CHAPTER
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CHAPTER OUTLINE

The Differential Diagnosis and Boundaries of Migraine

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INTRODUCTION

Migraine is the second most common pain condition, next to tension-type headache (Rasmussen et al., 1991; Russell et al., 1995). Its diagnosis relies exclusively on the patient's history and exclusion of secondary causes ruled out by a normal physical and neurologic examination or appropriate investigations (ICHD-II, 2004). The only objective marker in the most common types of migraine is the increased excretion of 5-hydroxyindoleacetic acid in urine after a migraine attack (Sicuteri et al., 1961), although some individuals with the rare sporadic or familial hemiplegic migraine might carry a point mutation in the *CACNA1A, ATP1A2,* or *SCN1A* genes (Ophoff et al., 1996; De Fusco et al., 2003; Dichgans et al., 2005). Thus the differential diagnosis and boundaries of migraine pose a real challenge.

DIFFERENTIAL DIAGNOSIS FOR MIGRAINE WITHOUT AURA

Migraine without aura is characterized by headache (symptoms) and accompanying symptoms (photophobia and phonophobia, nausea and vomiting). The most common differential diagnosis for migraine without aura is tension-type headache. The pain characteristics of migraine without aura and tension-type headache are complementary; that is, migraine without aura is usually a unilateral pulsating moderate/severe headache that is aggravated by physical activities, while tension-type headache is usually a bilateral pressing mild/moderate headache that is not aggravated by physical activities (ICHD-II, 2004). However, it is the usual lack of accompanying symptoms that makes the differential diagnosis of tension-type headache easy, although tension-type headache can also be accompanied by photophobia or phonophobia. The correct diagnosis of migraine without aura versus tension-type headache is important for correct management of the former condition, as triptans are not effective in tension-type headache (Tfelt-Hansen, 2007).

Cluster headache is another primary headache that is part of the differential diagnosis for migraine without aura. Usually it is easy to differentiate between cluster headache and migraine without aura owing to their different attack patterns—that is, attacks in clusters versus episodic attacks. Furthermore, cluster headache is characterized by one or more associated symptoms, such as lacrimation, conjunctival injection, miosis, eyelid edema, ptosis, nasal congestion, rhinorrhea, facial sweating, and a sense of restlessness or agitation that is not seen in migraine without aura (ICHD-II, 2004). At its onset, however, cluster headache might be mistaken for migraine without aura because the associated symptoms might be missed by the patient, may not be pronounced, or may

not be present (Russell & Andersson, 1995; Sjöstrand et al., 2005). Similarly, chronic cluster headache might be difficult to differentiate from chronic migraine, given that chronic cluster headache is sometimes characterized by a milder headache between the more severe attacks of cluster headache.

The differential diagnoses for migraine without aura also include secondary migraine without aura. A major reason to suspect secondary migraine without aura is its onset in close temporal relation to another disorder. Migraine without aura is caused by a combination of genetic and environmental factors (Russell et al., 1995). First-degree relatives of probands with migraine without aura have a 1.9-fold (statistically significant) increased risk of migraine without aura compared to the general population (Russell & Olesen, 1995). Interestingly, first-degree relatives of probands with migraine without aura that occurred in relation to a head trauma have no increased risk of migraine without aura (Russell & Olesen, 1996b). Thus head trauma in a susceptible individual might cause migraine without aura. However, head trauma is very common, and not all people experience onset of migraine without aura after trauma. Other secondary causes include atriovenous malformation, MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke), and antiphospholipid antibody disease (Pavalakis et al., 1984; Chabriat et al., 1995; Cervera et al., 2002).

Because migraine without aura is very common, co-occurrence of migraine without aura and other disorders is not rare. Thus, to establish a causal relationship, the occurrence of migraine without aura should be significantly increased as compared to the risk of migraine without aura in the general population (Weiss et al., 1982; Khoury et al., 1988). Suspicion of a secondary cause for migraine without aura should be raised if the symptoms are always located on the same side, attack frequency is dramatically changed, or age at onset is after age 40 years. This presentation requires a careful work-up that includes a physical and neurologic examination as well as magnetic resonance imaging (MRI) of the brain.

DIFFERENTIAL DIAGNOSIS FOR AURA

The migraine aura reflects reversible cerebral cortical dysfunction of vision, speech, sensory, and/or motor function. The gradual development and sequential march of the aura symptoms are caused by cortical spreading depression, in which a brief excitation of the occipital cortical neurons initiates a depolarization wave that moves across the cortex at a rate of 3–5 mm/min, and is followed by prolonged depression of the neurons (Leão, 1944a, 1944b). This event is followed by a reduction in the regional cerebral blood supply in persons with typical migraine with aura and hemiplegic migraine, which is not present in persons with migraine without aura (Olesen et al., 1981; Lauritzen & Olesen, 1984; Olesen et al., 1990).

