Clinical and neuroimaging spectrum of hyperglycemia-associated chorea-ballism: systematic review and exploratory analysis of case reports

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Summary

Hyperglycemia-associated chorea-ballism (HCB) is an infrequent neurological syndrome occurring predominantly in elderly females and in the setting of non-ketotic hyperglycemia (NKH). A systematic review was conducted in accordance with the PRISMA statement. Studies published between 1980 and 2018 that reported demographic, clinical, laboratory and imaging features from patients with HCB were screened. 136 studies describing 286 patients were included in the analysis. The patients included had a median age of 72 years; those with ketotic hyperglycemia (KH) were older (p<0.001). Women and NKH patients were the most frequently affected (63% and 92%, respectively). The median glucose level at admission was 420 mg/dL (IQR 328-535), and was significantly higher in KH (p=0.009). Moreover, the absence of a clear lesion on imaging studies and the finding of bilateral imaging evidence of lesions were each more frequent in the KH group (p=0.036 and p=0.008, respectively). 48 cases (19.4%) presented with bilateral CT/MRI lesions, having higher values of plasma osmolarity compared with the patients with unilateral lesions (p=0.011). Every patient received hypoglycemic treatment, but only 174 (60.84%) were prescribed neuroleptics. 213 patients (84.86%) showed a total recovery, after a median of 14 days (IQR 3-31). Bilateral chorea-ballism was supported by bilateral imaging evidence of involvement in only 60% of the cases (positive predictive value). Patients not prescribed neuroleptics, with negative lentiform nucleus involvement, and age within the third tertile (≥ 78 years) had an odds ratio of 6.6 (CI 95% 1.18-141.10) for a complete clinical recovery. Significant differences were identified between types of hyperglycemia and regarding the clinical and imaging laterality features. Furthermore, the predictor variables evaluated showed potential utility for assessing the prognosis of HCB patients.

Key Words: ballism, chorea, hyperglycemia, movement disorders.

Introduction

Among the various causes of chorea-ballism, metabolic conditions are an infrequent group that, mainly because of this low frequency of presentation, are often underestimated in clinical practice (Hermann and Walker, 2015). Within this group, hyperglycemia, resulting from poorly controlled or new-onset diabetes mellitus (DM), is the most common etiology, even though its prevalence reached only 1% of the total chorea-ballism cases in a recent study performed in the US (Ryan et al., 2018). In addition, only case reports and case series describing this etiology have been published in the literature, all of them proposing multiple theories about the origin of this disorder, but highlighting that the underlying pathophysiological mechanisms are still unclear (Rector et al., 1982; Dewey and Jankovic, 1989; Ifergane et al., 2001). Nevertheless, published studies have been able to elucidate the main features of the disease, showing an apparent predominance in the elderly and in the female gender. Patients usually develop hyperglycemia-associated chorea-ballism (HCB) after a long period of poorly controlled DM; however, in a significant proportion of cases, abnormal movements were the first symptom of the DM. With regard to the clinical presentation of HCB, patients tend to display involuntary, continuous, abrupt and irregular movements that most frequently show unilateral involvement of the extremities and may sometimes also affect the head. Non-ketotic hyperglycemia (NKH) is the most common laboratory finding in these individuals, typically associated with hyperdense area(s) on computed tomography (CT) scan or a hyperintense T1-weighted signal in the basal ganglia on magnetic resonance imaging (MRI). However, imaging is not always required for diagnosis of HCB, as there are cases with negative CT/MRI in whom hyperglycemia emerges as the only cause of the syndrome. Hyperdense/hyperintense area(s) in the basal ganglia of patients with HCB have been linked to a process of ischemia, necrosis and gliosis, as functional positron emission tomography (PET) studies with 18F-fludeoxyglucose have shown a

reduced regional metabolic rate in the affected areas (Gómez Ochoa and Espín Chico, 2018). Finally, patients with HCB have a good prognosis for recovery, commonly experiencing a total remission of the symptoms after two weeks of glucose-lowering treatment, although some need neuroleptic treatment to achieve total symptomatic recovery (Ahlskog et al., 2001; Higa et al., 2004; Roy et al., 2016; Satish et al., 2017). However, the fact that these general concepts stem from systematic reviews of studies that included small samples adds to the limitations of the analyses conducted (Oh et al., 2002; Chen et al., 2014).

