Brief Report

Tuberous Sclerosis in Early Infancy: A Case Report

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The diagnosis of tuberous sclerosis in an infant was delayed by 3 months. Failure to take an adequate patient history because of a language barrier between parents and caregivers and to observe the classic stigmata of tuberous sclerosis contributed to the delay. A brief review of the case and the diagnosis of tuberous sclerosis is presented.
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The occurrence of seizures in an infant is a frightening experience for parents and physicians alike. In this case report important historical information and unique physical findings are described that helped determine the cause of seizures in a 4-month-old infant.

Case Report

The infant weighed 9 lb 3 oz at birth. His mother had an uncomplicated prenatal course and an uneventful delivery. The infant's Apgar scores were 8/8 at 1 and 5 minutes. His parents, Spanish-speaking immigrants from Mexico, had two other healthy children. The family received all their medical care at a multiresidency teaching hospital.

During a well-child visit at 6 weeks of age, vitiligo was noted in the infant's chart. The physician described several small "café-au-lait–like spots [that] failed criteria in number and size." The remainder of the history and physical examination was unremarkable.

At 2 months of age, the baby was admitted to the hospital for treatment of a relatively uncomplicated bout of respiratory syncytial virus (RSV) bronchitis during a community-wide outbreak. He was discharged after 2 days. No observations of abnormal behavior or unusual cutaneous findings were noted. At a postdischarge follow-up visit, he was found to be well except for bilateral otitis media, for which an antibiotic was prescribed.

One month later, a physician recorded in the infant's chart the appearance of ash-leaf-shaped spots and suggested that tuberous sclerosis be considered. Further evaluation was apparently delayed because of a diagnosis of persistent otitis media, which required repeat administrations of antibiotics.

During the infant's 4th month of life, several visits to physicians were made for fussiness and fever. Otitis media was diagnosed several times. In addition, the parents observed and reported an abnormality in the baby's behavior that they described in Spanish as *ataques*, a term commonly used to describe fits or seizures. During clinical encounters interpreters translated conversations between the physicians and the parents. Because the *ataques* were of very brief duration and no abnormal physical findings were noted, the physicians concluded that the parents were observing normal infantile movements.

The *ataques* continued, however. The parents became very distressed and sought a second opinion at our family practice clinic. During the examination of the now 4½-month-old child, a 5-minute series of repetitive myoclonic jerks occurred. Although the child was afebrile the decision was made to test for meningitis so that it could be ruled out as a cause of the seizures.

During the process of lumbar puncture and blood collection, further historical data were gathered by a Spanish-speaking physician. The father reported that the infant jerked at times as if shocked ("*brincar como tocado con electricidad*") and he vividly demonstrated a full-body myoclonic jerk. The baby appeared agitated but not ill. The physician noted that a 2-cm patch of the infant's scalp hair was white. Several café-au-lait spots of approximately 1 to 2 cm were observed, as were two hypopigmented oval macules of 6 to 8 cm in length. A tentative diagnosis of tuberous sclerosis was made.

Administration of phenobarbital and antibiotics was begun. Laboratory data were entirely normal; however, a computed tomography (CT) scan of the head demonstrated multiple focal paraventricular calcifications consistent with tuberosous sclerosis. An ophthalmologic

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consultation confirmed hypopigmentation of the right optic disc and a right retinal astrocytic hamartoma. A pediatric neurologist observed six ash-leaf-shaped spots. An electroencephalogram (EEG) was normal. The child was discharged 2 days after admission, having had no more myoclonic jerks.

The parents met with the family practice team before discharging the infant. They expressed anger at the doctors who had not discovered their infant's "*infección*." Although they were carefully informed in Spanish that the infant was not suffering from an infection and was not contagious, they did not understand the genetic explanation for their son's symptoms. They had recognized pigmentary changes when the child was a few weeks old, and believed he had been "infected" at birth with the disease that was causing the *ataques*. They understood and accepted the need for antiseizure medication. When informed that the infant might be developmentally delayed and that their child's future health was uncertain, the parents responded in a manner appropriate to their culture: one of resignation and devoted care.

Discussion

This case presentation illustrates the importance of taking an adequate history. Despite linguistic and cultural barriers, earlier diagnosis might have been achieved in this case based on the clinical history alone. When the father was given the opportunity to mimic his child's seizure activity, he did so vividly. Parents, even those who are poorly educated or from different linguistic backgrounds, are the usual source of most valuable clinical information. A supportive environment and appropriate use of interpreters can provide parents with the reinforcement necessary to encourage them to share important information. Also in this case, dermal stigmata of tuberosis sclerosis were noted first at 6 weeks of age and then commented on in greater detail at 4 months of age. Had these findings been pursued sooner, a diagnosis might have been reached earlier.

