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REVIEW ARTICLE

Diagnostic criteria for CADASIL in the International Classification of Headache Disorders (ICHD-II): are they appropriate?

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Abstract We reviewed the characteristics of headache in patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), to verify the appropriateness of the International Classification of Headache Disorders, second edition (ICHD-II) criteria. Available data were found through Medline/PubMed using the keyword "cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)". The search was restricted to studies published in English in the years between 1993 and 2008. We excluded studies that did not report original data on CADASIL and information regarding the presence of headache. We found 34 studies reporting data on 749 patients overall; 387 (51.7%) patients had headache. According to the authors' definition, 356 (92%) patients were reported as having migraine and 31 (8%) as having headache. Of the 356 patients who were defined as migraineurs, 125 (35.1%) had migraine with aura, 7 (2%) migraine without aura, 156 (43.8%) unspecified migraine and 68 (19.1%) had more than one type of migraine. Among the 31 patients reported as suffering from headache, the headache was not further detailed in 18 (58.1%) patients; it was defined as chronic in 6 (19.3%), as resembling migraine with aura in 4 (12.9%), as resembling migraine without aura in 2 (6.5%) and as tension type in 1 (3.2%) patient. In patients with CADASIL, the headache was usually referred to as migraine and mostly as migraine with aura. However, this referral is formally incorrect since the diagnostic criteria for any type of migraine in the ICHD-II require that the disturbance is not attributed to another disorder. For this reason, we suggest updating the ICHD-II in relation to CADASIL. Our suggestion is to insert a new category referred to as *Headache attributed to genetic disorder* including *Headache attributed to CADASIL.*

Keywords Migraine · Headache · CADASIL · International Classification of Headache Disorders

Introduction

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an adult-onset inherited disease due to mutations in the Notch3 gene on chromosome 19p13 [1–3]. These mutations cause an abnormal accumulation of Notch3 in the cytoplasmic membrane of vascular smooth muscle cells both in cerebral and extracerebral vessels, which appear as granular osmiophilic deposits on electron microscopy [4]. The neuroradiological hallmark of the disease is represented by leukoencephalopathy with lacunaes in the basal ganglia, which can become evident at any stage of the disease [4]. The clinical spectrum of CADASIL includes migraine with or without aura, mood disturbances, transient ischemic attacks or strokes (usually lacunar infarcts) and progressive cognitive decline [1, 2, 4, 5]. Other disturbances are also reported, including epilepsy, acute reversible encephalopathy and myopathy [6, 7].

Headache in patients with CADASIL was first coded, according to the Classification and Diagnostic Criteria for Headache Disorders, Cranial Neuralgias and Facial Pain (ICHD), among headaches associated with other vascular disorders (code 6.9) [8]. Following the ICHD, second edition (ICHD-II), headache in patients with CADASIL is

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coded among the headaches attributed to cranial or cervical vascular disorder (code 6.7.1) on the implicit assumption that a vascular disorder is the cause of the headache [9], an interpretation that, in our opinion, should be reconsidered [5, 10].

To verify the appropriateness of the ICHD-II criteria, we deemed it to be of interest to review the studies reporting any headache in patients with CADASIL.

Methods

Available data for this review were found through Medline/PubMed using the keyword "cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)". For our study, we reviewed all studies published in English between 1993 and 2008. All the retrieved studies were examined by the two of us (SS and DD). We excluded studies that did not report original data on CADASIL such as reviews, meta-analyses, comments and editorials. Among studies describing clinical details of patients with CADASIL, we excluded those in which there was no mention of headache or migraine. To exclude overlapping of CADASIL cases by the same research group, we considered what authors wrote in their studies and, where necessary, contacted the corresponding author.

Two of us (SS and DD) evaluated and classified all the reported cases separately. Any possible disagreement was resolved by a third opinion (AC). We maintained the terminology used by the authors in their studies and, consequently, where authors classified the headache according to the ICHD-II we kept their classification and where they used terms not contemplated in the ICHD or ICHD-II we kept their terminology. We also considered whether the headache was the first symptom or whether it was preceded by an ischemic stroke, TIA or other symptoms such as cognitive and psychiatric disturbances.

Mean age ± standard deviation (SD) was calculated with the method of weighted mean.