For this reason, we performed a systematic review of the literature to characterize the demographic, clinical, laboratory and imaging features of HCB in order to improve understanding of this condition. An additional statistical exploratory analysis of the available case reports and series was performed to identify possible associations between variables of interest.

Methods

The present systematic review and meta-analysis 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 systematic literature search was performed, independently, by two authors using the Embase, Medline, PubMed, Scopus, Scielo and LILACS databases. The systematic procedure entailed separate searches for publications, carried out using the terms *"Hyperglycemia or Hyperglycaemia or Diabetes or Diabetes Mellitus"* and *"Chorea or Hemi-chorea or Ballism or Hemi-ballism",* followed by a search using a combination of both. The results were filtered to include only articles published between 1984 and 2018 (up to March 15th), and duplicate results were manually excluded. Moreover, the references sections of the retrieved articles were also searched (snowballing methodology) in order to include publications that could have been overlooked in the first search. Figure 1 is a flow diagram showing the number of articles retrieved at each stage of the procedure.

Eligibility criteria

Eligible studies included case reports, case series or epidemiological studies such as case-control and cohort studies, involving patients with HCB. Studies had to describe the demographic, clinical, laboratory and neuroradiological characteristics of reported patients in order to be included in the systematic review. A patient was considered to have HCB if he/she presented with typical clinical features of this condition (unilateral or bilateral irregular, poorly patterned and involuntary movements involving the proximal and/or distal parts of limbs or head), with concomitant hyperglycemia (random glucose testing from peripheral blood); neuroimaging findings were unnecessary for defining the diagnosis.

Cases that presented chorea-ballism simultaneously with comorbidities potentially related to abnormal movements (i.e. cerebral infarction, Huntington's disease, Friedreich's ataxia, neuroacanthocytosis, lupus erythematosus, thyroid disease, AIDS, toxoplasmosis, post-

