DR. BERTRAND C LIANG (Orcid ID : 0000-0002-5850-2615)

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Sporadic Adult-Onset Brainstem Hyperkalemic Periodic Paralysis Masquerading as Recurrent Transient Ischemic Attacks

Kathryn MA Liang[a] and Bertrand C Liang[b, c]

[a]Program in Health Behavior and Health Education, School of Public Health, University of Michigan, Ann Arbor, MI; [b]Department of Neurology, University of Colorado School of Medicine, Colorado Springs Branch, Colorado Springs, CO.

[c]Corresponding author:

liangbc@umich.edu

13 S. Tejon Street

Suite 500

Colorado Springs, CO 80921

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Abstract

We report a case of adult onset, sporadic, hyperkalemic periodic paralysis with primary brainstem musculature symptoms masquerading as recurrent transient ischemic attacks. Unilateral brainstem weakness could be induced with rapid eye blinking, which was followed by

lower extremity weakness and cramping. Treatment with acetazolamide and albuterol ameliorated the patient attacks.

Key Clinical Message

Focal weakness, particularly of brainstem musculature, is a common presentation in the emergency department and clinic, and often associated with vascular etiologies. This case illustrates primary muscle etiologies, specifically the periodic paralyses, should be considered in the differential diagnosis, particularly in patients with recurrent frequent episodes of brainstem muscular weakness.

Keywords

Periodic paralysis; hyperkalemic; brainstem muscle weakness; adult-onset; sporadic; recurrent transient ischemic attacks

Introduction

The primary periodic paralyses (PP) are often grouped into three main categories – hyperkalemic, hypokalemic, and Anderson-Tawil Syndrome. All present with episodic weakness, associated with an autosomal dominant transmission, typically beginning in the first or second decade of life, and are associated with sarcolemma channel alterations, frequently but not exclusively defined by genes SCN4A, CACNA1S, and KCNJ2 [1]. The most common form of these rare disorders is hypokalemic PP, associated with limb weakness and hypokalemia (<2.5mEq/L); Anderson-Tawil Syndrome is a unique form of the periodic paralyses, with a characteristic clinical phenotype and cardiac manifestations. Hyperkalemic PP is less frequently encountered clinically and described as having earlier onset (before the age of 10 years), with exercise, fasting, cold/extreme temperatures, and emotional stress as triggering factors, often but not necessarily associated with ingestion of high potassium foods, and/or increased serum

potassium during attacks [2]. The clinical phenotype has been described as episodic weakness of the limbs, and/or generalized weakness, typically lasting hours. While bulbar symptoms have been reviewed recently in secondary *hypo*kalemic PP [3], in hyperkalemic disease brainstem musculature symptoms are undescribed in the medical literature particularly as the prime manifestation of sporadic disease. We report here a case of adult onset, sporadic hyperkalemic periodic paralysis, with primary brainstem musculature involvement, thought to be recurrent transient ischemic attacks for decades.

Case

A 54-year-old man presented with a 24-year history of a recurrent left facial droop. The episode duration could last anywhere from minutes to two weeks, but typically were less than a day. Episodes would occasionally be associated with weakness of the bilateral lower extremities. There was also prominent cramping, particularly in the calves and feet. Exacerbating factors included exercise, stress as well as heat and severe cold, but the patient could not identify particular foods associated with the onset of attacks. His diet was a mix between carbohydrates and protein, with considerable amounts of red meat and starches at least 5 times per week. The frequency of attacks varied, from daily to biweekly. His workup had included numerous imaging studies, including MRI, MRA as well as CT angiogram evaluations, all of which were normal. A lumbar puncture had been performed, revealing a slightly increased protein, but otherwise unremarkable, as was a cardiac workup including transthoracic ultrasound, carotid doppler evaluation, EKG and aortic angiogram (including subclavian vessels). During an attack 2 months prior, potassium was reported to be 3.6 mEq/L, and during one approximately a year prior, 4.1mEq/L. He had been diagnosed with recurrent transient ischemic attacks of unknown etiology and placed on an aspirin (80mg) daily.

The patient's childhood history was unremarkable. He had grown up in the southern United States before moving recently and experiencing temperate climates. Family history was only

remarkable for a brother with migraines. Both parents were still alive, with cardiovascular disease reported in the father.

On the day of the clinic appointment, the patient noted he had had grits for breakfast. When initially examined, the general physical and neurologic examinations were normal. However, when the patient was asked to blink rapidly, eyelid myotonia was induced, followed by a prominent left facial droop in a matter of about two minutes. Prominent ptosis developed, with tearing. Palatal elevation and tongue weakness with deviation to the left was observed, along with slurred speech, and drooling. Diplopia was noted on extreme gaze in all directions and with accommodation, but not when looking at a distant object. Weakness and cramping in the lower extremities subsequently occurred about four minutes later. Over the next 40 minutes, the lower extremity weakness completely resolved, and the brainstem musculature weakness, over a 60-minute period. Follow up laboratory evaluation during the attack revealed a potassium of 3.6 mEq/L, with normal thyroid function tests, electrolytes, blood urea nitrogen, creatine, magnesium, calcium and creatine kinase. EKG was also normal, as was a chest x-ray. No acetylcholine receptor nor muscle specific kinase antibodies were detected. Sequence analysis did not reveal mutations SCN4A, CACNA1S nor KCNJ2 genes. Subsequent limited EMG/NCV testing outside of an attack revealed myotonia, induced by exercise testing in the gastrocnemius, and was otherwise normal.

