Neuroimaging of Neurocutaneous Diseases

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KEYWORDS

• Neuroimaging • Neurocutaneous diseases • Neurofibromatosis • Schwannomatosis • Tuberous sclerosis • von Hippel-Lindau • Sturge-Weber • Lhermitte-Duclos

KEY POINTS

- An in-depth knowledge of the imaging characteristics of the common neurocutaneous diseases (NCD) described in this article will help a neurologist understand the screening imaging modalities in patients with NCD.
- A neuroimager should be able to look for an associated neuroimaging stigmata in specific anatomic areas commonly involved, such as optic pathways in patients with neurofibromatosis type 1 to rule out optic pathway gliomas or high-resolution internal auditory canal images to rule out vestibular schwannomas.
- The detection of tumors and masses in NCD has greatly benefitted with improved availability of high-field strength 3T magnetic resonance imaging (MRI) machines in the past few years.
- Predicting cognitive impairment early on in children with NCS using imaging techniques, such as functional MRI, is not in the distant future.
- Neuroimaging will remain at the heart and soul of the multidisciplinary care of such complex diagnoses to guide early detection and monitor treatment.

INTRODUCTION

The neurocutaneous diseases (NCD) embrace an extensive group of developmental disorders with involvement of skin and central and/or peripheral nervous systems. The term *phakomatosis* was originally used by Jan Van der Hoeve[1] (an ophthalmologist) in 1933 to encompass the 3 known NCD at the time, known by their eponyms: Bourneville disease (tuberous sclerosis), Recklinghausen (neurofibromatosis type 1 [NF1]), and von Hippel-Lindau disease (VHL), referring to the lentiform retinal lesions (hamartomas) commonly seen in these 3 conditions. The subsequent inclusion of Sturge-Weber syndrome (SWS) in this group made this term less appropriate because

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Neurol Clin 32 (2014) 159–192
http://dx.doi.org/10.1016/j.ncl.2013.07.003 **neurologic.theclinics.com**
0733-8619/14/$ – see front matter Published by Elsevier Inc.

it was not associated with similar retinal lesions, necessitating the introduction of the term *neurocutaneous syndromes*.[2] Over the years, not less than 60 such NCD have been described.[3] Apart from the 5 common conditions with pathognomonic neuroimaging findings, namely, NF1, neurofibromatosis type 2 (NF2), tuberous sclerosis complex (TSC), VHL, and SWS, the other described NCD are quite rare; the associated neuroimaging stigmata are often nonspecific. The pathologic features in NCD are either caused by problems related to neural crest cells migration and terminal differentiation or from tumor-suppressor gene dysfunction; both of these processes are genetically regulated. The diagnostic criteria and extensive clinicopathologic features of these conditions have been described in many reference texts.[3] The emphasis of this article is primarily on neuroimaging characteristics of the common NCD and appropriate use of advanced imaging for the diagnosis and monitoring of these conditions.

NF1 (VON RECKLINGHAUSEN DISEASE)

NF1 is the most frequent of the NCDs, although age-dependent presentation, clinical variability, and increased mortality in adulthood make it difficult to obtain precise population-based prevalence estimates. A 1956 population survey among Michigan residents showed an estimated incidence at birth of 30 to 40 cases per 100 000,[4] which was similar to that reported in a more recent German study among elementary school children, with an estimated incidence of 30 to 38 cases per 100 000 live births.[5] Moreover, it was demonstrated that NF1 can be diagnosed by 6 years of age in most cases by routine physical examination with special attention to the disease-associated skin stigmata. About 50% of cases are autosomal dominant, with virtually 100% penetrance by adulthood,[6] and the rest resulting from de novo germline mutations in the NF1 gene located at chromosome17qll.2, which encodes for a negative regulator of the RAS oncogene, neurofibromin.[7] About 90% of new mutations occur on the paternally derived chromosome.[8] Some of the clinical features seen in NF1 are attributed to neural crest dysfunction, such as café au lait macules secondary to abnormal melanocyte differentiation from the rhombencephalic neural crest, and an increased incidence of hypertelorism caused by incomplete formation of the intercanthal ligament caused by the involvement of prosencephalic neural crest derivatives. Subcutaneous connective tissue, including adipocytes, and Schwann cell tumors are also, in part, caused by prosencephalic neural crest dysfunction, although impaired tumor-suppressor gene function predisposes to neoplasia. The median age at death for patients with NF1 was 59 years on a review of US death certificates from 1983 to 1997.[9] Another analysis found about 50% of patients with NF1 can expect to live beyond 71 years of age,[10] with the main causes of early mortality directly attributed to the increased incidence of malignant neoplasms, especially the malignant peripheral nerve sheath tumor (MPNST) and glioma. Because there are no preventative treatments available, the primary strategy to prolong life expectancy in NF1 is ostensibly through early detection by screening neuroimaging and treatment of the malignancies.

Neuroimaging Abnormalities in NF1

Intracranial neoplasms

Patients with NF1 are 5.5 times more likely to have an intracranial neoplasm listed on their death certificate and about 8 to 11 times more likely among those younger than 40 years, compared with the general population.[9] The most common intracranial neoplasms in NF1 include glioma, cranial nerve schwannoma, and plexiform