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Case Report

A Case of Reverse Shapiro Syndrome Responding to Cyprohepatadine

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Abstract

Reverse Shapiro syndrome consists of the association of unexplained hyperthermia and corpus callosum agenesis. The genetic basis is still unidentified; yet, neurochemical abnormalities as well as hypothalamic dysfunction have been proposed as possible etiologies. Only four cases of reverse Shapiro Syndrome have been reported to date and many therapeutic managements have been proposed without any radical success. Here we report a new case of a 6 months old male patient, with controlled cryptogenic epilepsy who is also presenting with a reverse Shapiro syndrome. The patient presented with recurrent episodes of hyperthermia that responded completely to a treatment by cyproheptadine.

Introduction

Reverse Shapiro syndrome was first described in 1994 by Hirayama [1] in a 14 years old female with an unexplained association of hyperthermia and agenesis of the corpus callosum (as opposed to the Shapiro syndrome described in 1969 by Shapiro et al. as an association of hypothermia, hyperhidrosis and corpus callosum agenesis). To our knowledge, there are only four cases of reverse Shapiro's syndrome reported to date, including Hirayama's patient, and those patients presented between the ages of 3 months and 14 years [1-4]. Here we report the first case in Lebanon and the Arab world of reverse Shapiro syndrome at the age of 6 month. We report as well the success of a treatment with the serotonin agonist cyproheptadine hydrochloride with immediate and complete resolution of the hyperthermia.

Case Report

We report here a 6 month old male patient, with the prenatal diagnosis of agenesis of the corpus callosum, who presented to our care for management of recurrent fever. The child was clinically stable until the age of 4 months when he started to have spasms with an EEG showing typical hypsarrythmia associated with neuro-motor regression. This was concordant with the diagnosis of West epilepsy, and the patient was started and controlled on vigabatrin. At 5 months of age, the patient started to present regular episodes of fever (38.5- 39°C) associated with diaphoresis during the fever episodes. The fever was periodic, occurring every day, peaking every 6 hours, and not associated with any symptoms of infectious or non-infectious origin. The patient had normal contact and interaction yet with a preserved baseline hypotonia, and a decreased activity when hyperthermic, yet without any autonomic abnormalities. The fever would last for 60 to 90 minutes, and decrease with or without antipyretics, before returning to its normal baseline raging between 36.5 and 37.6 degrees Celsius. Physical exam showed no dysmorphic features, no skin hypo or hyper pigmented lesions, with a head circumference 45cm (90th percentile), weight 8 kgs (90th percentile) and a height of 67 cm (90th percentile). The patient had flat anterior fontanel normal in size. Examination of the ears, nose and tonsils was normal, with no palpable lymphadenopathies. Lungs were normal, with no cardiac murmur on auscultation. There was no hepatosplenomegaly. The rest of physical exam was unremarkable, revealing no focus for his fever.

On neurological examination, patient had mild axial hypotonicity, and neurodevelopmental retardation. He was not able to hold his head, does not fix and follow, did not roll over nor grab objects.

Full sepsis workup was done to rule out any infectious etiology. Complete blood count, C-reactive protein, procalcitonin, liver function tests, blood Culture, chest X-ray, urine analysis and culture, Cerebrospinal fluid analysis and culture, as well as a total body CT scan, were performed, and all these investigations were normal with the exception of the corpus callosum agenesis. Thus, infection was ruled out as a cause of his fever.

Metabolic workup was done to rule out any metabolic derangement that can explain the recurrent fever. Serum levels of lactic acid, pyruvic acid, uric acid ammonia, and creatine phosphokinase, were all normal. Chromatography of amino acid in blood and organic acid in urine were also done and showed normal values. Therefore metabolic disease was also excluded as a cause of fever.

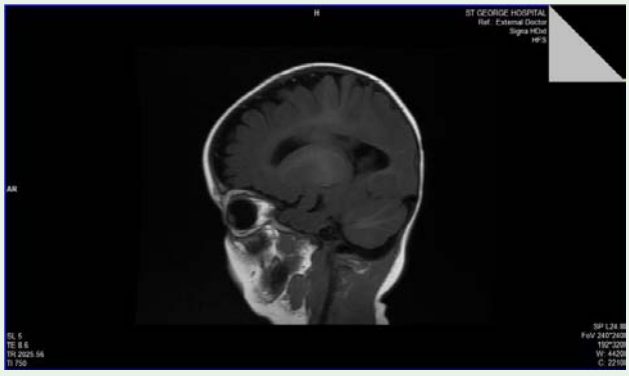

Figure 1: Brain MRI Sagittal Cut with corpus callosum agenesis.

Brain MRI done showed complete agenesis of the corpus callosum (Figure 1) without other anomalies.

And in order to complete the etiologic work up for the hypotonia, delay, the west syndrome as well as the Reverse Shapiro's syndrome, the patient also had a whole exomesequencing done on his DNA that did not reveal any known or suspect genetic variation associated with known disease phenotypes.

Neither infectious nor metabolic etiologies were able to explain the patient's recurrent and periodic fever. In the context of the complete agenesis of the corpus callosum, Reverse Shapiro syndrome was our main differential diagnosis. And with the recent studies [2] discussing the physiological similarity between Shapiro and reverse Shapiro Syndrome, a trial of cyproheptadine hydrochloride was proposed, and the patient was started on cyproheptadine hydrochloride of 0.25 mg/kg/day PO divided q8h.

Fever subsided after 2 days of initiation of the cyproheptadine hydrochloride, with no recurrence upon daily follow up and over a period of 6 months to date.