The patient was begun on twice daily acetazolamide. The patient's attacks decreased from an approximate daily occurrence, to one which occurred once every 3 weeks, with brainstem and lower extremity weakness. With an increase to thrice daily, and the addition of an albuterol inhaler at the onset of weakness, his attacks decreased to about once per month, manifest as facial "heaviness", which could be ameliorated with the inhaler.

Discussion

Transient ischemic attacks represent a common reason to visit the emergency department, due to vascular compromise involving small or large cerebral vessels. This often results in focal weakness and/or sensory changes, depending on the area of the brain involved, necessitating

prompt evaluation to minimize the amount of brain exposed to ischemia. Brainstem muscular weakness in this context can localize to the posterior fossa, and require expeditious evaluation of the posterior circulation as a result. In contrast, the PP are a primary muscle deficiency, and may include both truncal musculature as well as either/both proximal and distal muscles, with cramping. It may begin in recently exercised muscles, during stressful situations, extremes in temperature, and associated with high potassium diets; attacks can last hours, and occasionally, days. Attacks can also be frequent, including multiple times per day, and a family history or a history of recurrent attacks beginning in youth is an important aspect of the evaluation. The patient of this case study presented with adult-onset episodic weakness, thought to represent transient ischemic attacks with the frequency of events precluding the patient's ability to engage socially and professionally. The primarily brainstem manifestations and lack of family history no doubt contributed to the confusion of the presentation, leading clinicians caring for the patient more toward a unique vascular etiology rather than a primary muscular channelopathy. Indeed, while the brainstem symptoms were of primary concern, further questioning noted high levels of cramping in the lower extremities during attacks and with exercise, with subclinical weakness often following this activity. The ability to induce myotonia with rapid eye blinks, which evolved into the full facial droop and brainstem musculature syndrome and sequential lower extremity weakness suggested the diagnosis of a periodic paralysis. Records from his last two events confirmed normal to higher serum potassium both during and between the episodes of weakness. Not unexpectedly, isolated genetic testing of specific gene sequences did not reveal alterations in our patient, as up to 30% of patients with a periodic paralysis will not have detectable genetic mutations, a phenomenon noted previously in cases with atypical clinical presentation [4].

The treatment of this disorder is based on anecdote, due to the rareness of the disease, but various experiences have suggested carbonic anhydrase inhibitors (e.g. acetazolamide) may be beneficial prophylactically; indeed, acetazolamide and dichlorphenamide have been approved by FDA for the treatment of PP to decrease the frequency of attacks [5]. In addition, the use of beta agonists (e.g., albuterol) has been found to be beneficial during acute attacks of paralysis,

hypothesized to be due to shifts of potassium on the membrane-bound Na/K ATPase [1]. Other lifestyle changes, including mild exercise, higher carbohydrate diet, and avoidance of certain environments (e.g. extreme cold or heat) have been suggested. In this patient, with acetazolamide treatment, the frequency of attacks diminished considerably, and could be almost totally ameliorated by administration of albuterol. The patient indicated this was particularly notable as his presentation was in spring/summer, where the heat was associated with a significant increase of attacks, usually daily. With treatment, the patient in particular noted this was the first time in over 20 years he could not only function without fear of a weakness attack, but also could engage in full time employment.

Conclusion

In summary, we report a case of hyperkalemic periodic paralysis, which was sporadic, adult-onset, primarily involving the brainstem musculature and masquerading as recurrent transient ischemic attacks. In evaluating such patients, careful attention to the history, including cramping, recurrence of weakness, and relationship to diet and exercise should be assessed, which typically do not occur in transient ischemic attacks. Further, the presence of eyelid myotonia, either historically or evoked during the physical examination, should prompt consideration of the PP rather than a vascular etiology. Finally, imaging studies of the central nervous system will not demonstrate localizing focal lesions in patients with PP. Treatment of the PP include beta agonists as well as carbonic anhydrase inhibitors, which was able to ameliorate this patient's recurrent symptoms. Unreported previously, this very rare manifestation of a rare disease adds to the phenotypic description of hyperkalemic periodic paralysis for clinicians to consider in patients with recurrent, episodic, brainstem weakness without antecedent childhood or family history. Generally, an increased index of suspicion for such primary muscle disorders in those with potential transient ischemic attacks may identify patients with a treatable cause of focal weakness, and appropriate subsequent clinical management.

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Conflicts of interest

BCL: consultant to Inventprise, LLC, and Purple Biotech, Ltd.; holds patents in molecular biology gene identification techniques and approaches toward anti-inflammatory approaches in cardiovascular disease. KMAL: none.

Ethics Statement and Written consent of the patient: The authors have confirmed during submission that patient consent has been signed and collected in accordance with the journal's patient consent policy.

Author contribution

KMAL: Conceptualization, Writing- Original draft preparation, Editing. BCL: Conceptualization, Data curation, Writing- Original draft preparation, Editing.

Data availability: None

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