Table 1 Studies included in the review

First author	Year of publication	Publication type	Included patients (*n*)	Patients with any headache (*n*)
Arboleda	2002	OR	7	7
Bergmann	1996	OR	10	5
Bohlega	2007	OR	19	7
Brulin	2002	OR	50	32
Ceroni	2000	OR	8	6
Chabriat	1995	OR	45	10
Choi	2006	OR	20	6
Coto	2006	CR	1	1
Dichgans	1998	OR	102	48
Engelter	2002	CR	1	1
Finnilà	2001	CR	1	1
Hutchinson	1995	OR	10	6
Iwatsuki	2001	CR	3	1
Jung	1995	OR	10	3
Kim	2006	OR	5	1
Malandrini	2006	OR	14	4
Mandellos	2005	CR	4	1
Markus	2002	OR	83	31
Mellies	1998	CR	6	5
Pantoni	2004	CR	3	3
Peters	2004	OR	80	27
Ragno	2006	CR	6	1
Razvi	2005	OR	40	26
Rubio	1997	CR	3	3
Rufa	2004	CR	1	1
Sacco	2008	CR	1	1
Schon	2003	CR	6	6
Singhal	2005	OR	112	84
Saskia	2003	CR	6	3
Sullivan	1997	CR	5	2
Valko	2007	CR	1	1
Vahedi	2004	OR	72	41
Vérin	1995	OR	13	11
Williamson	1999	CR	1	1

OR original research, *CR* case report

Results

The Medline/PubMed search identified 590 studies; 508 studies were excluded because they did not report clinical data or because there was no mention of headache, and 48 because their data had been already included in other studies by the same authors. We finally reviewed 34 (5.8%) studies including 16 case reports or letters (Table 1) [1, 5–7, 11–40].

The reviewed studies provided data on 749 patients including 387 (51.7%) who had headache. According to the authors' definition, 356 (92%) patients were reported as having migraine and 31 (8%) as having headache (Table 2).

Out of the 356 patients described as migraineurs, 125 (35.1%) had migraine with aura, 7 (2%) migraine without aura, 156 (43.8%) unspecified migraine, and 68 (19.1%) had more than one type of migraine (Table 3). Among the 125 patients who had migraine with aura, 24 (19.2%) had migraine with typical aura, 7 (5.6%) migraine with prolonged aura, 5 (4.0%) familial hemiplegic migraine, 2 (1.6%) basilar migraine, while in 87 (69.6%) patients the migraine type was not reported. The aura was visual in 10

Table 2 Overall characteristics of patients with CADASIL

Characteristics	Migraine	Headache
Patients (*n*)	356	31
Gender[a] (%)		
Men	36.7	36.4
Women	63.3	63.6
Mean age at onset (years)	32.2	38.9

[a] Where available

(8%) patients, sensory in 7 (5.6%), motor in 5 (4%) and included multiple symptoms in 25 (20%); the aura type was not specified in 78 (62.4%) patients. Among the 68 patients with more than one type of migraine, 50 (73.5%) had migraine with aura, 38 (55.9%) migraine without aura, 18 (26.5%) migraine with aura and without headache, 13 (19.1%) basilar migraine, 11 (16.2%) familial hemiplegic migraine, 11 (16.2%) migraine with unspecified atypical aura, 4 (5.9%) acute onset aura without headache, 2 (2.9%) unspecified migraine, 1 (1.5%) migraine with prolonged aura, 1 (1.5%) migraine with acute onset aura, and 1 (1.5%) had status migrainosus (Table 3). At the onset of migraine, the mean age ± SD was 32.2 ± 13.1 years.

In the 31 patients reported as having headache, the headache was not further specified in 18 (58.1%) patients, was defined as chronic in 6 (19.3%), as resembling migraine with aura in 4 (12.9%), as resembling migraine without aura in 2 (6.5%), and as tension type headache in 1 (3.2%) patient. At the onset of headache, mean age ± SD was 38.9 ± 16.8 years.

