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ORIGINAL ARTICLE

Myasthenia gravis mimicking stroke: a case series with sudden onset dysarthria

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Abstract Myasthenia gravis (MG) is an immune-mediated disorder characterized by fluctuating fatigue of skeletal muscles, often involving extrinsic ocular or bulbar districts. Myasthenia gravis in the elderly is an under-recognized condition, sometimes confused with cerebrovascular disease. Here we present a case series of myasthenia patients which onset was characterized by sudden dysarthria, clearly raising this diagnostic dilemma. In the workout of sudden onset isolated dysarthria, MG should be always considered. In fact, even if myasthenia is a rare condition, lacunar stroke only with this clinical presentation is also unusual, and significant risks may arise (e.g., unexpected myasthenic crisis).

Keywords Myasthenia gravis · Dysarthria · Sudden onset · Differential diagnosis

Introduction

Myasthenia gravis (MG) is a post-synaptic neuromuscular junction (NMJ) disorder. The key clinical feature is fluctuating fatigue, often involving bulbar or extrinsic ocular muscles. MG suspicion is raised on clinical grounds and patients usually undergo confirmatory tests, such as repetitive nerve stimulation (RNS) and antibody serology. Antibodies against acetylcholine receptors (anti-AChR) are often implicated, but patients presenting with antibodies against muscle-specific tyrosine kinase (anti-MuSK) or double seronegative patients are significantly represented, with different clinical courses and prognosis [1]. Thymoma represents another common finding which should always be ruled out in these patients due to its important clinical implications. Regarding to age of onset, important variability has been described, and, in particular, late onset patients (i.e., over age 60–65) are well recognized [2]. Against the hypothesis that an autoimmune process should selectively hit young female patients, somehow unexpected high rates of MG or anti-AChR positive serology have been reported in elderly patients [2–4]. This is quite relevant since misdiagnosis has been reported in this age group, probably due to the tendency of either, overlooking disease symptoms and signs, regarding them as related to ageing (e.g., falls [5, 6]), and/or considering other more common disorders of the elderly [7]. Typical alternative diagnoses in MG elderly patients are motor neuron disease (MND [8]) or stroke/transient ischemic attack (TIA) [7, 9, 10]. However, the most typical presentation of bulbar MG involves dysarthria which represents by itself a recognized symptom of lacunar stroke as well [11], generating reasonable uncertainty, especially when other signs are missing and the onset is abrupt. We present here four cases of MG with sudden onset dysarthria, leading the neurologists, all the times, to an initial diagnostic hypothesis of cerebrovascular accident.

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Case 1

This 70-year-old hypertensive woman came to our attention for brief episodes of acute onset dysarthria repeating several times during the same day. In the ER she

underwent a brain CT scan which was negative; the patient was started on Aspirin 100 mg QD and admitted to a Stroke Unit. The following day mild dysphagia was documented together with persisting dysarthria; both got worse during the day and dysphonia was also present by the end of it. Without delay a CT angiogram for both intra- and extra-cranial vessels was performed with negative results. The next morning, mild dyspnoea was noted and RNS performed, documenting a profile compatible with MG. Anti-AChR antibodies were asked, and in few days they came back mildly positive (0.67 nM). Anti-platelet medication was stopped and Pyridostigmine started together with IVIG. The following day bilateral ptosis was present and dyspnoea got significantly worse until respiratory acidosis rapidly appeared, leading to seizures. Orotracheal intubation was necessary and the patient was immediately transferred to the ICU starting plasmapheresis. Anticoagulant therapy was introduced due to the finding of iliacocaval venous thrombosis. Steroid therapy was started and subsequently stopped due to the development of septic shock. Chest and abdominal CT scans were negative for neoplastic lesions. After normalization of the clinical picture in few days, steroid therapy was reintroduced together with Pyridostigmine and slowly progressive clinical improvement was noted. Few months later, the patient was started on Azathioprine.

