Understanding the pathophysiology of hyperglycemia-associated chorea-ballism: a systematic review of positron emission tomography findings

Sergio Alejandro Gómez Ochoa, MDa
Blanca Beatriz Espín Chico, MDb

a GERMINA-UIS Research Group, School of Medicine, Health Sciences Faculty, Universidad Industrial de Santander, Bucaramanga, Colombia
b Public Health Faculty, Escuela Politécnica Superior de Chimborazo, Riobamba, Ecuador

Correspondence to: Sergio Alejandro Gómez Ochoa
E-mail: sagomezo.182@gmail.com

Summary

Hyperglycemia-associated chorea-ballism (HCB) is an infrequent neurological syndrome whose pathophysiology remains poorly understood. Positron emission tomography (PET) studies have offered valuable information regarding regional glucose metabolism. The studies included were published between 1980-2017 and reported demographic, clinical, laboratory and imaging data from patients with HCB in whom a PET scan had been performed. Eleven patients were evaluated (women 82%, Asian origin 91%, mean age 71 years). The main findings were an increase in glucose metabolism at the contralateral motor cortex related to recent episodes of hemibal-lism-hemichorea in 2 patients, and an altered metabolism in the affected basal ganglia in all of them: decreased in 10 patients (91%) and increased in 1 (9%). However during the acute period the patients showed only an increased metabolism, or even no changes. Contrary to what has previously been suggested in a metabolic failure hypothesis, changes in glucose metabolism in the basal ganglia may not be a key factor in the pathogenesis of HCB, and may potentially be a direct result of histological changes such as cellular ischemia and gliosis related to HCB development.

KEY WORDS: ballism, basal ganglia, chorea, hyperglycemia, positron emission tomography.

Introduction

Chorea-ballism is a neurological disorder characterized by irregular, involuntary and poorly patterned movements, most frequently, although not exclusively, presenting with unilateral involvement of the extremities (Hermann and Walker, 2015). The condition may be attributed to a wide variety of pathologies, such as neo-

plastic, cerebrovascular, neurodegenerative, infectious, immunological and metabolic diseases. Although hyperglycemia is the most common metabolic cause of chorea-ballism, its pathophysiological mechanisms are still largely unclear (Rector et al., 1982; Dewey and Jan-kovic, 1989).

The literature contains numerous case reports highlighting the association between hyperglycemia and chorea-ballism; these reports have shown an apparent predominance in elderly females and in non-ketotic hyperglycemia, usually showing hyperintensity changes in the basal ganglia region in T1-weighted magnetic resonance images (Higa et al., 2004; Roy et al., 2016; Sati-sh et al., 2017). Among the other imaging techniques that have been used to describe the alterations present in this syndrome, one of the most representative is positron emission tomography (PET), a functional study that makes it possible to trace the metabolism of certain brain areas. Although PET evidence is valuable in the process of understanding the pathophysiology of hyperglycemia-associated chorea-ballism (HCB), the literature contains only reports of isolated cases (Nguyen, 2007). Due to the importance of this technique, we performed a systematic review including all studies that involved patients with hyperglycemia who underwent a PET scan, in order to synthesize and analyze their imaging findings.

Materials and methods

The present systematic review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) Statement and the Cochrane Handbook for meta-analyses and systematic reviews.

Search strategy

The literature search was performed by two Authors using the Embase, Medline, Pubmed, Scielo and LILACS databases. The search algorithm used was the following:

1. (Hyperglycemia or Hyperglycaemia or Diabetes or Diabetes Mellitus)
2. (Chorea or Hemi-chorea or Ballism or Hemi-ballism)
3. 1 and 2
4. Results were filtered to include only articles written in English, Spanish or Portuguese
5. Repeated results were excluded. Moreover, an additional search was performed in the references of the evaluated articles, in order to include any references that may have been missed in the search.
Eligibility criteria
Eligible studies were case reports or case series that involved patients with hyperglycemia in whom a PET scan had been performed to characterize the pathology. The studies had to describe the demographic, clinical, laboratory and neuroradiological characteristics of the included patients (specifically the PET results). Studies published in the period 1990-2017 and written in English, Spanish or Portuguese were considered. On the other hand, cases in which chorea-ballism presented simultaneously with other comorbidities potentially related to abnormal movements (such as cerebral infarction, Huntington’s disease, Friedreich’s ataxia, neuroacanthocytosis, lupus eruthematosis, hyperthyroidism, hypothyroidism, AIDS, toxoplasmosis, post-streptococcal autoimmune disorder and certain drugs/toxins), in which the true etiology of the chorea-ballism was not clear, were excluded.

