Malignant tumors can also occur, likely due to malignant transformation.

Clinical Presentation

Patients can present with NF1 in a variety of ways. All NF1 patients can be identified by clinical criteria before 20 years of age, but those with mild symptoms may not realize they have the disorder. Diagnosis is based on clinical criteria, having two or more of the following: (1) six or more café-au-lait macules larger than 5 mm in prepubertal patients or more than 15 mm in postpubertal individuals (Fig. 115-2), (2) two or more neurofibromas of any type or one plexiform neurofibroma, (3) axillary or inguinal freckling, (4) sphenoid bone dysplasia, (5) optic nerve glioma, (6) iris Lisch nodules, and (7) a family history of NF1. Other comorbid conditions frequently seen are learning disabilities, macrocephaly, and epilepsy. Important complications of NF1 include scoliosis, gastrointestinal neurofibromas, pheochromocytomas, and renal artery stenosis.

Diagnosis/Differential

The diagnostic criteria outlined above are highly sensitive and specific. Neuroimaging and DNA testing can be useful as well. There are many other disorders that present with hyperpigmented skin macules. Schwannomatosis and neurofibromatosis type 2 (see Neurofibromatosis type 2) may also be mistaken for NF1.

Treatment

Most individuals with NF1 do not require specific treatment though ongoing periodic surveillance is recommended. Many identified tumors can be followed without surgery. Painful subcutaneous neurofibromas can be excised, though they may recur. Genetic counseling should be provided to all patients and families.

Prognosis

There is as much variability in disease course as there is in clinical presentation. Even within families, some individuals may have only skin findings with no symptoms, while others have more complications including malignant transformation of plexiform neurofibromas. While it is an autosomal dominant condition, about half of the cases are sporadic due to new mutations.

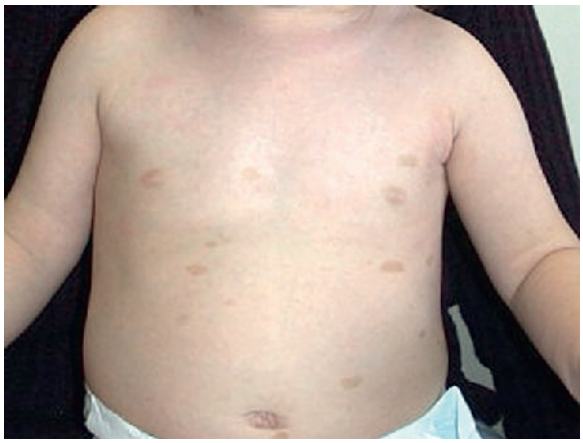

FIGURE 115-2 Multiple café-au-lait spots in a child with neurofibromatosis type 1. (From Shah KN: The diagnostic and clinical significant of café-au-lait macules, Pediatr Clin N Am 57:1131-1153, 2010, Fig. 3.)

Neurofibromatosis 2 (NF2)

Definition/Epidemiology

Neurofibromatosis type 2 (NF2) is an autosomal-dominant adult onset disease characterized by bilateral vestibular schwannomas and brain tumors. It is caused by mutations in the gene, *NF2*, whose protein product is merlin (schwannomin). It affects approximately 1/30,000 individuals.

Pathology

Despite the name, the primary tumor types seen in NF2 are schwannoma and meningioma. Merlin behaves as a tumor suppressor gene.

Clinical Presentation

The diagnosis is generally made when bilateral VIII nerve tumors are identified (often by MRI). The diagnosis can be made based on other clinical criteria (some combination of family history of NF2; presence of characteristic tumors—meningioma, schwannoma, neurofibroma, or posterior subcapsular lenticular opacities.) Symptoms of NF2 begin in the second to fourth decades usually with onset of hearing loss. Skin lesions are present in a minority of patients with NF2.

Diagnosis/Differential

NF2 is frequently misdiagnosed as NF1, especially if there are café-au-lait spots. Patients with NF2 may be misdiagnosed as having isolated meningioma or unilateral vestibular schwannoma if other findings are not sought. Schwannomatosis can be distinguished by the absence of vestibular schwannomas.

Treatment

Eventual removal of the schwannomas and other tumors is usually indicated, though later in life when the tumors are larger and causing significant symptoms. There may be post-surgical complications and tumors may recur.

Prognosis

The vestibular tumors, leading to deafness and vestibular symptoms contribute greatly to the morbidity of this condition. Mortality is related to tumor growth.

Tuberous Sclerosis Complex (TSC)

Definition/Epidemiology

Tuberous Sclerois Complex (TSC) is an autosomal dominant disorder of early cellular differentiation, proliferation, and migration, which results in hamartomatous lesions involving multiple organs at different stages. Sporadic cases are frequent because of spontaneous mutations. The incidence is 1/6000. Two genes, *TSC1* and *TSC2*, are known to cause TSC and account for