Neurofibromatoses in Clinical Practice

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Preface

Over the last 20 years there has been a rapid increase in our understanding of the disease mechanisms underlying neurofibromatosis 1 (NF1) and neurofibromatosis 2 (NF2), and related disorders. The neurofibromatoses are inherited diseases that involve the nervous system predominantly, but are distinct on both clinical and genetic grounds. Advances in molecular biology and mouse models have paved the way for clinical trials to combat benign and malignant tumors that characterize both diseases.

NF1 and NF2 are well documented in the medical literature, but partly due to the nomenclature, the distinction between the two conditions is blurred by clinicians. Furthermore the characterization of related and overlapping disorders has added to the complexity of diagnosis and management. The media has focused inexorably on people with NF1 who have extreme disfigurement, aiming to titillate rather than educate us, while NF2 is largely unknown outside of hospital practice.

In this book we aim to provide an accessible, up-to-date guide for nonspecialists on the diagnosis, management, and long-term care of people with NF1 and NF2. We emphasize the referral pathways to specialist centers for individuals with complex disease and highlight the available support networks. Above all we wish to show that coping with the neurofibromatoses relies on a partnership between patient and clinician, based on mutual trust and an ability to listen to the needs and choice of the individual.

Rosalie E. Ferner

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Introduction

Rosalie E. Ferner

Definition of Neurofibromatosis 1 and Neurofibromatosis 2

Neurofibromatosis 1 (NF1) and neurofibromatosis 2 (NF2) are inherited neurocutaneous conditions that are clinically and genetically distinct and carry a high risk of tumor formation.[1] NF1 occurs in 1 in 2,500 births while NF2 is rare and has a birth incidence of 1 in 33,000.[2,3] NF1 and NF2 encode proteins that act as tumor suppressors by controlling cell growth and proliferation. The NF1 gene is on chromosome 17q11.2 and the protein product is neurofibromin; the gene for NF2 is on chromosome 22q 11.2 and encodes a protein known as merlin.[4-8] NF1 is characterized by café au lait patches, skin fold freckling, iris Lisch nodules, bony dysplasia, and benign peripheral nerve sheath tumors called neurofibromas.[9] The complications are variable, unpredictable, and widespread, ranging from learning difficulties, high blood pressure, and gastrointestinal symptoms to disfigurement and malignancy.[1]

Bilateral vestibular schwannomas are the hallmark lesion of NF2 and cause hearing and balance disturbances.[1,10] Schwannomas may develop on other cranial nerves, spinal nerve roots and peripheral nerves. Meningiomas, ependymomas and gliomas are associated with NF2.[1,10] Skin manifestations are less conspicuous than in NF1, but eye problems including juvenile cataracts are recognized.[1,10]

Recent Advances

Recent advances in molecular biology, mouse models of disease, and improvements in neuroimaging have permitted the distinction between NF1 and NF2 and the characterization of the many clinical manifestations.[1] They have resulted in the development of clinical trials that are underway to evaluate targeted therapy for disease complications. Conditions can be delineated that overlap with NF1 and NF2 but are distinct genetically and have different clinical outcomes. Legius syndrome is associated with mutations in the tumor suppressor gene *SPRED1* on chromosome 15, and is characterized by café au lait patches, freckling, and mild learning problems, without neurofibromas or Lisch nodules.[11] People with schwannomatosis have mutations in the *INI1/SMARCB1* tumor suppressor gene and develop multiple schwannomas in the absence of vestibular schwannomas or other NF2 tumors.[12,13]

Aims

Neurocutaneous diseases are complex to diagnose and treat and many patients require specialist multidisciplinary management and surveillance. However, due to multiple disease manifestations people with NF1 and NF2 present to different clinicians without specialist expertise in these diseases. Our aim is to provide a succinct accessible guide to the neurofibromatoses for the nonspecialist, including diagnosis, current management protocols, and indications for referral to specialist centers. The goal is optimum provision of care for neurocutaneous disease throughout the UK through partnership between local clinicians, specialist NF centers, and people with NF1 and NF2.

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