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Case Report

Carnitine Deficiency in a Patient with Shapiro Syndrome

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ABSTRACT

Spontaneous hyperhidrosis with hypothermia and agenesis of the corpus callosum is known as Classical Shapiro Syndrome (CSS) and was first reported by Shapiro and Plum in 1967. We report a well-documented case of a 39-year-old woman with SS diagnosed at the age of 5-years-old who was diagnosed with Carnitine deficiency at 30-years-old. This is the first reported case of SS with Carnitine deficiency, which was treated with levocarnitine. Our patient also carries with her several comorbid diagnoses which have been reported in other cases of SS. These include primary amenorrhea (untreated), primary hypothyroidism (treated with levothyroxine and liothyronine), seizure disorder (treated with lamotrigine, levetiracetam, and eslicarbazepine acetates), and hypothermia-induced cytopenia (resolved with the addition of liothyronine). Additionally, this case offers unique insights gained from longitudinal care.

Keywords: Shapiro syndrome, Hypothermia, Agenesis of the corpus callosum

INTRODUCTION

Spontaneous hyperhidrosis with hypothermia and agenesis of the corpus callosum is known as Classic Shapiro Syndrome (CSS); presence of the corpus callosum is known as Variant Shapiro Syndrome (VSS). In total, CSS accounts for 40% of the approximately 60 reported cases of SS [1]. The first CSS case was reported by Shapiro and Plum in 1967, with a better-known case series of two patients in 1969. Recent discussion has been raised about the biochemical underpinning of SS, especially since the discovery of familial and VSS. Leading theories involve the hypothalamic "thermostat" regulation and includes melatonin or norepinephrine dysfunction [2,3]. Many diagnoses have been found to be comorbid with SS, including hematologic abnormalities, endocrine dysfunction, and even depression [4-6]. However, no cases of SS with carnitine deficiency have been reported.

CASE REPORT

Here we describe a case of SS diagnosed in a 5-year-old girl who is currently 39-years old. She has a recent diagnosis of carnitine deficiency along with prior diagnoses of intracerebral hemorrhage resulting in a lifelong history of cognitive impairment. She also has primary amenorrhea leading to osteoporosis, primary hypothyroidism, cholestatic disease, and seizure disorder. The patient first presented at the age of 5-years-old for idiopathic spontaneous intracerebral hemorrhage (ICH) with ventricular involvement, primarily affecting the left hemisphere. The resulting compressive hematoma was treated with a craniotomy and the hydrocephalus was treated with bilateral ventriculoperitoneal shunt placement and active cooling. Several revisions to her shunt were made over the next six years, with one complete revision due to shunt malfunction. The patient was left with residual cognitive impairment; she is able to complete basic activities of daily living and obtains support from her parents with more complex activities.

At the time of initial evaluation for ICH she was found to have partial agenesis of the corpus callosum, with the presence of a hypotrophic splenium. Shortly after surgical intervention, she began having bouts of bradycardia with hypothermia with temperatures ranging from 91-93°F. Over the next three years, she had cyclical drops in her core temperature. However, further work up was not pursued at that time since no complications occurred. Her hypothermia resolved without intervention. At the age of 14-years-old the patient developed amenorrhea due to primary ovarian failure. She did not receive hormone therapy due to concern for a lowered seizure threshold. The patient did well until 30-years-old. Then, over a one-year period, she had a

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decline in functional status which included cerebellar ataxia, confusion, bouts of transaminitis , and decreased muscle tone, ultimately leaving her wheelchair-bound. During this period, she was hospitalized with many episodes of encephalopathy, which precluded her from taking her medications thereby resulting in breakthrough seizures. She failed several antiepileptic medications due to adverse effects, including levetiracetam (psychosis), lacosamide (emotional lability), and topiramate (worsened bone marrow suppression). Lamotrigine monotherapy was ultimately found to be safe and effective. During this time the patient received a battery of mitochondrial and cerebellar disease testing resulting in negative anti-Yo, anti-Ma, anti-Yi, anti- Hu, anti-NMDA, and anti-GAD. Although all testing was negative, there was a high suspicion that the patient had some form of mitochondrial disease. After she developed cardiomyopathy with an ejection fraction of 30%, along with seizures and cerebellar findings, the differential was revisited. Suspicion for carnitine deficiency was raised. She was found to have a decreased free urine carnitine of 6 (77-214 micro-mol/g), decreased total urine carnitine of 82 (180-412 micro-mol/g), and increased serum Acylcarnitine-Total Free Carnitine ratio of 12.7 (0.7-3.4 for age). Her urine organic acids and serum free fatty acids were within normal limits and a muscle biopsy was normal. She was subsequently placed on levocarnitine, which significantly improved the strength, balance, and ataxia. Over the next six years, with the help of physical therapy, she returned to her baseline of ambulating independently. Her most recent echocardiogram showed a left ventricular ejection fraction of greater than 55%. The decline in functional status and periodic episodes of altered mental status with encephalopathy coincided with attacks of episodic hypothermia (nadir of 83.8°F). These attacks were marked by bradycardia with hypotension. On multiple occasions she was found to be hyponatremic, hyperkalemic, hypoglycemic, and pancytopenic. On three such admissions her anemia (Hb<6) required transfusions. Erythropoietin was administered in attempts to correct her pancytopenia without success. A bone marrow biopsy showed normocellular trilineage hematopoiesis. Cytogenetics were of normal female chromosome and clonal composition. There was no evidence of infectious, infiltrative, or neoplastic processes. During one admission, clomipramine was attempted for thermoregulation. After a week and a half of continued body temperature dysregulation, it was discontinued. The patient was then started on carbamazepine, which did not alleviate her hypothermic cycles. Then, she was started on liothyronine, after which she has not had another episode of hypothermia, cytopenia, or encephalopathy.