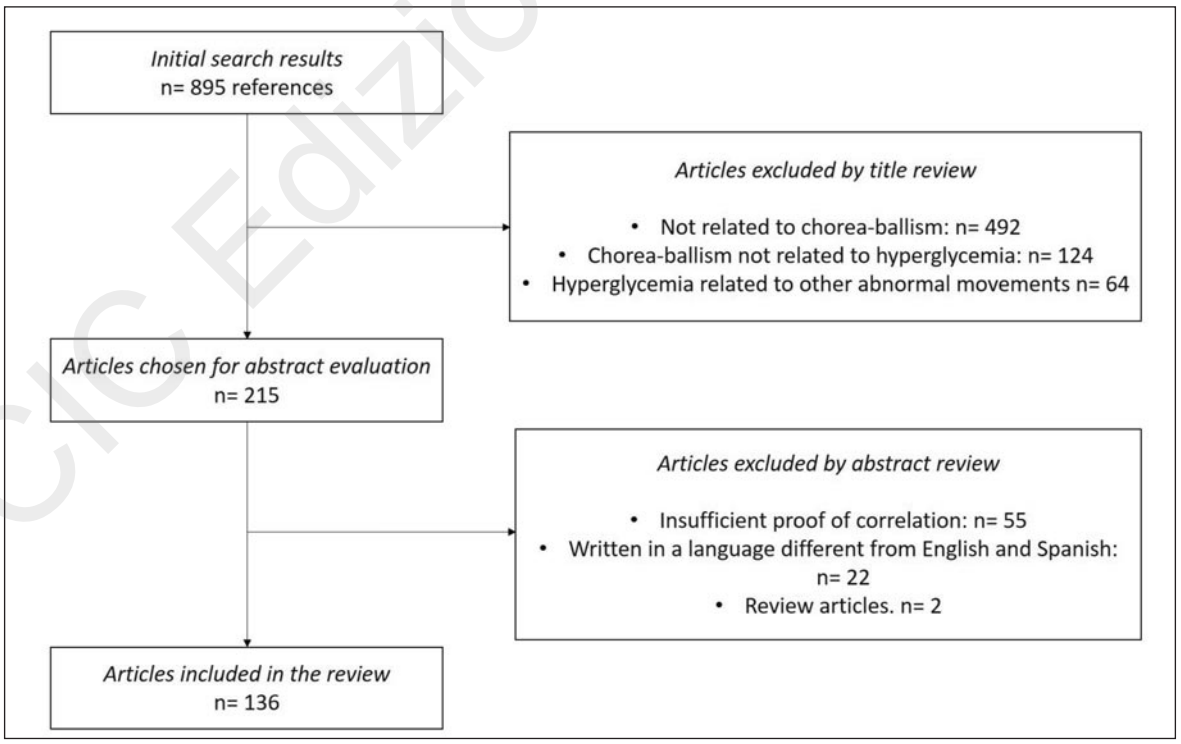

Figure 1 - Flowchart for selection of the studies.

streptococcal autoimmune disorder and/or certain drugs/toxins) and an unclear etiology of the chorea-ballism were excluded.

Study selection and data collection

The study selection procedure started with a review of the titles, excluding manuscripts unrelated to the objective of the study. After this an abstract review was performed, classifying the studies as eligible, unclear or not eligible, according to their fit with the inclusion criteria. The articles marked as eligible or unclear were submitted to full-text review. The two reviewers then compared their results, resolving any differences by consensus with the supervision of a third author.
The database was created in Microsoft Excel 365 (Microsoft Corp., Redmond USA), and it included sociodemographic variables (age, sex and country of origin), laboratory variables (DM history, DM duration, glycemia, serum osmolarity, ketones in urine and ketones in serum), clinical variables (involvement of extremities and clinical laterality of the involvement), imaging variables (type of imaging [CT/MRI], presence of a lesion, density/intensity, location [not specified, caudate nucleus, putamen, globus pallidi, striatum, lentiform nucleus]), use of neuroleptics (haloperidol, tiapride, quetiapine, olanzapine, others) and outcome variables (clinical remission and days to clinical remission).

Statistical methods

Due to the lack of normal distribution, quantitative variables were described with medians and interquartile ranges, while categorical characteristics were analyzed with counts and percentages. To summarize the comprehensive clinical, laboratory and neuroimaging features collected, the sample was divided into NKH and ketotic hyperglycemia (KH) patients. An exploratory analysis based on aggregation of cases (Jackson et al., 2014) was performed using the Mann-Whitney U statistic and Pearson's X^2 or Fisher's exact test according to the frequencies on the contingency tables. Unadjusted odds ratios were estimated based on a logistic regression, with the intention of modeling the presence of KH-associated chorea ballism (K-HCB) and complete clinical recovery. The linktest was applied to assess the determination of the model and significance was defined with p values ≤ 0.050. Furthermore, diagnostic test statistics (sensitivity [Se], specificity [Sp], positive [PPV] and negative predictive [NPV] values) and likelihood ratios (positive [PLR] and negative [NLR]) were calculated for the correspondence between bilateral clinical involvement and neuroimaging findings on both MRI and CT imaging.
Data mining has previously been applied as a meta-analytical method for case report aggregation (Kamel et al., 2017). A priori association rules for the clinical sequence of events with a minimum confidence (conf.) of 0.9 were evaluated. Likewise, inductive classification rules were proposed after analyzing the information gain (Kullback-Leibler divergence) of each attribute within the system and were diagramed on a pruned decision tree (J48graft). For its construction, variables with missing data higher than 30% were excluded. Subsequently, every feature that did not exhibit sufficient information gain to be depicted, and those with conceptual redundancy within the tree, were eliminated. To obtain the most parsimonious representation, the relative entropy of each of the remaining variables was tested, eliminating those with an impact lower than 10% of the initial area under the curve (0.93). Information from patients with complete data for these factors was finally modelled. Clinical improvement was set as the class and testing was performed on the same set that the classifier was trained on; the confidence factor was set at 0.25 by default. Classification statistics and Cohen's Kappa coefficient were calculated as well.
Data were analyzed on Stata v. 14 (Stata Corp., College Station USA) and Weka v. 3.6.9. (University of Waikato, Hamilton New Zealand).