We also analyzed whether the headache was the first symptom or whether it was preceded by an ischemic stroke, TIA or by other symptoms. After excluding patients for whom data were not reported, 81 patients were described as suffering from migraine and 19 from headache. While 9 of the 81 patients (11.1%) had a previous stroke or TIA, migraine was the first symptom in 66 patients (81.5%) and in 6 (7.4%) it was preceded by other symptoms. While 3 of the 19 patients (15.8%) had a previous stroke or TIA, headache was the first symptom in 14 (73.7%) and in 2 (10.5%) it was preceded by other symptoms.

Discussion

From the 34 reviewed studies, we collected data on 387 patients [1, 5–40]. In none of the cases, the headache was coded according to the ICHD [8] or ICHD-II [9] criteria. The ICHD-II diagnostic criteria for *Headache attributed to CADASIL* required the following: (A) attacks of migraine with aura, with or without other neurological signs; (B) typical white matter changes on magnetic resonance imaging T2-weighted sequences; (C) diagnostic

Table 3 Distribution of migraine subtypes in patients with CADASIL

Migraine subtype	ICHD code	ICHD-II code	Patients	
			n	%
Migraine without aura	1.1	1.1	7	2.0
Migraine with aura	1.2	1.2	125	35.1
Migraine with typical aura[a]	1.2.1	1.2.1	24	
Migraine with prolonged aura	1.2.2	–	7	
Familial hemiplegic migraine	1.2.3	1.2.4	5	
Basilar migraine	1.2.4	1.2.6	2	
Unspecified	–	–	87	
Unspecified migraine[c]	–	–	156	43.8
More than one type of migraine	–	–	68	19.1
Migraine with aura[b]	1.2	1.2	50	
Migraine without aura	1.1	1.1	38	
Migraine aura without headache	–	1.2.3	18	
Basilar migraine	–	1.2.6	13	
Familial hemiplegic migraine	1.2.3	1.2.4	11	
Migraine with unspecified atypical aura	–	–	11	
Acute-onset aura without headache	–	–	4	
Unspecified migraine[c]	–	–	2	
Migraine with prolonged aura	1.2.2	–	1	
Migraine with acute-onset aura	–	–	1	
Status migrainosus	–	1.5.2	1	

[a] Includes one patient diagnosed with migraine accompagnée[23]

[b] Includes two cases of migraine accompagnée[23]

[c] Unspecified migraine includes cases defined as migraine by authors without any further detail

Table 4 Proposal for a new classification of headache in patients with CADASIL based on available data

15 Headache attributed to genetic disorder
15.1 Headache attributed to CADASIL
15.1.1 Migraine without aura attributed to CADASIL
15.1.2 Migraine with aura attributed to CADASIL
15.1.2.1 Typical aura with migraine headache
15.1.2.2 Typical aura without headache
15.1.2.3 Hemiplegic migraine
15.1.2.4 Basilar-type migraine
15.1.3 Complications of migraine attributed to CADASIL
15.1.3.1 Status migrainosus
15.1.3.2 Persistent aura without infarction
15.1.5 Unspecified headache
15.2 Headache attributed to other genetic disorders[a]

[a] This category is to be expanded and detailed

confirmation from skin biopsy evidence or genetic testing (Notch3 mutations) [9]. The coding of headache according to the ICHD or ICHD-II criteria might not have been done due to the paucity of details reported in the previous and present classification. Had authors correctly applied the ICHD-II criteria, patients with CADASIL would have been diagnosed as suffering from headache attributed to CADASIL without any further detail. In the reviewed studies, we found that 51.7% of patients with CADASIL were reported to have suffered from headache. Anyhow, despite that headache represents one of the major clinical features of CADASIL, we cannot exclude that some patients suffered from a primary headache. Besides, based on age of onset and clinical characteristics of the headache in CADASIL resembling those of some primary headaches, it was not possible to establish the proportion of primary headaches in the same patients. The headache in patients

Table 5 Proposed diagnostic criteria for the new category of headache attributed to genetic disorder