DISCUSSION

Our patient represents a case of cyclical hypothermia with agenesis of the corpus callosum leading to the diagnosis of SS at the age of five years old, shortly after an ICH with ventricular involvement. She developed baseline cognitive deficit which is otherwise not seen in SS. Although our patient had intracerebral hemorrhage and resulting hydrocephalus, we do not feel this caused her hypothermia. Although the differential for hypothermia includes thalamic injury and hydrocephalus, her hemorrhage did not affect thalamic nuclei. Additionally, thalamic injury would likely result in lifelong temperature dysregulation, where-as our patient had transient cycles, lasting only a few years. Tambasco et al. report thirteen pediatric cases of CSS and VSS [7]. In each case, the cyclic hypothermia resolved after an average of three years regardless of treatment. This is consistent with our case. Secondly, our patient had hydrocephalus due to interventricular hemorrhage, which was treated with bilateral shunts. Despite improvement in her intracerebral pressures, the patient continued to have cycles of hypothermia. Since pressures were not directly related to hypothermic events, this places hydrocephalus lower on the differential. Although seizure is listed as a possible cause of hypothermia, it is rarely reported in literature. Our patient did not have seizures correlating to hypothermic events as evidenced by normal EEGs. In addition, hypothermic events for our patient lasted longer than a typical seizure, well into the window of status epilepticus. Given the top diagnoses for spontaneous hypothermia, CSS is most likely. Spontaneous recurrence of SS in late adulthood has not yet been reported. Perhaps this is due to decreased clinical recognition of the childhood stage, which in most cases remits regardless of pharmacological intervention. This suggests that adults with new-onset of the disease may actually represent reemergence. Another possibility is that recurrent cases may not yet be published due to a long latency period and lack of follow-up time necessary for recently diagnosed children. Our patient was diagnosed with CSS when she was five-years-old. Then, during a time of physiologic stress at the age of thirty-two years-old, she began having episodes of hypothermia, encephalopathy, hyperkalemia, hyponatremia, and associated pancytopenia; which have been seen in other cases of SS [5]. She also developed a clinically significant cardiomyopathy, leading to the diagnosis of carnitine deficiency. Treatment with levocarnitine decelerated her functional decline, but it wasn't until a few years passed and liothyroxine was added to her regiment that her temperature and cytopenia ultimately stabilized. Although severe hypothyroidism can cause hypothermia, it is unlikely that this is the sole cause of hypothermia in our case. However, there are a few case reports of severe myxedema coma causing pancytopenia. Our patient had a slightly elevated TSH with a slightly decreased Free T4 during these episodes, which may represent euthyroid sick syndrome or a mild state of hypothyroidism [8]. The other issue at play is that most adults appear to have spontaneous resolution of symptoms after 2-3 years, which further confounds the treatment-resolution paradigm.

The rate of carnitine deficiency is often quoted as 1 in 50,000 [9]. The discovery of this relatively rare mitochondrial disorder in the setting of our patient's complicated medical background makes for an interesting case presentation. Classically, carnitine deficiency has findings ranging from encephalopathy, hypoglycemia, decreased muscle tone, cardiomyopathy, and liver abnormalities. Our patient demonstrated clinical and laboratory findings consistent with carnitine deficiency. Treatment with levocarnitine helped bring her back to baseline functional status. Systemic primary carnitine deficiency is thought to be autosomal recessive. The patient's parents did not have additional children, so additional familial workup was not possible. Neither our patient nor her parents have been tested

for genetic changes. The original report by Shapiro and Plum describes a patient that developed primary amenorrhea at 16 years of age [4]. Our patient developed primary amenorrhea at the age of 15 years old. No other reports have mentioned primary amenorrhea with SS. It is unclear if these represent two incidental cases or if a link between SS and amenorrhea will at some point be elucidated. In our case, discontinuing hormone therapy was important for ensuring better seizure control. However, the lower levels of estrogen and progesterone lead to her development of osteoporosis with a current z-score < -3 in all measured areas. Bisphosphonate therapy is currently being discussed. The low incidence of SS and even lower incidence of SS with concomitant primary hypothyroidism makes it difficult to find a link between these two conditions. For our patient, the diagnosis of hypothyroidism serves to complicate and obscure findings which might be related to SS.

CONCLUSION

Spontaneous hypothermia and agenesis of the corpus callosum is a rare disease with many patients carrying comorbid diagnoses. This is the first reported case of SS with Carnitine deficiency. Our patient also carries some previously reported comorbid diagnoses including cyclical cytopenia, seizure disorder, primary amenorrhea, and hypothyroidism. Recurrent episodes of hypothermia later in life may be a newly published event as well. It is possible that this is a manifestation of SS either as a stand-alone phenomenon or as a result of un-masking due to stressful physiologic events. We hope that this report provides insights gained from longitudinal care that can be applied to other patients presenting with this rare condition.

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