Results

Search results

From the six databases evaluated, 895 potentially relevant publications were identified. After the initial title screening, 215 articles were selected for full-text review. Of these, 85 articles were excluded, leaving 130 suitable papers that met the inclusion criteria. Similarly, six articles were retrieved from manual search of other articles' references. Consequently, 136 case reports/series, the majority published over the last decade, were included in the systematic review (Supplementary material 1). The fact that recent decades and years have seen an increase in the number of publications on this topic might indicate a growing interest in this infrequent syndrome (Figure 2).

Study and patient characteristics

In total, 286 patients were retrieved from the included studies. They had a median age of 72 years (IQR 64-77) and showed a female predominance (n=182, 65%). As regards their origins, the majority of reports referred to Asian populations (175 cases, 61.2%), mainly from Japan (n=44, 25%), Taiwan (n=40, 23%) and China (n=30, 17%).

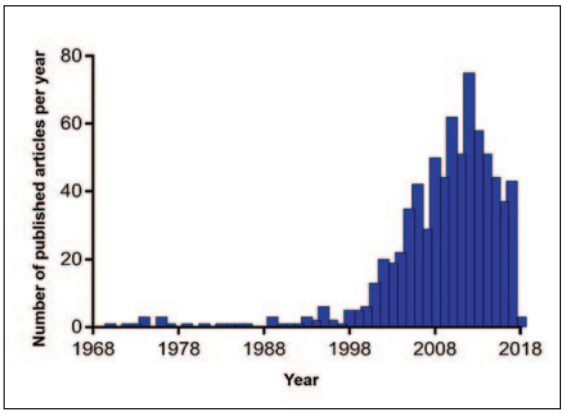

Figure 2 - Bibliometric trend for HCB publications in Scopus (1968-2018)

Diabetes history and chorea characteristics

A previous history of DM was found in 97 patients (34.7%), with a median duration of 36 months (IQR 0-96). Interestingly, 60 patients (21%) exhibited abnormal movements as the initial presenting symptom of their DM. As regards the type of hyperglycemia, only 26 patients (9.1%) presented with ketosis or had a diagnosis of diabetic ketoacidosis. With respect to the clinical manifestations, 193 patients (67.5%) presented with unilateral chorea, while 73 (25.5%) reported bilateral symptoms. Finally, in 7% of the patients there was no information about the specific clinical characteristics.

Laboratory findings

The median level of serum glucose at onset of symptoms was 420 mg/dL (IQR 328-535), while HbA1c levels (reported for 164 patients) showed a median value of 14% (IQR 12-15). Serum osmolarity was less frequently reported (n=123), with a median of 307 mOsm/kg (IQR 300-322).

Neuroimaging findings

Neuroimaging (CT or MRI) at admission was performed in 247 patients. Of these, 194 (78.5%) demonstrated the typical imaging findings of basal ganglia T1 hyperintensity on MRI or hyperdensity on CT. Bilateral basal ganglia lesions were reported in 48 patients (19%). Data from cases with topographical specification (n=189, 76.5%) showed that there main areas involved were the putamen (n=109, 58%) and the caudate nucleus (n=46, 24%), with both structures found to be affected at the same time in 31 cases (16%).

Treatments and outcomes

Regarding the management of the clinical condition, all the patients received insulin treatment for glycemic control; however, only 174 (60.8%) received neuroleptics, with haloperidol (n=129; 74.13%) and tiapride (n=10; 5.74%) being the ones most frequently prescribed.
Finally, a description of the clinical outcome was provided for 251 patients. Just 38 patients exhibited, over a variable follow-up period, an incomplete recovery, which was mainly described as the presence of residual symptoms. On the other hand, 213 patients recovered totally from the disease, with a median time to resolution of symptoms of 14 days (IQR 3-31).

