REVIEW ARTICLE

Tension Headaches and Vertigo in a Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy Patient

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ABSTRACT

Background: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is caused by mutations in *NOTCH3* gene, and it is the most common cause of inherited cerebral small vessel disease. **Patient Description:** We present a 37-year-old male patient, member of a family with the C162R mutation of the *NOTCH3* gene. Instead of migraine with aura, and ischemic events, he presented with tension headaches and episodes of vertigo. Later on, he developed mild cognitive impairment. **Conclusions:** Atypical presentations are not unusual in CADASIL including non-specific tension headaches and vertigo.

Key words: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, migraine, tension headache, vascular cognitive impairment, vertigo

INTRODUCTION

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is caused by mutations in *NOTCH3* gene, and it is the most common cause of inherited cerebral small vessel disease, inherited stroke, and inherited vascular dementia.[1] The patients typically present with various combinations of migraine, stroke or transient ischemic attacks, behavioral and psychiatric symptoms, and vascular cognitive decline in the presence of diffuse microischemic lesions in brain magnetic resonance imaging (MRI).[2,3] However, the phenotype may be highly variable and atypical presentations or unusual symptoms may occur, causing difficulties in the differential diagnosis.[4]

REPORT OF PATIENT

This is a 37-year-old male patient seeking medical attention due to cognitive decline of 10-month duration. He is the patient II-5 of the family published by Andreadou *et al.* carrying the C162R mutation at exon 4 of the *NOTCH3* gene.[5] At that time, he had refused clinical examination and imaging. Now, he gave written informed consent for inclusion in the study.

His history started at age 28 with a severe headache attack. It was throbbing in quality, located in the left frontotemporal area. It had a severity of 9/10 and was accompanied by phono- and photo-phobia, nausea, and vomiting. It was exacerbated by physical activities and required bed rest in a quiet, dark room. Acetaminophen (1000 mg) reduced pain intensity only to 6–7/10 and the headache finally remitted by itself after a total of 36 h. No prodromal symptoms were reported. However, 2 h after headache onset, he noted a transient diffuse blurring of vision for 15 min, followed by transient numbness and weakness of his right arm and leg of 5 h duration. No other headaches of this type were reported. However, diffuse pressure-like or constrictive bilateral headaches followed, with a frequency of 2 per month. They

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were characterized by duration of 2–3 h, an intensity of 3/10 and complete remission by 500 mg of acetaminophen. They were not accompanied by nausea and phono- or photophobia. They were not exacerbated by (nor they prohibited) physical activity. They were never preceded or followed by any neurological symptom.

During the past 8 years, he has experienced five episodes of rotational vertigo of 5 min duration that appears unexpectedly, unrelated to positional change, and not accompanied or followed by a headache.

The past 10 months he gradually noted some degree of cognitive decline. He has no difficulty in everyday living, yet "his memory is not enough" to cope anymore with complex professional requirements. On physical examination, his tendon reflexes were very brisk with extensor plantar responses. Some disinhibition with inappropriate laughter was evident, but there were no pseudobulbar signs, depression, or other psychiatric symptoms. Neuropsychological testing[6-12] was compatible with mild cognitive impairment of the frontosubcortical type [Table 1]. Brain MRI revealed multiple lesions of increased signal intensity in the white matter [Figure 1a], including the anterior temporal lobe [Figure 1b].

Table 1: Scores in neuropsychological testing of the patient

Test	Score
Clinical dementia rating[6]	0.5
Mini-mental state examination[7]	28/30
Frontal assessment battery[8]	14/18
Mattis dementia rating scale, attention subscale[9]	17/18
Mattis dementia rating scale, initiation-perseveration[9]	23/37
CLOX 1[10]	10/15
CLOX 2[10]	11/15
5-words memory test, immediate recall[11]	5/5
5-words memory test, delayed recall[11]	5/5
Geriatric depression scale (short version)[12]	1/15

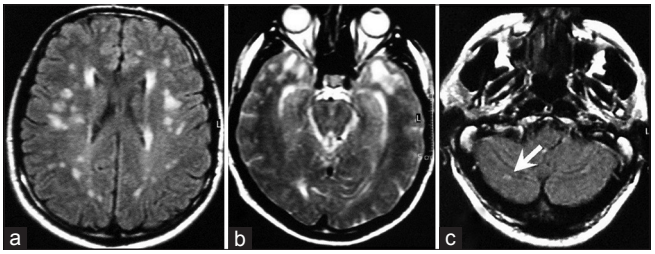

Figure 1: Magnetic resonance imaging of the patient. (a) Fluid-attenuated inversion recovery (FLAIR) image showing multiple confluent white matter lesions. (b) T2-weighted image showing the characteristic lesions in the anterior temporal lobe. (c) FLAIR image showing a small, ill-defined lesion in the right cerebellar hemisphere

DISCUSSION

The patient reported, comes from a CADASIL family carrying the C162R mutation, and has typical MRI findings. He had experienced only one episode consistent with migraine with prolonged aura. However, for this diagnosis to be met, at least two such episodes are required,[13] while he had not suffered any other similar episodes for the past 8 years. Instead, he had episodes fulfilling the criteria for episodic tension-type headache.[13]

Headaches in CADASIL occur in roughly 1/3 of patients and are of the migraine type, usually with aura.[2,13] Tension headaches are neither included in the types of CADASIL-related headaches[13] nor they receive a score in the widely used CADASIL scale.[14] However, they have been described in occasional patients[15] and, in some families with the R544C mutation, they are the prevailing type of headache (87.5%), with migraine being extremely rare.[16]

Vertigo seems to be a rare (<7%) symptom in CADASIL[17] but may occur in occasional patients, even mimicking Meniere's disease.[18] In Chinese mainland patients, vertigo may be present in up to 25%.[19] Ischemic lesion in the pontomedullary junction, involving the vestibular nucleus and the root entry zone of the vestibular nerve, was incriminated for acute vestibular symptoms mimicking peripheral vestibulopathy in a patient with CADASIL.[20] In our patient, no lesion in the brainstem was present; however, an ill-defined lesion in the right cerebellar hemisphere was observed [Figure 1c].

