

Cerebral arteriopathy with subcortical infarcts and leukoencephalopathy in acromegalic patient with severe headache

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Abstract

A 68-year-old female patient was admitted in our clinic with severe frontal bilateral headache, dizziness, depression and cognitive decline in the context of a previously diagnosed acromegaly. She also had high blood pressure, dyslipidemia, secondary diabetes mellitus. Acromegaly was caused by a growth hormone (GH) secreting-pituitary macroadenoma, so a transsphenoidal surgery was performed. The postoperative magnetic resonance imaging (MRI) scan revealed a 20/22/25 mm pituitary mass remnant and medical therapy with somatostatin analogues (SSAs) was started. After nine months of treatment with SSAs, she continued having severe headache, the blood pressure was well controlled, but GH secretion was only partially controlled with insulin-like growth factor-1 (IGF-1) level still above the normal value. The MRI scan showed the same pituitary tumor remnant with supra- and parasellar right extension and also multiple fronto-temporo-parietal subcortical lesions that could suggest in the clinical context cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). According to a pregenetic screening tool, the Pescini Scale, the patient had a 19 points score, which is highly suggestive for CADASIL, an inherited cerebrovascular disease due to mutations of the Notch3 gene at the chromosome locus 19p13. In the absence of genetic testing, an alternate way to prove small vessels disease, the skin biopsy, was performed. Electron microscopy showed granular osmiophilic material (GOM) surrounding the vascular smooth muscle cells on that are pathognomonic for the disease. Our report underscores the importance of repeated investigations even in patients with apparently obvious explanations of their condition since they may have multiple diseases with the same presenting clinical signs.

Keywords: headache, acromegaly, CADASIL, electron microscopy.

Introduction

Acromegaly is a rare condition, caused by excessive secretion of growth hormone (GH). The incidence of acromegaly is approximately three cases per one million persons per year and the prevalence is about 60 cases per million [1]. In the majority of cases, the condition results from benign pituitary adenomas (over 98% of cases) [2]. Regardless of the cause, chronic GH hypersecretion leads to excessive generation of insulin-like growth factor-1 (IGF-1) and results in acral overgrowth, soft tissue proliferation, with enlargement of the hands and feet, coarsening of the facial features and bone overgrowth. The symptoms occur insidiously and the estimated time between onset of disease and diagnosis is about 5 to 10 years [2]. The death rate for acromegalic patients is two to three times higher than that of the general population, but with appropriate reduction of GH

hypersecretion it tends to shift into the normal range [2–4]. Factors contributing to increased mortality in acromegaly include higher prevalence of hypertension, hyperglycemia or diabetes mellitus (DM), cardiac dysfunction, obstructive sleep apnea and colonic neoplasia [3–5].

Treatment is aimed at normalizing GH secretion, complete resection of the pituitary tumor while preserving normal pituitary function, and managing the associated complications. The treatment modalities available to achieve these objectives include transsphenoidal surgery, medical therapy with somatostatin analogues (SSAs), dopaminergic agonists and GH receptor antagonist and radiotherapy [3, 6–8]. Acromegaly is a chronic disease in which it is very important to identify and treat the cause, focusing especially on the complications that alter the quality of life in these patients. One of the most important aspects that interfere with the quality of life is

the presence of headache that frequently accompanies acromegaly and is due to several mechanisms including dural stretch, cavernous sinus invasion, endocrine activity of the tumor and SSAs therapy.

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited cerebrovascular disease due to mutations of the *Notch3* gene at the chromosome locus 19p13 [9, 10]. The clinical features of this disease include migraine with/without aura, recurrent subcortical ischemic attacks and/or strokes, cognitive deficits leading progressively to dementia, motor disability [11] and psychiatric disorders – mood disturbances and apathy [9, 12, 13].