Exploratory analysis

In the initial bivariate analysis, patients with KH showed a lower median age than those with NKH (p=0.003), as well as higher levels of glucose (p=0.025) and HbA1c (p=0.016). Also, a higher rate of negative neuroimaging results (p=0.024) and an increased probability of bilateral anatomical distribution of the lesions on CT/MRI (p=0.013) were reported for the KH patients (Table I).
Un-adjusted odds ratios showed that glycemia (OR 1.002, CI95% 1.000-1.004, p=0.010) and HbA1c levels (OR 1.21, CI95% 1.04-1.40, p=0.016), as well as unspecified (OR 8.21, CI95% 1.72-39.18, p=0.008) and bilateral basal ganglia lesions (OR 3.32, CI95% 1.28-8.55, p=0.013) were associated with K-HCB. On the contrary, age in years (OR 0.95, CI95% 0.93-0.97, p<0.001) and positive neuroimaging findings (OR 0.31, CI95% 0.11-0.86, p=0.024) were more likely in NK-HCB. After multivariate adjustment, only glycemia (p=0.014) and age

Table I - Clinical characteristics of reported patients with HCB according to the type of hyperglycemia.

Variable	Non-ketotic hyperglycemia	Ketotic hyperglycemia (n=260)	p value (n=26)
Age, years (Median and IQR)	72 (65-77)	58 (29-78)	0.003
Female, n. (%)	163 (62.69%)	19 (73.08%)	0.365
Diabetes duration, months (Median and IQR)	42 (0-96)	24 (0-120)	0.997
Asian ethnic origin, n. (%)	160 (61.54%)	15 (57.69%)	0.701
Glycemia, mg/dl (Median and IQR)	420 (320-510)	535 (360-791)	0.009
HbA1C, % (Median and IQR)	13 (12-15)	15 (13-16)	0.016
Osmolarity, mOsm/kg (Median and IQR)	311 (303-320)	316 (295-349.5)	0.55
Unilateral chorea, n. (%)	182 (70%)	11 (42.31%)	0.073
Brain MRI/CT evidence of lesion, n. (%)	200 (76.92%)	20 (76.92%)	0.036
MRI, n. (%)	199 (76.54%)	20 (76.92%)	0.046
Unilateral basal ganglia lesion, n. (%)	161 (61.92%)	11 (42.31%)	0.008
Hyperintensity on T1-weighted MRI, n. (%)	175 (67.31%)	19 (73.08%)	0.318
Basal ganglia non-specific involvement, n. (%)	23 (8.84%)	5 (19.23%)	0.179
Caudate nucleus involvement, n. (%)	42 (16.15%)	4 (15.38%)	0.794
Putamen involvement, n. (%)	102 (39.23%)	10 (38.46%)	0.456
Involvement of globus pallidi, n. (%)	19 (7.31%)	0 (0%)	0.235
Striatal involvement, n. (%)	24 (9.23%)	0 (0%)	0.087
Lentiform involvement, n. (%)	126 (48.46%)	12 (46.15%)	0.303
Neuroleptic use, n. (%)	162 (62.31%)	12 (46.15%)	0.108
Haloperidol, n. (%)	122 (46.92%)	7 (26.92%)	0.051
Non-haloperidol neuroleptics, n. (%)	40 (15.38%)	5 (19.23%)	0.608
Improvement, n. (%)	190 (73.08%)	23 (88.46%)	0.776
Days to symptom remission, (Median and IQR)	14 (4-90)	7 (3-20)	0.112

(p <0.001) remained in the model (pseudo R^2 0.131). Nevertheless, specification of the model was not sufficient (hat p=0.001, hatsq=0.019).
Another aspect analyzed was the laterality of lesions observed on CT/MRI. KH was significantly associated with bilateral involvement on neuroimaging (p=0.008). Serum osmolarity was significantly higher in patients in whom a bilateral lesion was reported (p=0.011) (Table II).
With regard to outcome, it was observed that patients who were reported as showing complete symptomatic recovery had less frequent involvement of the lentiform nucleus on CT/MRI (p=0.002). Additionally, these patients were prescribed neuroleptics in a significantly smaller proportion when compared with those who showed an incomplete recovery (p<0.001), as emerged when analyzing the use of neuroleptics other than haloperidol (Table III).
Multivariate analysis showed lentiform (OR 4.30, CI95% 1.58-11.72, p=0.004) and, specifically, putaminal involvement (OR 3.06, CI95% 1.33-7.05, p=0.008) to be associated with incomplete improvement. The same was found for neuroleptic use (OR 7.45, CI95% 2.22-24.99, p=0.001), mainly, for non-haloperidol medications (OR 2.49, CI95% 1.12-5.53, p=0.026). Lentiform involvement (p=0.005) and prescription of neuroleptics (p=0.002) continued to be significant in the model after the adjustment (pseudo R^2 0.155). Linktest results suggested adequate specification (hat p=0.004, hatsq=0.288).

