Chapter 22
Overview of Neurocutaneous Syndromes

Amanda Bergner

The neurocutaneous syndromes are a diverse group of over 100 described disorders that are unified by involvement of the nervous system and the skin. Other organ systems, such as the eyes, kidneys, and heart, are often involved. Outside of the nervous system, common findings include hypo- or hyper-pigmentation of the skin, cutaneous and/or internal vascular dysplasias, neoplasms (primarily benign, but sometimes malignant) and overgrowth. Primary neurocutaneous syndromes are developmental conditions that involve genetic dysregulation. Secondary neurocutaneous disorders are not developmental in nature, but rather result as a complication of another condition, often metabolic. The distinction between primary and secondary neurocutaneous syndromes is important, as both pathogenesis and prognosis differ.

Diagnosis of primary neurocutaneous syndromes is typically made using a combination of clinical exam and diagnostic testing. Most primary neurocutaneous syndromes can be diagnosed based on established clinical criteria and do not require genetic testing, though genetic testing can sometimes assist with the diagnostic process and is often used to inform management of the family. The most frequent clinical evaluations include neurology, dermatology, and ophthalmology to obtain the clinical history and examine the most commonly affected body systems for the presence of characteristic features of each condition. Diagnostic testing that can assist evaluation includes X-ray, MRI, CT scan, EEG, and blood and/or urine tests.

Although the majority appear to be sporadic, many primary neurocutaneous syndromes exhibit Mendelian inheritance patterns. All types of Mendelian

A. Bergner (✉)
Department of Neurology, Johns Hopkins University School of Medicine, 600 North Wolfe Street, Phipps 117, Baltimore, MD 21287, USA

McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, 600 North Wolfe Street, Phipps 117, Baltimore, MD 21287, USA
e-mail: abergne1@jhmi.edu

J.S. Goldman (ed.), *Genetic Counseling for Adult Neurogenetic Disease*,
DOI 10.1007/978-1-4899-7482-2_22

inheritance patterns have been described among the primary neurocutaneous syndromes, including autosomal dominant (as in neurofibromatosis and tuberous sclerosis), autosomal recessive (as in ataxia telangiectasia), and X-linked (as in incontinentia pigmenti) [1]. The most common syndromes based on known incidence are neurofibromatosis (including neurofibromatosis 1, neurofibromatosis 2, and schwannomatosis) and tuberous sclerosis, which will be discussed in this chapter. As with other conditions addressed in this book, the counseling issues presented in the context of the conditions reviewed in detail here may be relevant to many other primary neurocutaneous syndromes.

22.1 Genetic Counseling Issues for Neurocutaneous Syndromes

Primary neurocutaneous syndromes are developmental, and therefore, present at birth. However, many symptoms may not appear until later in life. As such, patients can experience lifelong issues and concerns. When considering the genetic counseling issues for adults with primary neurocutaneous syndromes, several common themes recur.

22.1.1 Accuracy of Diagnosis

In many primary neurocutaneous syndromes, features present at birth or in childhood may recede, fade, be corrected, or be removed by adulthood, potentially making a physical exam less than fully informative when assessing for specific diagnostic criteria. Additionally, medical records from childhood may not be readily available for review, and adults may not remember the details of their medical care from childhood. Another concern is that a diagnosis made in childhood may no longer be accurate given changes in medical understanding during the intervening years. Prior to offering genetic counseling for an adult with a primary neurocutaneous syndrome, it is imperative to confirm the diagnosis by current standards. A thorough physical exam coupled with a detailed medical history and review of medical records is often necessary to determine the accuracy of a diagnosis. In cases in which the current diagnostic criteria cannot be met, but a particular diagnosis is suspected, genetic counseling should be undertaken with the caveat that the information provided only applies if the diagnosis is in fact accurate. In these situations, genetic testing can often assist in confirming a specific diagnosis.

22.1.2 Inheritance Pattern and De Novo Mutations

In order to provide accurate genetic counseling, the inheritance pattern of the condition in question must be known, as primary neurocutaneous syndromes can be inherited in a variety of ways. Additionally, in the setting of autosomal dominant conditions, not every affected adult has an affected parent. Each autosomal dominant primary neurocutaneous syndrome has its own rate of *de novo* mutation. For instance, while 50 % of adults with neurofibromatosis have an affected parent, only about a third of adults with tuberous sclerosis do [1, 2].

22.1.3 Mosaicism

Adults with an autosomal dominant primary neurocutaneous syndrome due to a *de novo* mutation may have a mosaic form of the condition in question. The original putative mutation could have been somatic and occurred during the cascade of cell divisions during pregnancy rather than in the germ cells. Mosaicism can impact the calculation of reproductive risk for an adult with a primary neurocutaneous syndrome who is interested in having children, as the mutation may not be present in every cell of their body, including their germ cells. The possibility of mosaicism can also impact the ability to locate a mutation, depending on the tissue type that is used for testing [3].

22.1.4 Availability of Comprehensive Genetic Testing

The availability of comprehensive genetic testing for primary neurocutaneous syndromes varies. Many conditions are single-gene disorders for which genetic testing is available and comprehensive. For example, one gene, *Nf1*, causes neurofibromatosis 1 (NF1), and approximately 97 % of people meeting clinical criteria for this condition are found to have a mutation in this gene [3]. Some conditions are associated with multiple genes, though still have a fairly high rate of mutation detection when combined. Thus, tuberous sclerosis, which is associated with *TSC1* and *TSC2*, has a combined sensitivity of approximately 85 % for people meeting clinical criteria for this condition [4]. However, other primary neurocutaneous syndromes have not yet been fully characterized, such as schwannomatosis for which the known genes only account for approximately 40–50 % of affected individuals.