CADASIL should be highly suspected in the presence of a family history of headache, recurrent ischemic attacks and psychiatric disorders. Genetic testing is the gold standard for the diagnosis of CADASIL, but because it is costly, the Pescini *et al.* CADASIL scale can be used as a pregenetic screening tool [12]. The magnetic resonance imaging (MRI) scans demonstrate the extensive cerebral white matter lesions and subcortical infarcts [14]. A cutaneous biopsy from a normal appearing skin area can be helpful in diagnosing CADASIL. The histopathological hallmark of CADASIL is accumulation of electron dense granules (GOM) in the media of arterioles using electron microscopy. Additionally, a skin biopsy also helps to detect a carrier status [9].

To date, there is no effective treatment of CADASIL [9]. Migraine with an aura should be managed with non-steroidal anti-inflammatory agents and analgesics. The acute complex migraines episodes may benefit from intravenous sodium valproate [15] and for migraine prophylaxis in CADASIL patients the antiepileptic drugs, beta-blockers and acetazolamide have been reported to be effective [9, 16]. For cognitive decline, the behavioral intervention has demonstrated its feasibility [17]. Rehabilitation and physiotherapy for motor disability, and, of course, the support from family and relatives is an important component [9].

Considering these, we present the case of a patient previously diagnosed with acromegaly that experienced severe headache despite her condition being partially controlled. During follow-up a suspicion of CADASIL was raised upon MRI imaging, that was eventually confirmed by the characteristic extracellular deposits in electron microscopy that are pathognomonic for the disease.

☞ Case presentation

A 68-year-old female patient was admitted in our clinic for the evaluation of SSAs therapy three months postoperative. The patient complained of aggravation of her frontal bilateral headache and dizziness; depression and cognitive decline were also noted during the clinical evaluation comparing to the acromegaly's diagnostic moment.

On admission, the patient was informed about the protocol and gave her written informed consent. The institutional Ethics Committee of the "Elias" University Hospital, Bucharest, Romania, approved the protocol.

From her family history, we note that both her son and sister complain of headache and her sister also had

dementia; from her medical history, we mention chronic hepatitis C, type 2 diabetes mellitus, dyslipidemia and high blood pressure. After being evaluated for severe headache and dizziness, one year ago, the patient was diagnosed with acromegaly caused by a GH secreting-pituitary macroadenoma. The computed tomography (CT) scan performed then also showed diffuse cortical atrophy, cerebral lacunarism and periventricular leukoaraiosis, but the lesions were not interpreted as being relevant for her symptoms. In view of the fact, the patient experienced a severe pituitary tumor-associated headache; transphenoidal surgery was considered to be the best option. The patient's postoperative course was uneventful, the patient experienced no polyuria or polydipsia, visual changes or cerebrospinal fluid leak, but she still complained about having frontal headache and dizziness. Her postoperative biochemical results showed an increased hemoglobin A1c, a persistence in GH hypersecretion and the visual field pointed out to both supero- and infero-nasal narrowing in her visual field with diffuse paracentral scotomas (Table 1). The postoperative MRI scan revealed a 20/22/25 mm pituitary mass remnant with right parasellar invasion in the cavernous sinus and medical therapy with SSAs was started after three months (Figure 1).

All data pointed out to the fact that the tumor had not increased in the last few months, yet the patient complained about aggravating headache, so an associated disorder was considered. She was sent to the psychiatrist who pointed out to depression and a moderate cognitive decline. Due to her hepatic function impairment, she was given a natural anti-depressive agent as well as analgesics for her disabling headache, but with no clinical improvement, therefore she was referred to the neurologist for further evaluation.