Study selection and data collection
Two Authors performed the database review, starting with the removal of the duplicates found in the different searches. The titles were then reviewed to identify studies related to the main topic of this review. In this step, all articles showing no relation to the purpose of this study were excluded. Finally, a full text review of the suitable studies was performed. The two reviewers then compared their results, resolving any differences through consensus. A uniform collection format was created to record the included patients’ demographic, clinical, laboratory and imaging information.

Statistical methods
A database was created in the Excel® program to record the information, and a descriptive analysis was performed in which the qualitative variables were expressed as percentages and the quantitative ones as means with standard deviation.

Results
The literature search identified 3076 articles related to the search algorithm. Of these, only 8 met all the inclusion criteria. Figure 1 shows the relative PRISMA flow diagram. From the included articles, 11 patients with HCB and PET scan data were analyzed (Hsu et al., 2004; Nguyen, 2007; Abe et al., 2009; Hashimoto et al., 2012; D’souza et al., 2014; Tan et al., 2014; Lee et al., 2016; Sato et al., 2016).

Demographic and clinical data
The demographic, clinical, laboratory and imaging characteristics of the included patients are shown in Table I. The patients were prevalently women (82%) with a mean age at presentation of 71 ± 11.02 years (range 50 - 84 years), moreover 91% of the patients was of Asian ethnic origin. The clinical manifestations of HCB were predominantly unilateral, without one side being more frequently involved, but the upper extremities were more commonly affected. HCB was the first manifestation of diabetes mellitus (DM) in 2 patients, while in the other 9, HCB appeared after a mean interval of 9.6 years after DM diagnosis. Poor glyemic control was reported in almost all these 9 patients.

Laboratory data
The blood glucose level at patient entry was 402.5 ± 160 mg/dl (range 165 - 660 mg/dl), HBA1c values ranged from 7.4 to 19% (mean 14.1%), and there was evidence of ketone bodies in only 2 patients.

Neuroradiological findings
Magnetic resonance imaging studies were available for 10 patients, while the other patient was studied by computed tomography. The cases showed very similar imaging results, i.e. images typical of basal ganglia involvement. The most affected regions were the putamen (63.6%) and the caudate nucleus (36.3%). No cortical or cerebellar impairment was found.

With regard to the PET studies, in all the evaluated cases the radiolabeled ligand 18F-fludeoxyglucose ([18F] FDG) was used to estimate the regional metabolic rate (RMR) of glucose. In seven cases the timing of the PET examination was known: it was carried out at a mean of 23 days after the onset of the symptoms, by which time, in most cases, the abnormal movements were already controlled. The main finding was a decreased uptake of the ligand in the affected basal ganglia (91% of the total cases), reflecting reduced glucose metabolism in this region. However, this finding was not present during the acute period when the HCB was still present in most cases. Indeed, three cases in which PET was performed within the first 10 days of symptom onset showed no change in the RMR of the basal ganglia, or even an increase in this rate. By contrast, the PET studies that showed a decrease in local glucose metabolism were all performed at a longer interval (a mean of 32.5 days) from symptom onset.

Another important finding was the presence of in-
creased radiotracer accumulation in the contralateral motor cortex related to recent episodes of hemiballism-hemichorea in 2 patients, a rare finding with other imaging methods, showing an opposite trend to the one reported for the basal ganglia (Table II).

Treatments and outcome
Eight patients received neuroleptics to control their abnormal movements. Haloperidol was the drug most frequently used (100%), achieving successful symptom control in most of the cases (Hsu et al., 2004; Abe et al., 2009; Hashimoto et al., 2012; Tan et al., 2014). However, in three cases, complete resolution of the clinical manifestations was not possible with this neuroleptic alone, and it was necessary to use other drugs such as clonazepam, baclofen, artane, tetrabenazine, clozapine, levodopa, and even surgical procedures, such as pallidotomy. Insulin was administered to all patients to lower their serum glucose levels.