Without the availability of comprehensive genetic testing, many aspects of genetic counseling can be complicated, such as confirming a diagnosis, offering

reproductive options, and interpreting negative test results. Additionally, it is important to know the conditions for which one gene test is appropriate versus a panel of gene tests. One must also know which tissue to send for testing to allow for the greatest likelihood of mutation detection. Thus, prior to offering genetic testing to an adult with a primary neurocutaneous syndrome, a complete understanding of the genes involved, the tests available, the sensitivity of each test, and the appropriate tissue to send for testing must be obtained.

22.1.5 Reproductive Decision-Making

Adults with primary neurocutaneous syndromes are often diagnosed prior to having children themselves, though this is not always the case. Symptoms may be subclinical and diagnosed only when an affected child is born. When working with an adult with a primary neurocutaneous syndrome, it is important to assess whether they already have children and whether they are desirous of having children in the future. Genetic testing and counseling regarding recurrence risk and options for prenatal testing and interventions are appropriate for this population and frequently requested. Some adult patients indicate that they have already decided not to have children of their own, either to prevent passing a syndrome to their children or because of the uncertainty about their own health and capacities as they age. It is important to assess the patient's understanding about the inheritance pattern and likelihood of passing a syndrome to a child to be certain that the information upon which these decisions are based is correct and complete.

22.1.6 Stigma and Discrimination

Many adults with primary neurocutaneous syndromes will have symptoms that are evident to others, including both physical and functional differences. It is common for people with these disorders to report experiences of stigmatization and discrimination throughout their life, particularly if symptoms occur in routinely exposed parts of the body, such as the face or hands [5]. In order to provide appropriate support to maximize current psycho-emotional functioning, it is important to assess whether stigma or discrimination has been a large part of a patient's life. It is also common for these experiences to impact reproduction and medical care decision-making. Providers with an understanding of this aspect of their patients' experience are often better able to form positive partnerships around management choices.

22.1.7 Recurrent Loss/Progression of Symptoms

Primary neurocutaneous syndromes are often progressive, with symptoms increasing in number and/or severity across the life span. Additionally, medical interventions can themselves introduce further morbidity, as in the loss of hearing upon surgical removal of a vestibular schwannoma that was impinging on the brain stem of a patient with neurofibromatosis 2 (NF2). By adulthood, many people with primary neurocutaneous syndromes have already experienced multiple functional losses and may have many ahead of them. It is important for providers working with this population to appreciate the chronicity of loss that might exist for their patients and to address this directly as part of the management plan. Depression and anxiety are frequently reported comorbidities with primary neurocutaneous disorders, and can be related to the current or expected progression of symptoms.

22.1.8 Uncertainty

Uncertainty about possible future symptoms is a reality with these conditions. It is not possible to predict which symptoms will occur, when they will arise, or how much of an impact they will have. This uncertainty can challenge both emotional and psychological well-being. Directly addressing the uncertainty can be beneficial to the patient by identifying ways in which they may manage this aspect of their condition most successfully.

22.2 Family History Questions Pertinent to Primary Neurocutaneous Syndromes

Targeted questions about family history can help determine if a condition is hereditary and assist with diagnosis. A three generation pedigree should always be obtained and include documentation of any medical condition, particularly those impacting the neurologic, dermatologic, and ophthalmologic systems. When taking a pedigree, questions that are relevant to the specific diagnosis under consideration should be asked. Some examples are listed below:

- Does anyone have spots on their skin that are either darker or lighter than the rest of their body?
- Does anyone have cancer or tumors?
- Has anyone had a growth/mass removed?
- Does anyone have lumps or bumps under their skin that do not go away?
- Does anyone have trouble hearing or have ringing in their ears?
- Does anyone have trouble seeing or any other eye problems?

- Does anyone have seizures?
- Does anyone have a heart defect or an arrhythmia?
- Did anyone have bone problems at birth or as a young child?
- Does anyone have kidney problems, including diabetes?
- Does anyone have trouble walking?
- Does anyone have hypertension, stroke, or other vascular problems?

References

1. Jenterra, G., Synder, S. L., & Narayanan, V. (2006). Genetic aspects of neurocutaneous disorders. *Seminars in Pediatric Neurology, 3*(1), 43–47.
2. DeBella, K., Szudek, J., & Friedman, J. M. (2000). Use of the National Institutes of Health criteria for diagnosis of neurofibromatosis 1 in children. *Pediatrics, 105*(3), 608–615.
3. Boyd, K. P., Korf, B. R., & Theos, A. (2009). Neurofibromatosis type 1. *Journal of the American Academy of Dermatology, 61*(1), 1–14.
4. Sancak, O., Nellist, M., Goedbloed, M., Elfferich, P., Wouters, C., Maat-Kievit, A., et al. (2005). Mutational analysis of the TSC1 and TSC2 genes in a diagnostic setting: Genotype–phenotype correlations and comparison of diagnostic DNA techniques in Tuberous Sclerosis Complex. *European Journal of Human Genetics, 13*(6), 731–741.
5. Vranceanu, A. M., Merker, V. L., Park, E., & Plotkin, S. R. (2013). Quality of life among adult with neurofibromatosis 1, neurofibromatosis 2 and schwannomatosis: A systematic review of the literature. *Journal of Neuro-Oncology, 114*(3), 257–262.