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.
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.