The outcome was reported in nine cases, a total improvement without recurrences being the most frequent finding (78%). Recurrence was reported in only 1 patient in a context of multiple comorbidities and poor glycemic control (Lee et al., 2016). Unfortunately, the time to resolution was reported in only 3 patients, and it was a mean of 42 ± 43 days (range 9-90 days) (Hashimoto, Oguchi & Takeuchi, 2012; Sato et al., 2016).

Discussion
Since Bedwell's first description of HCB in 1960 (Bedwell, 1960), many reports from around the world have described this complex syndrome. As revealed by our extensive literature search, HCB shows a significant predominance in non-ketotic hyperglycemia in the context of type 2 MD among older females of Asian origin (91% of our cases), which suggests a potential genetic basal ganglia susceptibility to hyperglycemia in this population, among many other ethnicity-related hypotheses (Guo et al., 2014; Lee et al., 2015). Moreover, multiple theories have been advanced to explain the pathophysiology of this disease, namely: 1) increased dopamine receptor sensitivity that could trigger the hyperkinesia

Table I - Clinical features of the patients with hyperglycemia-associated chorea-ballism.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age</th>
<th>Sex</th>
<th>Country</th>
<th>Chorea characteristics</th>
<th>DM duration</th>
<th>Blood glucose</th>
<th>Ketosis</th>
<th>HbA1c (%)</th>
<th>CT/MRI Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hsu JL et al 2004 (1)</td>
<td>81</td>
<td>M</td>
<td>Taiwan</td>
<td>Right UL</td>
<td>10 years</td>
<td>527</td>
<td>No</td>
<td>NR</td>
<td>T1MRI: Left putaminal, globus pallidus and caudate nucleus hyperintensity</td>
</tr>
<tr>
<td>Hsu JL et al 2004 (2)</td>
<td>72</td>
<td>F</td>
<td>Taiwan</td>
<td>Left UL/LL</td>
<td>10 years</td>
<td>350</td>
<td>No</td>
<td>NR</td>
<td>T1MRI: Right basal ganglia hyperintensity</td>
</tr>
<tr>
<td>Nguyen BD et al 2007</td>
<td>72</td>
<td>F</td>
<td>USA</td>
<td>Right UL</td>
<td>New Onset</td>
<td>660</td>
<td>No</td>
<td>NR</td>
<td>T1MRI: Left striatal hyperintensity</td>
</tr>
<tr>
<td>Abe Y et al 2009</td>
<td>64</td>
<td>F</td>
<td>Japan</td>
<td>Right UL/LL</td>
<td>7 years</td>
<td>165</td>
<td>No</td>
<td>7.4</td>
<td>T1MRI: Left putaminal and caudate nucleus hyperintensity</td>
</tr>
<tr>
<td>Hashimoto T et al 2012 (1)</td>
<td>77</td>
<td>F</td>
<td>Japan</td>
<td>Left UL/LL</td>
<td>NR</td>
<td>632</td>
<td>No</td>
<td>19%</td>
<td>T1MRI: Right striatal hyperintensity</td>
</tr>
<tr>
<td>Hashimoto T et al 2012 (2)</td>
<td>78</td>
<td>F</td>
<td>Japan</td>
<td>Left UL/LL</td>
<td>NR</td>
<td>456</td>
<td>No</td>
<td>14.4</td>
<td>T1MRI: Bilateral globus pallidus hyperintensity</td>
</tr>
<tr>
<td>D’souza M et al 2014</td>
<td>50</td>
<td>F</td>
<td>India</td>
<td>Bilateral UL</td>
<td>New Onset</td>
<td>362</td>
<td>No</td>
<td>13.5</td>
<td>T1MRI: Bilateral caudate nucleus and putaminal hyperintensity</td>
</tr>
<tr>
<td>Tan Y et al 2014 (1)</td>
<td>83</td>
<td>F</td>
<td>China</td>
<td>Right UL</td>
<td>10 years</td>
<td>295</td>
<td>Yes</td>
<td>12.6</td>
<td>CT: Left putaminal hyperintensity</td>
</tr>
<tr>
<td>Tan Y et al 2014 (2)</td>
<td>59</td>
<td>F</td>
<td>China</td>
<td>Right UL/LL</td>
<td>10 years</td>
<td>360</td>
<td>Yes</td>
<td>13.2</td>
<td>T1MRI: left putaminal and lentiform nuclei hyperintensity</td>
</tr>
<tr>
<td>Sato K et al 2016</td>
<td>64</td>
<td>M</td>
<td>Japan</td>
<td>All four extremities</td>
<td>NR</td>
<td>427</td>
<td>No</td>
<td>16.5</td>
<td>T1MRI: Bilateral putaminal and caudate nucleus hyperintenisties</td>
</tr>
<tr>
<td>Lee D et al 2016</td>
<td>62</td>
<td>F</td>
<td>Republic of Korea</td>
<td>Left UL/LL</td>
<td>NR</td>
<td>195</td>
<td>No</td>
<td>16.2</td>
<td>T1MRI: Right putaminal hyperintensity</td>
</tr>
</tbody>
</table>