The typical migraine with aura is characterized by visual aura followed by headache, with one-fourth and one-third of patients also experiencing dysphasic (speech) and sensory aura in some of their attacks (Russell & Olesen, 1996a). The sequence observed usually consists of first visual, then dysphasic, and finally sensory aura. If motor aura is present, the presentation is classified hemiplegic migraine (ICHD-II, 2004). Most persons with hemiplegic migraine experience all types of aura, including basilar-like aura, usually in the sequential order of visual, sensory, motor, aphasic, and basilar-like aura, although the order is different in approximately 30% of affected individuals (Thomsen et al., 2002, 2003). If the sequential order of the aura symptoms is not logical according to the locations of the different areas in the brain, the symptoms might be due to memory bias, and prospective recordings of the aura might illuminate this issue (Russell et al., 1994).

The gradual development and duration of the migraine aura over at least 20 minutes is unique for migraine with aura—that is, for typical migraine with aura and hemiplegic migraine. In contrast, an epileptic aura has a duration of a few seconds, transient ischemic attacks have a sudden onset with a duration of less than 24 hours, and stroke causes permanent neurologic signs. Thus a precise history of the aura will, in most cases, provide the crucial information necessary for a precise diagnosis.

DIFFERENTIAL DIAGNOSIS FOR TYPICAL MIGRAINE WITH AURA

The aura in typical migraine with aura can be followed by a migraine headache, a tension-type headache, or no headache. Onset may occur at all ages, though it usually takes place within the first four decades of life; by comparison, the typical migraine with aura without headache might have an onset later in life. Cautions should be taken with people in whom attack frequency is dramatically changed, as this alteration in pattern may be caused by reversible cerebral vasoconstriction (Ducros et al., 2007). The risk of typical migraine with aura is also increased in people with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy

(CADASIL) (Tournier-Lasserve, 1993). Other secondary causes could be similar to those causing hemiplegic migraine (discussed in the next section). Visual aura is nearly always present in typical migraine with aura (Russell & Olesen, 1996a). Thus a person without visual aura should be suspected to have a secondary cause.

DIFFERENTIAL DIAGNOSIS FOR HEMIPLEGIC MIGRAINE

Stroke is the first differential diagnosis considered for hemiplegic migraine, especially if the aura description is insufficient. A young age at onset points the diagnosis in the direction of a hemiplegic migraine attack. Although typical migraine with aura is a risk factor for stroke, particularly in young women, the risk of stroke in hemiplegic migraine is unknown (Tzourio et al., 1995).

Alternating hemiplegia of childhood (AHC) is characterized by paroxysmal episodes of hemiplegia, quadriplegia, choreoathetotic movements, and nystagmus that disappear immediately after sleep, along with progressive mental retardation and development of permanent neurologic deficits such as choreoathetosis, dystonia, and ataxia (Bourgeois et al., 1993). AHC is usually a sporadic disorder with onset prior to age 1½ year, whereas onset of hemiplegic migraine usually occurs at an older age. In addition, co-occurrence of mental retardation is rare in hemiplegic migraine.

Coma sometimes occurs in severe attacks of hemiplegic migraine. Its emergence requires an extensive work-up to exclude other symptomatic causes such as hypoglycemia, cerebral hemorrhages, mass lesion, and infections. Fever and meningismus can be observed during attacks of hemiplegic migraine, and their presence requires exclusion of bacterial and viral meningitis, sepsis, and inflammatory diseases from the diagnosis. Permanent cerebellar signs occur in 40% of the families with familial hemiplegic migraine caused by point mutations in the *CACNA1A* gene (Ducros et al., 2001).

A series of secondary causes of hemiplegic migraine have been reported. In one case reported in the literature, a parasagittal meningeoma in the left parietal-occipital region caused alternating attacks of typical migraine with aura and sporadic hemiplegic migraine for 17 years in a 42-year-old woman. The aura was strictly right-sided and spread in the sequential order of visual, aphasic, sensory and motor aura, including dysarthria, and then headache (Vetvik et al., 2005). Other secondary causes of hemiplegic migraine may include Sturge-Webers syndrome, Epstein-Barr virus infection, avascular necrosis associated with anticardiolipin antibodies, childhood lupus erythematosus, progressive facial hemiatrophy, ornithine transcarbamylase deficiency, MELAS, and CADASIL (Leavell et al., 1986; Montagna et al., 1988; de Grauw et al., 1990; Seleznick et al., 1991; Klapper, 1994; Parikh et al., 1995; Hutchinson et al., 1995; Woolfenden et al., 1998; Dora & Balkan, 2001). A secondary cause of hemiplegic migraine should be suspected if the aura symptoms always occur on the same side, as nonsymptomatic attacks of hemiplegic migraine usually change side from attack to attack. Other reasons to be suspicious for a symptomatic cause are atypical aura symptoms, increasing frequency of attacks, a change in the headache pain's character, a change in the efficacy of the usual medication, and occurrence of persistent neurologic symptoms or signs.

CONCLUSIONS

The paroxysmal nature of migraine and its reversible neurologic symptoms usually make the diagnosis of this condition straightforward, especially if a precise headache history and aura description are ascertained. The health-care provider should be suspicious of a secondary cause if the migraine headache and/or aura symptoms are always located on the same side, if the attack frequency increases significantly, if the efficacy of the usual medication changes, or if the neurologic symptoms or sign become permanent.

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