Laterality of involvement: diagnostic test statistics

In the majority of cases, clinical laterality was correlated with lesion laterality on imaging. Nonetheless, this was not true in every case, as 10 patients with unilateral symptoms (6.4%) showed bilateral lesions on CT/MRI and 25 patients with bilateral chorea-ballism (40%) showed involvement of only one side in the neuroimaging studies (Se 79.2% and Sp 85.5%). Consequently, a clinical finding of unilateral chorea-ballism was highly correlated with a unilateral lesion on CT/MRI (NPV 93.6%), while a finding of bilateral chorea-ballism was supported by bilateral imaging evidence in only 60% of the cases (PPV).
For this study, the probability of exhibiting a bilateral lesion on neuroimaging was 27.87% overall. This probability was increased to 60.25% (PLR 5.44) when the clinical findings were concordant (bilateral symptoms) and decreased to 6.35% when the symptoms were unilateral (NLR 0.24).

Classification tree model

Consistent with the clinical sequence of events, *a priori* association rules were defined after excluding conceptual redundant variables (olanzapine, quetiapine, tiapride prescription, and unspecified, pallidal and putaminal involvement). A positive past medical history of chronic diabetes mellitus (n=164) was associated with a positive neuroimaging finding (conf. 0.92) and the absence of striatal involvement (conf. 0.93). Moreover, the diagnosis of non-ketotic hyperglycemia (n=182) was also associated with this last feature (conf. 0.92). Finally, considering the importance of the clinical outcome, a classification tree was designed using all of the aforementioned variables to create a model for complete versus partial remission of the HCB symptoms (Figure 3). Age was divided into tertiles to optimize its analysis (1st: 0-67 years, 2nd: 68-77 years, 3rd: 78-92 years).
Following the method described, data from 223 patients were considered for the construction of a six-level and 12-leaf decision tree, an area under the curve of 0.878 and 92.27% of instances correctly classified (Cohen's Kappa 0.659). This representation showed that the pre-

Table II - Clinical characteristics of reported patients with HCB according to clinical outcome.

Variable	Complete remission (n=213)	Incomplete remission (n=38)	p value
Ketotic, n (%)	23 (10.8%)	3 (7.89%)	0.588
Age, years (Median and IQR)	72 (63-77)	69 (63-77)	0.825
Female, n. (%)	130 (61.03%)	27 (71.05%)	0.239
Diabetes duration, months (Median and IQR)	42 (0-96)	12 (0-96)	0.896
Asian ethnic origin, n. (%)	124 (58.22%)	23 (60.53%)	0.79
Glycemia, mg/dl (Median and IQR)	420 (332-528)	469 (346-597)	0.235
HbA1C, % (Median and IQR)	14 (13-15)	13.5 (11-15)	0.491
Osmolarity, mOsm/kg (Median and IQR)	318 (303-325)	306 (298-335)	0.813
Unilateral chorea, n. (%)	143 (67.14%)	26 (68.42%)	0.876
Brain MRI/CT evidence of lesion, n. (%)*	164 (76.99%)	27 (71.05%)	0.428
MRI, n. (%)	162 (76.06%)	29 (76.31%)	0.972
Unilateral basal ganglia lesion, n. (%)*	124 (58.22%)	22 (57.89%)	0.971
Hyperintensity on T1-weighted MRI, n. (%)	139 (65.26%)	27 (71.05%)	0.487
Basal ganglia non-specific involvement, n. (%)	22 (10.33%)	0 (0%)	0.038
Caudate nucleus involvement, n. (%)	37 (17.37%)	5 (13.16%)	0.522
Putamen involvement, n. (%)	80 (37.56%)	21 (55.26%)	0.041
Involvement of globus pallidi, n. (%)	12 (5.63%)	4 (10.53%)	0.255
Striatal involvement, n. (%)	14 (6.57%)	1 (2.63%)	0.345
Lentiform involvement, n. (%)	100 (46.95%)	25 (65.79%)	0.032
Neuroleptic use, n. (%)	130 (61.03%)	35 (92.11%)	<0.001
Haloperidol, n. (%)	100 (46.95%)	24 (63.16%)	0.066
Non-haloperidol neuroleptic use, n. (%)	30 (14.08%)	11 (28.95%)	0.022

Table III - Clinical characteristics of reported patients with HCB according to clinical outcome.