Abbreviations: M=male, F=female, UL=upper limbs, LL=lower limbs, DM=diabetes mellitus, NR=not reported, CT: computed tomography, MRI=magnetic resonance imaging


under certain conditions; 2) striatal infarction, given that petechial hemorrhages have been described in some cases; 3) increased gamma-aminobutyric acid (GABA) metabolism, resulting in decreased GABA levels and a reduction of the epileptic seizure threshold; 4) a disruption of the blood-brain barrier caused by the hyperglycemia and the consequent hyperviscosity, leading to cellular acidosis and regional metabolic failure (Cheema et al., 2011; Slabu et al., 2011). These latter two are the strongest theories that have been advanced in order to explain the etiology of basal ganglia susceptibility to hyperglycemia (Narayanan, 2012). Shan et al. proposed a combined hypothesis that may explain MRI changes in these patients, suggesting a dysfunction of GABAergic neurons in the putamen and caudate nucleus caused by a process of ischemia related to the hyperglycemia, leading to a dysfunction of the indirect pathway neurons, with preservation of the direct pathway ones. These direct pathway neurons would then start to be fired due to the low epileptic threshold in the context of hyperosmolarity, all of this finally causing a process of metabolic irregularity, resulting in neuronal loss and gliosis in the striatal region, as shown in the autopsy studies performed in this syndrome (Shan et al., 1998; Nath et al., 2006).

Table II - PET imaging results in patients with hyperglycemia-associated chorea-ballism.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Timing of PET*</th>
<th>PET imaging in basal ganglia</th>
<th>Other PET findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hsu JL et al (1)</td>
<td>40 days</td>
<td>Decreased uptake of FDG in the left putamen and globus pallidum</td>
<td></td>
</tr>
<tr>
<td>Hsu JL et al (2)</td>
<td>30 days</td>
<td>Decreased uptake of FDG in the whole right basal ganglia</td>
<td></td>
</tr>
<tr>
<td>Nguyen BD et al</td>
<td>NR</td>
<td>Decreased uptake of FDG in the head of the left caudate nucleus and left lentiform nucleus</td>
<td>Increased radiotracer accumulation in the left motor cortex related to a recent episode of right hemiballism-hemichorea</td>
</tr>
<tr>
<td>Abe Y et al</td>
<td>21 days</td>
<td>Decreased uptake of FDG in the left striatum</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Period with chorea (5 days): Right putaminal RMR was increased compared with that of the left side, but not increased compared with values of normal subjects</td>
<td></td>
</tr>
<tr>
<td>Hashimoto T et al (1)</td>
<td>5 and 19 days</td>
<td>-Period without chorea (19 days): Right putaminal and globus pallidus RMR were decreased by 14.9% and 6.2%, respectively</td>
<td></td>
</tr>
<tr>
<td>Hashimoto T et al (2)</td>
<td>3 and 30 days</td>
<td>-30 days (Period with moderate chorea): Metabolic rates of bilateral putamen and the right caudate and globus pallidus were decreased by ≥15% a month after onset</td>
<td></td>
</tr>
<tr>
<td>D’souza M et al</td>
<td>NR</td>
<td>Diffuse hypometabolism in bilateral basal ganglia</td>
<td>Increased radiotracer accumulation in the left motor cortex related to a recent episode of right predominant choreiform movements</td>
</tr>
<tr>
<td>Tan Y et al (1)</td>
<td>9 days</td>
<td>Increase in glucose metabolism in left basal ganglia</td>
<td></td>
</tr>
<tr>
<td>Tan Y et al (2)</td>
<td>55 days</td>
<td>Decrease in glucose metabolism in left basal ganglia</td>
<td></td>
</tr>
<tr>
<td>Sato K et al</td>
<td>NR</td>
<td>Metabolic dysfunction with decreased glucose metabolism in the bilateral striatum</td>
<td></td>
</tr>
<tr>
<td>Lee D et al</td>
<td>NR</td>
<td>Decreased uptake of FDG in the right putamen</td>
<td></td>
</tr>
</tbody>
</table>