Tuberous sclerosis (TS), which has also been called hereditary multiple hamartomatosis, is a multisystem disease of relatively low incidence. The incidence of TS is variously reported as from 1 to 15 cases per 300,000.[1–7] Tuberous sclerosis was first described in 1862 by von Recklinghausen.[1] In 1911, Sherlock coined the term *epinoia* (*epi* stemming from "epilepsy" and *anoia* from "mindless").[1] Bourneville, whose name is associated with the disease, coined the term *tuberous sclerosis*.[1] Vogt is associated with the diagnostic triad of mental retardation, adenoma sebaceum, and epilepsy.[8] Tuberous sclerosis has traditionally been described as one of the phakomatoses or neurocutaneous syndromes.[4,8] The hallmark lesions are fibroangiomas, or tubers, that vary in size and location. A variety of other associated skin lesions are discussed below. Central nervous system fibroadenomas become calcified and may cause focal or generalized seizures and, in some cases, hydrocephalus. Retinal hamartomas are pathognomonic, and their radiographic appearance has been likened to candle wax drippings or gutterings. So-called mulberry tumors or phakomas are noted on the retina. Half of affected children are reported to have rhabdomyomas of the heart. There is also a very high incidence of renal tumors, and lung lesions are sometimes encountered.

Tuberous sclerosis classically presents during infancy with seizures or myoclonic jerks. It is generally believed that the earlier the seizures occur, the more severe the syndrome will be.[2] It is estimated that only one third of afflicted individuals have normal intelligence.[3] Seizures can appear as early as 1 week of age; in one series only 8% of those children with seizure onset before 1 year of age had normal intelligence.[3]

Traditionally, the skin has been believed to be the most commonly affected organ system in TS. A white tuft of hair, poliosis, is often the earliest sign of TS. Poliosis occurs in only 3% of normal births.[9] Other dermal stigmata that may be identified early include café-au-lait spots, oval hypopigmented macules, and port wine hemangiomas.[1,10–12] As the afflicted child grows, subungual and periungual fibromas are noted, as are polyps in other parts of the body. Adenoma sebaceum, pathognomonic lesions, begin to be visible from age 2 to 6 years and occur in more than 50% of patients. So-called shagreen patches develop at about the same time of onset of adenoma sebaceum in 15% to 20% of afflicted individuals. Lancate white macules or ash-leaf-shaped spots, are not pathognomonic. Gomez[10] cautions that "there are individuals with typical hypomelanotic macules who do not have TS [and] there are individuals with TS who do not have even one hypomelanotic skin macule even under ultraviolet light illumination."

Tuberous sclerosis is considered a genetic disease of variable penetrance and has been linked to abnormalities of the long arm of chromosome 9.[8,13,15,16] Linkage studies are underway in an attempt to confirm localization of a specific gene. Eventually, molecular DNA analysis may provide more information about the cause of TS.[14] Because of the putative genetic origin of this disease, careful investigation of family members is indicated. All first-degree relatives should undergo a complete physical examination and evaluation.

The majority of TS patients develop seizures. The most common seizures, as in the case discussion, are

Table 1. Primary Diagnostic Criteria of Tuberous Sclerosis

- Cortical tubers
- Facial angiofibromas
- Retinal hamartomas
- Subependymal glial nodules
- Ungual fibromas

Modified from Gomez[14] and Roach, et al[23,24]

infantile spasms. Some series have reported that up to 70% of TS patients suffer from infantile spasms.[17] Other commonly seen seizure types include generalized tonic clonic seizures and focal seizures. In up to 75% or more of TS patients, EEGs are reportedly abnormal. The most common abnormal findings include epileptiform abnormalities and slow-wave abnormalities. Twelve percent of TS patients are reported to have normal EEGs.[14] It has been argued that the degree of EEG abnormality is proportionate to the degree of mental retardation.[14] Patients with generalized seizures are generally believed to experience greater retardation than those patients with focal seizures.[14] The development of CT and magnetic resonance imaging (MRI) has facilitated the diagnosis of TS.[4,18–22] Definitive diagnosis of tuberous sclerosis can be made in the presence of any of the findings found in Table 1.

The prognosis of patients with TS is difficult to predict with certainty. As a general rule, it is observed that the earlier the onset of seizures or the larger the number of lesions identified at an early age, the more severe the impact of the disease will be and the poorer the prognosis. In individual cases, however, it is probably best to adopt an expectant attitude, as a significant minority of TS patients develop normally.[3]

The occurrence of myoclonic jerks in an infant should suggest TS. Cutaneous stigmata should also raise suspicion of TS, if not identify infants with the disease. As there is no definitive treatment for TS, the physician should focus on identifying and treating associated lesions and on providing genetic counseling for the family. Referral to regional or state agencies that have special resources for the care of individuals with central nervous system genetic conditions would also be appropriate.

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