Discussion

In 1969 Shapiro first described Shapiro Syndrome as an association of hypothermia, hyperhidrosis and corpus callosum agenesis [5] with more than 50 reported cases until now [2]. The finding of hyperthermia instead of hypothermia along with hyperhidrosis and corpus callosum agenesis, was first described as a "reverse Shapiro syndrome" by Hirayama *et al.* in 1994. Hirayam reported a case of a 14 year-old girl with periodic hyperthermia and corpus callosum agenesis [1]. Since then, only three cases of reverse Shapiro syndrome were published. Lin and Wang in 2005 reported a case of a 9-month-old girl presenting with fever of unknown origin who had agenesis of corpus callosum [4], in 2012 Guha*et al.*reported a case of a 3 months old female with reverse Shapiro's syndrome who did not show any response to any treatment [3], and Topcu*et al.* in 2013 reported a case of 3.5-year-old girl with complete agenesis of corpus callosum presenting with recurrent fever and vomiting [2]. In all these cases, the cause of fever could not be explained by any infectious, metabolic or endocrinological etiology, and the association of isolated fever with corpus callosum agenesis was referred to reverse Shapiro syndrome.

To date, several hypotheses have been suggested regarding the pathophysiologic mechanisms underlying this syndrome. Clearly, the agenesis of the corpus callosum by itself does not cause thermal dysregulation, as callosotomy did not lead to defective thermoregulation and hypothermia does not ordinarily accompany callosal agenesis [1].

A first anatomical structural theory is based on hypothalamic dyregulation. The hypothalamus is central in thermo regulation and when affected with any tumor or degenerative disorders or any microlesions, this can result in unexpected thermal changes [5]. The body temperature is controlled by two different hypothalamic centers, the posterior center conserves heat by vasoconstriction, while the anterior center dissipates heat by inducing vasodilation and sweating. Any injury to either centers may cause either hypo- or hyperthermia, and many post mortem studies have shown, spongiosis and gliosis as well as neuronal losses within the hypothalamic tissues in patients suffering for thermal dysregulation [2]. A neurochemical theory is proposed in parallel to the anatomical structural theory, with the dysregulation of the dopamine related thermoregulatory function, resulting in a dopamine super sensitivity caused by developmental lesions that reduced the number of afferent inputs to the hypothalamic thermoregulatory center [4,6].

To date, no definitive treatment for this disorder has been reported, but it is advised to start with a low dose of levodopa initially [6]. Yet in thermal dysregulation of central, and specifically hypothalamic origin, many trials have been reported with success of various therapies for recurrent hyperthermia. Treatments that have been proposed were dopamine agonists [1] and antiserotonergic agents like cyproheptadine [7]. These treatments have been reported to abort or control these episodes [8]. Hirayama *et al.* reported that the hyperthermia in their patients with reverse Shapiro's syndrome was controlled effectively with the dopamine agonist. Ling and Wang reported that dopamine agonists (levodopa with carbidopa) and the serotonin antagonist (cyproheptadine hydrochloride) failed to control the hyperthermia.

Hirayama et al. reported that hyperthermia in their case with reverse Shapiro's syndrome returned to normal with a dopamine agonist, the patient responded well to Levodopa [1], while in the case of the patient reported by Guha *et al.*medication therapy failed and the patient was treated with tepid sponging and other physical measures [3].

All the reported cases have dealt with Shapiro and reverse Shapiro's syndrome as two different entities, yet very innovatively, Topcu *et al* [2] suggest that these two diseases are a manifestation of a same disease, and the same patient can have hypo and hyperthermia episodes. And with the response to similar medication in both condition, differently in different patients, we have a therapeutic support for this theory. All the four other reported cases noted a failure in response to cyproheptadine, yet; in the patient we are reporting cyproheptadine gave a rapid and complete resolution of the symptoms.

On a parallel path to the therapeutic aspect, no genetic basis have been described for either Shapiro or Reverse Shapiro's Syndrome, and in our patient the whole exome sequencing did not identify any known or relevant mutation, which suggests acrytpotogenic etiology to the disease associating the reverse Shapiro syndrome and the west syndrome, probably in a specific receptor in the hypothalamic cells, or a disease of a degenerative etiology probably activated by the

west syndrome. But a symptomatic reverse Shapiro syndrome, or (Shapiro syndrome), secondary to a primary disease, should always be considered. A variant of Shapiro syndrome has been reported as secondary to a head trauma with a proposed, secondary induced, trans-synaptic degeneration of neurons in the hypothalamic area resulting in the hypothalamic dysfunction [9]. Our case we have a patient with West syndrome, which an epilepsy that can be due to a severe neuronal cells inflammation [10], and like any other epilepsy, it can cause ongoing neuronal cell damage and neuronal cell death in single or multiple seizures [11]. One of the possible theories can be that the hypothalamic dysregulation was a consequence to the present epileptic syndrome.

Conclusion

Reverse Shapiro syndrome remains an under diagnosed entity that should be considered in every case of corpus callosum agenesis and unexplained hyperthermia or thermal dysregulation. Shapiro syndrome and reverse Shapiro syndrome might represent the same clinical entity. Until now both entities remain an exclusion diagnosis, and a full paraclinical work up (laboratory and imaging investigations) should be performed before confirming this diagnosis. Dopamine agonists can be proposed as a first line treatment, but cyproheptadine should be considered as a possible treatment in reverse Shapiro syndrome. The genetic basis of the disease is still not defined although the possibility of a mechanism secondary to injury should be considered. The response of our patient to cyproheptadine falls in favor of the unicity of the physiological causative mechanism for Shapiro and Reverse Shapiro syndrome, while the variability of the response to this treatment can be due to the variable level of neuroendocrine dysfunction and the residual enzymatic activity within the thalamic cells.

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