Case 2

This 69-year-old hypertensive man, during a sea cruise, was struck by sudden onset isolated dysarthria that did not improve over the next hours. He rapidly reached for neurological consultation and a brain MR scan was performed, ruling out a lacunar stroke. Past medical history was also significant for slowly progressive distal amyotrophy and weakness at the lower limbs, started when he was about 55-years old and not present in any other member of the family. At the neurological examination dysarthria was present without other signs of bulbar involvement; the already described amyotrophic pattern with moderate-to-severe walking impairment was noticeable. Fatigue was not present. However, on further questioning the patient recollected that fatigue during chewing and swallowing was subtly present since about 4 weeks and that some gestures involving upper limbs produced more quickly fatigue than in the past months. RNS was asked documenting a profile compatible with MG. EMG was concomitantly performed documenting lower limbs neuropathic involvement. Anti-AChR antibodies came back significantly raised and TSH was above normal limits. MG in suspected Charcot–Marie-Tooth disease was diagnosed and the patient treated with Pyridostigmine and thyroid hormone replacement with a favourable clinical response. At the follow-up few months later, dysarthria was not present anymore.

Case 3

This 81-year-old man with a past medical history significant for dyslipidemia, hypertension, and anxious-depressive syndrome (one previous suicide attempt) was treated with Duloxetine and Trazodone. The patient was admitted in the ER for mild dysarthria of sudden onset since the day before and still present. He also reported altered sensitivity into the oral cavity. The neurological examination documented mild left facial nerve deficit of central type. A brain CT scan was negative for new lesions and documented a previous right striatocapsular lesion. 45 % stenosis was documented by ultrasonography within the right internal carotid artery. Laryngoscopy was within normal limits and the patient was discharged with the suggestion to start anti-platelet therapy, interpreting the event as due to a novel lacunar lesion. During the following days, dysarthria worsened and dysphagia and dysphonia progressively developed. During a second ER access, the neurological examination documented: marked VII cranial nerve peripheral weakness with bilateral lagophthalmos, dysarthria, dysphonia, rhinolalia, and very marked dysphagia. Ocular movements were not affected and neck flexion strength was 4/5. No other signs were evidenced, albeit deep tendon reflexes were diffusely reduced. Urgent brain MR scan demonstrated mild diffuse atrophy and chronic ischemic damage, without evidence for acute lesions. The patient underwent to lumbar puncture which failed to demonstrate albuminocytologic dissociation or other anomalies. RNS was asked and documented a profile compatible with MG. Furthermore, nerve conduction studies documented a chronic sensory-motor axonal neuropathy more evident at the lower limbs. Bilateral vocal cord palsy developed associated with dyspnoea and tracheostomy became necessary. The patient was started on IVIG without significant clinical improvements. Anti-AChR serology came back frankly positive (7.23 nM). Chest and abdominal CT scans were negative for neoplastic lesions. Steroids and Pyridostigmine were started together with plasmapheresis. Following five trials, the clinical picture significantly improved and only dysphagia persisted together with mild weakness of the left orbicularis oculi muscle.

Case 4

This 62-year-old man with a past medical history positive for hypertension, dyslipidemia and ischemic heart disease,

was admitted to the emergency room for acute onset of mild dysarthria. A first neurological evaluation disclosed only slurred speech. An urgent brain CT and angio-CT of intra- and extra-cranial vessels were negative. The next day, the neurological examination disclosed bilateral mild weakness of orbicularis oculi muscles and neck flexors (4/5 MRC) besides dysarthria. RNS was significant for a decremental response and anti-AChR antibody serology was found positive (11.8 nM). A chest CT was negative for thymoma. Pyridostigmine (60 mg QID) and Prednisone (1 mg/kg QD) were started with clinical improvement. During the following months Pyridostigmine was suspended, steroid was gradually reduced and Azathioprine was introduced as steroid-sparing-agent. At the last follow-up, 18 months after the onset, the patient was in pharmacological remission.