15.1 Headache attributed to CADASIL
A. Attacks of headache with or without neurological symptoms
B. Typical white matter changes on MRI (T_2W)
C. Diagnostic confirmation from skin biopsy evidence or genetic testing (Notch 3 mutations)
15.1.1 Migraine without aura attributed to CADASIL
A. Attacks of headache fulfilling criteria A–D for 1.1 *Migraine without aura*
B. Attributed to CADASIL
15.1.2 Migraine with aura attributed to CADASIL
A. Attacks of headache fulfilling criteria A and B for 1.2 *Migraine with aura*
B. Attributed to CADASIL
15.1.2.1 Typical aura with migraine headache attributed to CADASIL
A. Attacks of headache fulfilling criteria A–D for 1.2.1 *Typical aura with migraine headache*
B. Attributed to CADASIL
15.1.2.2 Typical aura without headache attributed to CADASIL
A. Attacks of headache fulfilling criteria A–D for 1.2.3 *Typical aura without headache*
B. Attributed to CADASIL
15.1.2.3 Hemiplegic migraine attributed to CADASIL
A. Attacks of headache fulfilling criteria A–C for 1.2.5 *Sporadic hemiplegic migraine*
B. Attributed to CADASIL
15.1.2.4 Basilar-type migraine attributed to CADASIL
A. Attacks of headache fulfilling criteria A–D for 1.2.6 *Basilar-type migraine*
B. Attributed to CADASIL
15.1.3.1 Status migrainosus attributed to CADASIL
A. Attacks of headache fulfilling criteria A and B for 1.5.2 *Status migrainosus*
B. Attributed to CADASIL
15.1.3.2 Persistent aura without infarction attributed to CADASIL
A. Attacks of headache fulfilling criterion A for 1.5.3 *Persistent aura without infarction*
B. Attributed to CADASIL
15.1.5 Unspecified headache
A. Headache is or was present
B. Not enough information to classify the headache in a patient otherwise diagnosed with CADASIL

with CADASIL was more frequently and clearly defined as migraine and the majority of the migrainous patients were reported as suffering from migraine with aura (35.1%). Formally, this codification was inappropriate since diagnostic criteria for any type of migraine in the ICHD-II require that the disturbance is not attributed to another disorder. If the classification of CADASIL in the ICHD-II was not revised, clinicians will be induced to commit a formal error defining the headache as migraine or omit useful clinical details attributing the headache to CADASIL without giving any further characteristic. As much as 31 cases were diagnosed with disturbance other than migraine; in those cases, the authors used a generic terminology and possibly included patients suffering from primary headaches such as tension-type headache.

The inclusion of headache in CADASIL, in chapter 6 of ICHD-II, among *Headache attributed to cranial or cervical vascular disorder*, implies that the headache is caused by a vascular disease. This implication may rely on two possibilities: the former is that the headache in CADASIL might be considered secondary to the presence of an organic vascular lesion and the latter is that a disorder of the vascular system might be considered as the common underlying pathogenic mechanism that causes both headache and stroke. Referring to the former possibility, in CADASIL, the headache is usually the first symptom of the disease (73.7–81.5% according to reviewed data) preceding the onset of stroke or TIA. Moreover, a diagnosis of secondary headache is usually evident only when the headache resolves or greatly improves within a specified time interval after its onset or after the acute phase of the vascular disorder; however, this evolution is not reported in patients with CADASIL since the headache persists across the years. Consequently, for all the above reported reasons, this possibility is unlikely. Referring to the latter possibility, we have to consider that the underlying pathology in CADASIL is represented by an angiopathy with a unique type of ultrastructural basal lamina deposits and by degeneration of vascular smooth muscle cells, which are the major source of the Notch3 expression. The evidence for a functional impairment of vascular smooth cells is in line with this latter hypothesis [41] and consequently the pathogenic assumption reported in the ICHD-II is correct. However, we would underscore that the primary mechanism is not represented by the vascular damage, but by the genetic alteration in the Notch3 expression. For all these reasons, we suggest considering the possibility of revising the ICHD-II when referring to CADASIL. Specifically, we suggest adding a new category that could be named *Headache attributed to genetic disorder* including *Headache attributed to CADASIL* (Table 4). The new category might include also other genetic diseases in which headache represents a major clinical feature. Moreover, the new category should also report subtypes according to specific clinical details to allow the precise characterization of headache in the single patient (Table 4). The proposed diagnostic criteria for headache attributed to CADASIL are reported in Table 5. If our proposal is shared by the experts in the field, we think that it shall be easier from now on to characterize patients with CADASIL uniformly and that a good step forward will be realized.

Conflict of interest None.

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