The severe headache, mood disturbances, cognitive decline, together with the MRI lesions (ischemic strokes and cerebral microhemorrhages), in addition to family history compatible with an autosomal dominant inheritance raised the suspicion of CADASIL. According to a pregenetic screening tool, the Pescini Scale, the patient had a 19 points score, which recommended a genetic testing. The genetic testing was not available at the moment, but an alternate way to prove small vessels disease, the skin biopsy, was performed after obtaining the informed consent of the patient. The transmission electron microscopy was performed on skin biopsy, which was processed according to resin-embedding procedure. Small fragments were fixed in 4% glutaraldehyde, postfixed in 1% osmium tetroxide, dehydrated in ascending grades of ethanol and embedded in Agar 100 resin (Agar Scientific, Essex, United Kingdom). Thin sections (about 60 nm) were cut with a RMC ultramicrotome (Boeckeler Instruments, Tucson, USA) and examined with a Morgagni 268 transmission electron microscope (FEI Company, Eindhoven, The Netherlands) at 80 kV. Digital electron micrographs were acquired with a MegaView III CCD and iTEM-SIS software (Olympus, Soft Imaging System GmbH, Münster, Germany). The skin biopsy showed granular osmiophilic material (GOM) surrounding the vascular smooth muscle cells on electron microscopy (EM) that were pathognomonic for the disease (Figure 2).

Table 1 – Biochemical features and treatment of acromegaly and associated disorders (hypertension, diabetes)

	Medium GH [ng/mL]	IGF-1 [ng/mL]	HbA1c [%]	Antihypertensive medication	Medication for diabetes	Therapy for acromegaly
Diagnosis (February 2013)	NA	NA	NA	Metoprolol 50 mg 1/2–0–1/2	Glibenclamide 1–1/2–1	Transsfenoidal adenomectomy
October 2013	3.51	357	8.2	Metoprolol 50 mg 1/2–0–1/2	Glibenclamide 1–1/2–1	
March 2014	3.94	385	8.8	Indapamide 1.5 mg 1–0–0 Metoprolol 50 mg 1/2–0–1/2	Glibenclamide 1–1/2–1	Lanreotide 30 mg every two weeks
September 2014	4.49	375.41	8.1	Indapamide 1.5 mg 1–0–0 Metoprolol 50 mg 1/2–0–1/2	Insulin glargine 30 IU/day	Lanreotide 30 mg every week
February 2015				Indapamide 1.5 mg 1–0–0 Metoprolol 50 mg 1/2–0–1/2	Insulin glargine 30 IU/day Glimepiride 3 mg/day	Octreotide 40 mg/month

GH: Growth hormone; IGF-1: Insulin-like growth factor-1; HbA1c: Hemoglobin A1c; NA: Not available.

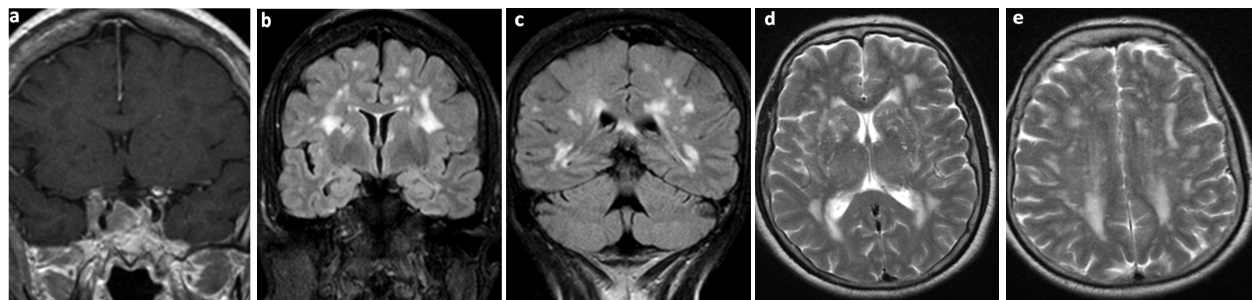


Figure 1 – Magnetic resonance imaging on the brain: (a) Coronal T1-w (weighted) postcontrast sellar tumor with supra and right parasellar extension and mass effect on the right internal carotid artery (black arrow), no contrast enhancement of the white matter hypointensities; (b and c) Coronal FLAIR and (d and e) T2-w sequences showing widespread bilateral confluent white matter hyperintensities with no cortical involvement, highly suggestive of subcortical infarcts and leukoencephalopathy.