Discussion

Here we present four cases of isolated sudden-onset dysarthria in elderly patients who were eventually found to be affected by MG. All the patients received an initial diagnosis of ischemic stroke or TIA, together with neuroimaging tests; this is an understandable mistake which has already been repeatedly reported [7, 9, 10, 12, 13]. When elderly and hypertensive subjects are abruptly involved, the neurologist tends to hypothesize this diagnosis first, considering the high rate of ischemic cerebrovascular disease. Conceivably, this decision is based on the principle now better known in medicine as "the zebra aphorism" [attributed to Prof. T. Woodward (1914–2005)], correctly suggesting to consider first common causes of diseases in the diagnostic process. Dysarthria due to stroke is undeniably frequent but it is usually accompanied by other neurological signs, such as hemiparesis, hemiataxia, clumsy hand, central facial paresis and/or tongue deviation upon protrusion [14]. Actually, isolated dysarthria has been reported in stroke syndromes, although very rarely [11, 15]; for example, a previous paper documents this presentation in 0.4 % of lacunar strokes [16]. Therefore, we must conclude that isolated dysarthria with sudden onset is rare in stroke and that the lack of accompanying signs or symptoms should probably prompt the neurologist to enlarge the diagnostic flowchart including other conditions that are usually present with a more chronic course. Furthermore, stroke risk factors, such as hypertension, are very common in the elderly and should not be elements that lead to the failure of questioning the diagnosis. Also neuroimaging might be misleading since silent strokes are very common in the elderly, as already reported [9]; moreover, ischemic stroke might be silent at the CT scan during the first hours, reducing the amount of supporting data for the clinician challenged with this differential diagnosis. Last but not least, current procedures for stroke management impose to consider therapeutic interventions that might represent potential sources of further complications, such as brain haemorrhages following thrombolysis.

On the other side, MG is a rare condition. Notably, however, MG in the elderly is plausibly under-recognized and anti-AChR positivity up to 10 per 100,000 has been reported [7]. Besides, when a neurologist faces a congruous clinical presentation (e.g., skeletal muscle oscillating fatigue or diplopia worsening along a circadian pattern) the diagnostic suspect is often correctly expressed regardless of the rarity of the condition. Ruling out a thymoma might be very important in elderly patients with MG, as this tumour is more common in this age group [17]. Moreover, albeit representing a remote possibility, an unexpected myasthenic crisis might suddenly strike. Dysarthria might characterize MG clinical course [18]; in particular, the differential diagnosis with stroke will inevitably encompass MG bulbar presentations [19], since the specific pattern of limb weakness in generalized MG, or the involvement of extrinsic ocular muscles alone in ocular MG tend to lead the clinician on the correct direction. Bulbar MG typically presents with a combination of slurred or nasal speech with alterations of the voice and reported difficulties during swallowing, chewing, and even breathing. In these patents limb weakness has been reported to occur in $\sim$20 % of the cases and to be difficult to differentiate from non-specific fatigue [19]. Bulbar MG might present also with acute onset, for example with isolated dysphonia [10]; dysphagia may also be present at onset, typically with poor response to treatments [20]. In these cases the role of a detailed anamnesis is crucial; since the suspicion of fatigue might prompt the neurologist to ask as soon as possible for anti-AChR antibody testing that is usually subject to delay [21]. Considering that NCS data might be difficult to obtain and interpret in acutely deteriorating patients, the neurologist might end up to handle, in the first phases, a suspect of MG merely on clinical grounds [21].

In our four cases, the diagnostic procedures were initially applied incorrectly since the neurologist was conceivably dragged by the pattern of sudden onset dysarthria, looking for a stroke involving the bulbar region, whose prevalence is definitely exorbitant ("horses") if compared to a new diagnosis of MG ("zebra"). However, when there is a lack of accompanying signs, these figures should be rerun. In fact, the zebra principle might have been applied incorrectly, since the clinical presentation pattern with isolated sudden dysarthria is not a common presentation of stroke. Obviously this bias arises from a sort of "pattern extension" since sudden dysarthria, when not isolated, indeed is almost often due to this very common condition.

Formes frustes undeniably exist but probably belong to the category of fascinomas as much as MG in the initial assumptions of the clinician. Anyway, leaving out the discussion of which of the two conditions is less zebra striped than the other, our conclusion is that MG should be always considered in the diagnostic workout of isolated dysarthria, even when presenting with abrupt onset. This conclusion has been already reached before but the skewed diagnostic procedure still persists [22].

Eventually, the diagnosis, in all our patients, was reached following further clinical progression and surfacing of new symptoms, including dysphonia or dysphagia. Considering the possible aggressive course of MG these diagnostic delays are potentially dangerous and should be avoided.

Conflict of interest None.

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