CONCLUSIONS

Atypical presentations are not unusual in CADASIL. Tension headaches may occur in addition to or instead of migraine, while episodes of vertigo may be an underestimated symptom.

DECLARATIONS

This case report is part of the study named "Migraine and Specific Vasculopathies Registry" of the first Department of Neurology, National and Kapodistrian University of Athens, which has been approved by the Scientific and Ethics Committee of Eginition Hospital (approval 277/27-7-2011) and is not supported by any funding.

AUTHORS' CONTRIBUTIONS

George P. Paraskevas: Concept, examination of patient, design of paper, and preparing of draft. Sophia Vassilopoulou: Examination of patient and design of paper. Evangelos Anagnostou: Examination of patient and neuroimaging and

design of paper. Vasilios C. Constantinides: Examination of patient and preparing of draft. Elisabeth Andreadou: Concept, design of paper, and preparing of draft. Konstantinos Spengos: Concept, examination of patient, and reviewing of draft. Elisabeth Kapaki: Concept and reviewing of draft.

REFERENCES

1. Federico A, Di Donato I, Bianchi S, Di Palma C, Taglia I, Dotti MT, *et al.* Hereditary cerebral small vessel diseases: A review. J Neurol Sci 2012;322:25-30.
2. Chabriat H, Joutel A, Dichgans M, Tournier-Lasserve E, Bousser MG. Cadasil. Lancet Neurol 2009;8:643-53.
3. Hervé D, Chabriat H. CADASIL. J Geriatr Psychiatry Neurol 2010;23:269-76.
4. Inzitari D, Quattrone A, Federico A. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL): A proteiform neurological disease of expanding importance. Reasons for establishing an Italian registry. Neurol Sci 2006;27:301-2.
5. Andreadou E, Papadimas G, Sfagos C. A novel heterozygous mutation in the NOTCH3 gene causing CADASIL. Swiss Med Wkly 2008;138:614-7.
6. Morris JC. The clinical dementia rating (CDR): Current version and scoring rules. Neurology 1993;43:2412-4.
7. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189-98.
8. Dubois B, Slachevsky A, Litvan I, Pillon B. The FAB: A frontal assessment battery at bedside. Neurology 2000;55:1621-6.
9. Mattis S. Mental status examination for organic mental syndrome in the elderly patients. In: Bellack L, Karasu TB, editors. Geriatric Psychiatry: A Handbook for Psychiatrists and Primary Care Physicians. New York, NY: Grune and Stratton; 1976. p. 77-121.
10. Royall DR, Cordes JA, Polk M. CLOX: An executive clock drawing task. J Neurol Neurosurg Psychiatry 1998;64:588-94.
11. Dubois B, Touchon J, Portet F, Ousset PJ, Vellas B, Michel B, *et al.* "The 5 words": A simple and sensitive test for the diagnosis of alzheimer's disease. Presse Med 2002;31:1696-9.
12. Sheikh JI, Yesavage JA. Geriatric depression scale (GDS): Recent evidence and development of a shorter version. In: Brink TL, editor. Clinical Gerontology: A Guide to Assessment and Intervention. New York: Haworth Press; 1986.
13. Headache Classification Committee of the International Headache Society (IHS). The international classification of headache disorders, 3rd edition (beta version). Cephalalgia 2013;33:629-808.
14. Pescini F, Nannucci S, Bertaccini B, Salvadori E, Bianchi S, Ragno M, *et al.* The cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) scale: A screening tool to select patients for NOTCH3 gene analysis. Stroke 2012;43:2871-6.
15. Vyshka G, Kruja J. Clinical variability of the cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy phenotype in two siblings of a large family showing the same mutation. Int Med Case Rep J 2013;6:59-63.
16. Choi JC, Song SK, Lee JS, Kang SY, Kang JH. Headache among CADASIL patients with R544C mutation: Prevalence, characteristics, and associations. Cephalalgia 2014;34:22-8.
17. Bianchi S, Zicari E, Carluccio A, Di Donato I, Pescini F, Nannucci S, *et al.* CADASIL in central Italy: A retrospective clinical and genetic study in 229 patients. J Neurol 2015;262:134-41.
18. Oki K, Nagata E, Ishiko A, Shimizu A, Tanaka K, Takahashi K, *et al*. Novel mutation of the Notch3 gene in a Japanese patient with CADASIL. Eur J Neurol 2007;14:464-6.
19. Tan QC, Zhang JT, Cui RT, Xu QG, Huang XS, Yu SY, *et al.* Characteristics of CADASIL in Chinese mainland patients. Neurol India 2014;62:257-61.
20. Rufa A, Cerase A, Monti L, Battisti C, Forte F, Federico A, *et al.* Acute vestibular syndrome in a patient with cerebral autosomal dominant leukoencephalopathy with subcortical infarcts and leukoencephalopathy (CADASIL). J Neurol Sci 2008;271:211-3.

How to cite this article: Paraskevas GP, Vassilopoulou S, Anagnostou E, Constantinides VC, Andreadou E, Spengos K, Kapaki E. Tension Headaches and Vertigo in a Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy Patient. Asclepius Med Res Rev 2018;1(1):1-3.