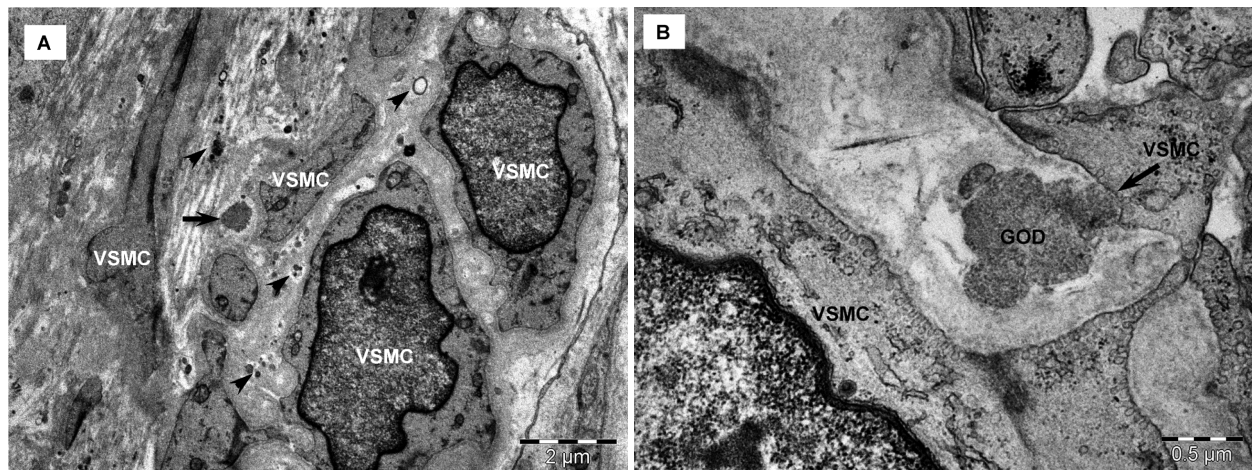


Figure 2 – Transmission electron microscopy images of a skin vessel from the upper arm showing the characteristic extracellular dense deposits (arrows) near vascular smooth muscle cells (VSMC): (A) Granular dense deposit (arrow) and small calcifications (arrowheads) are visible between VSMC; (B) Higher magnification shows a granular osmiophilic deposit (GOM) in direct contact with the cell membrane of VSMC (arrow). GOM: Granular osmiophilic deposit; VSMC: Vascular smooth muscle cells.

Discussion

The extracellular deposits (GOM), which appear electron-dense when viewed with the electron microscope, are a typical feature of CADASIL. A study of Moronni *et al.* (2013) demonstrated that all GOM-positive patients exhibited Notch3 mutations and *vice versa*, confirming that EM is highly specific and sensitive for CADASIL diagnosis [18]. Although the age of the patient made the

diagnosis questionable, the presence of GOM in the extracellular space close to vascular smooth muscle cells was a strong argument for CADASIL; our patient could have an atypical form with late onset.

Pituitary tumors are sometimes associated with severe headache, especially during apoplectic events. The reported incidence of headache in pituitary disease ranges with tumor type from 33% to 72% [19, 20] and has been reported to be particularly high in prolactinomas [19].

Traditionally, the proposed mechanism for headache in pituitary adenomas was dural stretch by the development of a pituitary tumor within the *sella turcica* that stimulates the afferent meningeal fibers innervating the *dura mater*, thus producing pain. The cavernous sinus invasion was considered to be another causative factor since the sinus contains the ophthalmic branch of the trigeminal nerve and the internal carotid artery [19, 20]. A study of Levy *et al.*, which included 63 patients first diagnosed with acromegaly, found no positive correlation of headache with pituitary tumor volume or with cavernous sinus invasion, demonstrating that dural stretch and local cavernous sinus invasion are probably not the primary mechanisms behind pituitary tumor-associated headache in most patients [19, 21].

Small functional pituitary adenomas may present with disabling headache without cavernous sinus invasion or suprasellar extension [22]. 12.5% of patients with acromegaly due to a pituitary microadenoma complain about headache [19], emphasizing the importance of the biological activity of the tumor in determining the presence of this symptom [22]. It is remarkable that only patients with prolactinomas and acromegaly experience tumor-associated headache and they have a high prevalence of rare headache phenotypes [19].

