan-4 by PDZ2 provides direct evidence for the coupling of syndecan-mediated signaling to actin regulation by merlin.

Kanno et al. (10) describes the case report of a 66-year-old man with Von-Hippel Lindau disease and a meningioma showing \( VHL \) gene inactivation. There was a partial loss on 22q in the meningioma tissue that suggests inactivation of the \( NF2 \) gene.

Lallemand et al. (18) showed that the major cellular consequence of \( Nf2 \) deficiency in primary cells is an inability to undergo contact-dependent growth arrest and to form stable cadherin-containing cell:cell junctions. Merlin colocalizes and interacts with adherens junction (AJ) components in confluent wild-type cells, suggesting that the lack of AJs and contact-dependent growth arrest in \( Nf2^{-} \) cells directly results from the absence of merlin at sites of cell:cell contact. Their studies indicate that merlin functions as a tumor and metastasis suppressor by controlling cadherin-mediated cell:cell contact.

Lohez et al. (20) found that arrest of mammalian fibroblasts in G1 in response to actin inhibition is dependent on retinoblastoma (RB) pocket proteins but not on p53. They found that G1 arrest was accompanied by inhibition of surface ruffling and by induction of NF2/merlin. Their results establish that RB pocket proteins can be uniquely targeted for tumor chemotherapy.

Pineau et al. (26) performed homozygous deletion scanning in hepatobiliary tumor cell lines and revealed alternative pathways for liver carcinogenesis. They detected homozygous deletions at the \( PTEN, NF2, STK11, BAX, \) and \( LRPDIT \) genes that were not previously implicated in human liver tumorigenesis.

Szijan et al. (31) report on the comprehensive and efficient detection of somatic mutations of the \( NF2 \) tumor suppressor gene by denaturing HPLC and microarray-CGH. They analyzed \( NF2 \) mutations in 26 specimens: 14 meningiomas, 4 schwannomas, 4 metastases, and 4 other histopathological types of neoplasms. Small mutations were identified in six out of seventeen meningiomas and schwannomas, one of which was novel. Large deletions were detected in six meningiomas. All mutations were predicted to result in truncated protein or in the absence of a large protein domain. No \( NF2 \) mutations were found in other histopathological types of CNS tumors. These results provide additional evidence that mutations in the \( NF2 \) gene play an important role in the development of sporadic meningiomas and schwannomas.

Utermark et al. (32) evaluated the effect of quinidine on the proliferation of human malignant mesothelioma (HMM) cell lines in relation to the \( NF2 \) status. They found that
quinidine selectively reduces the proliferation of merlin-deficient HMM cell lines by causing a G0/G1 arrest, whereas the proliferation rates of merlin-expressing HMM cell lines remain unchanged. Thus, quinidine or quinidine analogs are of potential therapeutic interest for the subset of merlin-deficient mesothelioma tumors.

**Schwannomatosis**

Du et al. (5) describe the case report of a 17-year-old girl without evidence of neurofibromatosis with a cystic schwannoma of the anterior tentorial hiatus and posterior cavernous sinus. The tumor was completely resected and the patient remained neurologically intact after surgery.

**Reference List**


20. Lohez, O. D.; Reynaud, C.; Borel, F.; Andreassen, P. R., and Margolis, R. L. Arrest of mammalian fibroblasts in G1 in response to actin inhibition is dependent