*After the onset of symptoms. PET = positron emission tomography, FDG: fludeoxyglucose, NR: not reported.
been theorized to produce a loss of pallidal inhibitory input to the thalamus, reflected in the clinical manifestations of the disease (Chang et al., 1996; Kim et al., 2002). Moreover, cortical involvement was described by Hwang et al., in their study, in which 10 patients with cortical chorea/ballism (cases without MRI evidence of basal ganglia lesions) were evaluated by SPECT (Hwang et al., 2013). Decreased perfusion or perfusion defects in the parietal cortex were the most common SPECT finding in these patients, as was reported previously in the literature in other clinical conditions (Mizushima et al., 1997; Lee et al., 2000; Lyoo et al., 2000; Al-Yacoub et al., 2004). Moreover, frontal cortex involvement has also been reported, strengthening the hypothesis of a network disruption generated by both frontal and parietal cortex dysfunction as the etiology of chorea-ballism in cases without basal apparent ganglia involvement, a theory that could be applied to HCB cases without basal ganglia lesions or with evidence of cortical involvement, as seen in two cases in this review (Hwang et al., 2013). With regard to these patients, the increase in radiotracer accumulation in the motor cortex was related to recent episodes of hemiballism-hemichorea, a characteristic found in other conditions such as epilepsy, some kinds of encephalitis and obsessive compulsive disorder, among many others, supporting the hypothesis of a dysfunction of a subcortical-cortical motor network involved in the pathogenesis of HCB (Nishida et al., 2008; Fisher et al., 2012; Roussakis and Piccini, 2015). However, this finding may not be in accordance with the aforementioned SPECT findings of cortical hypoperfusion, which, on the other hand, would potentially be reflected in a regional decrease of radiotracer accumulation, as in neurodegenerative diseases like corticobasal syndrome and multisystem atrophy, which have shown a marked cortical and basal ganglia hypometabolism (Kwon et al., 2008). This trend may suggest a different mechanism of cortical involvement in HCB as opposed to other types of cortical chorea-ballism. Positron emission tomography (PET) can offer useful information in the study of HCB syndrome and its pathogenesis, as it is a functional imaging technique that involves the use of a radiolabeled ligand that can bind to specific structures of interest. For example, using [18F]FDG it is possible to demonstrate changes in cerebral glucose metabolism (Ehrlich and Walker, 2017), a critical point in one of the aforementioned HCB etiology theories and also the most important result in our study, which showed a progression from a normal/increased RMR in the initial stages of the HCB to a marked decrease of glucose metabolism in the affected basal ganglia several weeks after the HCB onset, regardless of whether or not the abnormal movements were already controlled. This differed with the concept that predominated in published case reports, which stated that the hypometabolic state reflected a regional metabolic failure, assuming this to be one of the causal factors of the HCB (Bizet et al., 2014; Chen et al., 2014; Danve et al., 2015). However, metabolic changes in these areas have been reported in variable stages of multiple neurological conditions, and in inflammatory diseases, like antiphospholipid syndrome, autoimmune diseases and drug-induced disorders, in which PET studies have shown striatal hypermetabolism (Goldman et al., 1993; Furie et al., 1994; Vela et al., 2004; Demonty et al., 2010). On the other hand, striatal hypometabolism has been found in neurodegenerative choreic disorders, such as neuroacanthocytosis syndrome and Huntington’s disease (Feigin et al., 2001; Selcuk and Fenercioglu, 2010; Ciarmiello et al., 2012; Herben-Dekker et al., 2014; Cui et al., 2015). Because of this lack of correlation between symptom expression and RMR we conclude that metabolic changes in the basal ganglia may not be a key factor in the pathogenesis of HCB, but rather a direct result of histological changes related to its development, as hypometabolism in the late HCB stages may reflect cellular ischemia and its resulting gliosis (Ohara et al., 2001; Nath et al., 2006).

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