Furthermore, treatment with somatostatin analogues can have an immediate analgesic effect in patients with acromegaly in the absence of reduction in tumor size, possibly due to the interference with the opioidergic system [23] and a study by Fleseriu *et al.* demonstrated a significant headache improvement after transsphenoidal surgery in patients with pituitary microadenoma [24]. These observations support the fact that pituitary tumor-associated headache may be a complex mechanism encompassing both structural and biochemical problem [25]. The significant association between family history and pituitary tumor-associated headache suggests that genetic factors are important in predicting whether a patient who has a pituitary tumor will develop headache as part of the clinical picture [26].

In our case, headache, hypertension and diabetes mellitus were associated, being comfortably explained by acromegaly at the first glance. The pituitary tumor associated headache is significantly improved after surgery/medical treatment of acromegaly; thus, aggravation and association with depression and cognitive decline, found during the first follow-up visit, raised the urge for differential diagnosis. In spite of lacking genetic testing, the CADASIL diagnostic is highly supported by the clinical signs, MRI revealed lesions (Pescini score above 15 points) and the GOM found on electron microscopy in the skin biopsy.

Our patient's evolution will be influenced by the crosstalk between acromegaly and CADASIL mechanisms. Cerebral microhemorrhages (CMs) that are often seen in CADASIL patients are correlated with blood pressure and HbA1c as well as with lacunar infarcts and white matter high signal areas. Thus, modulation of blood pressure and glucose levels might influence the course of the disease [27].

Interventions to reduce microhemorrhages could be effective in reducing disease-related disability, as it has been shown that antihypertensive treatment and strict

glucose control are associated with a reduction in white matter lesion progression in patients with this disease.

Hypertension is highly prevalent, occurring in more than 40% of patients with acromegaly, and early diagnosis and early aggressive treatment of elevated blood pressure is important irrespective of which acromegaly treatment is employed [3]. Impaired glucose tolerance occurs in more than half of the patients, owing to GH-induced insulin resistance and is an important predictive factor for increased mortality in patients with acromegaly [3, 4].

The lacunar lesions seen on MRI in patients with CADASIL are the most important factors that impair cognitive function and disability. Therefore, preventive strategies to decrease the risk of lacunar lesions may help control cognitive decline in these patients [11].

Depression has been found to be a prominent feature of CADASIL and recent studies suggest the relationship between the presence of lacunar strokes and depression. This is probably due to the disruption of cortical-subcortical connections implicated in the regulation of mood by white matter ischemia [13].

In our particular patient, the high blood pressure and poorly controlled diabetes mellitus are aggravating factors for the evolution of CADASIL; on the other hand, the presence of acromegaly is expected to worsen the hypertension and glucose intolerance. Nevertheless, after surgery and medical treatment with SSAs, acromegaly symptoms should have improved, yet the persistence of headache and dizziness point out to the fact that CADASIL could be the cause for our patient's complaints.

Pituitary tumor-associated headache is frequently encountered and possible mechanisms include dural stretch, cavernous sinus invasion and tumor progression. CADASIL is also accompanied by severe headache in more than half of the patients. In this case, the headache is less likely due to acromegaly, but may be related to CADASIL, which may also contribute to our patient's neurological findings. Our patient's disabling depression may be related to the presence of CADASIL and can be improved by interventions that normalize glucose levels and arterial blood pressure, thus lowering the risk for subsequent lacunar infarcts and microhemorrhages. This is an important prophylactic measure for cognitive impairment as well.

☞ Conclusions

Our reported case underscores the importance of multi-disciplinary approach even in patients with apparently obvious explanations of their condition since they may have multiple diseases with same presenting clinical signs. The key point of this case is how an electron microscopic evaluation of skin biopsy shed light in a complex neuro-genetic and neuroendocrine tumor case setting.

Conflict of interests

The authors declare that they have no conflict of interests.

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