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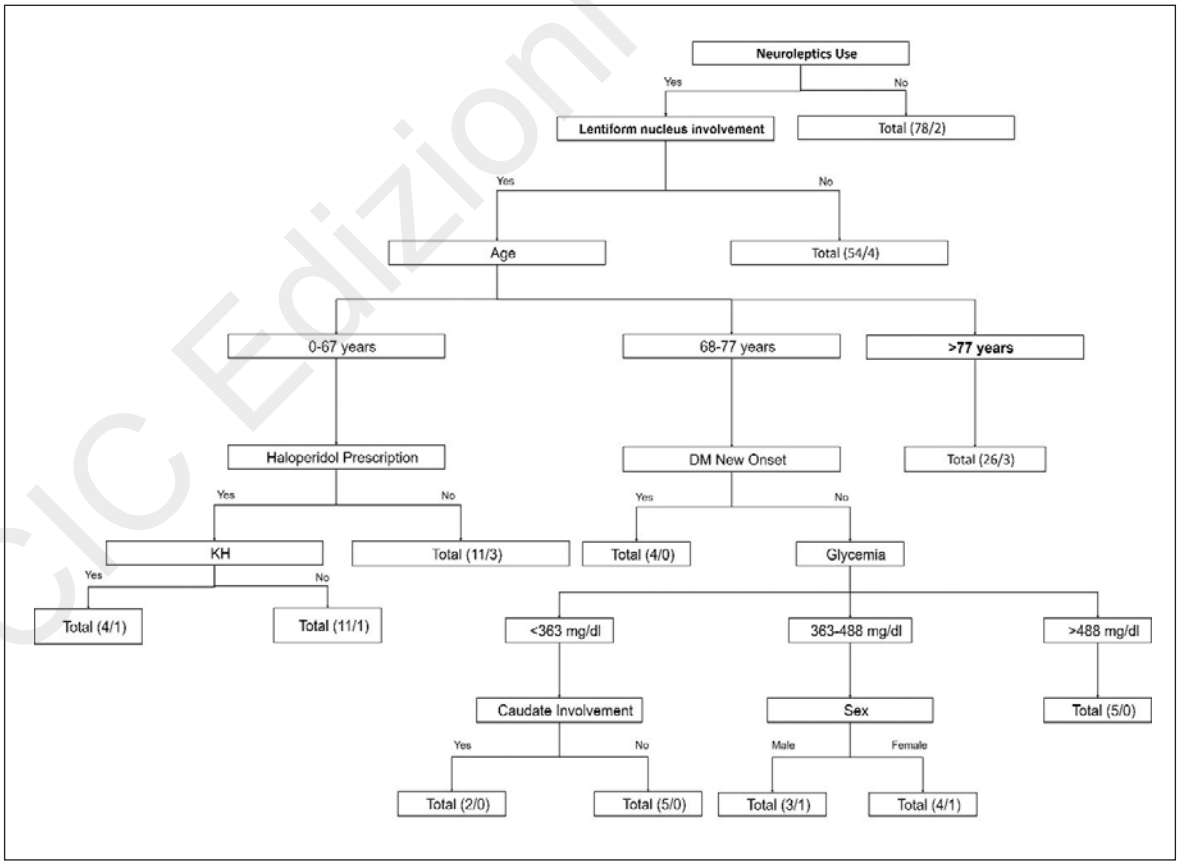

Figure 3 - Classification tree model indicating variables with the highest information gain for the clinical improvement.

scription of neuroleptics and the presence of a lesion in the lentiform nucleus were more likely to occur in patients with an unsatisfactory outcome (partial recovery, non-recovery or death). These findings were coherent with those of the bivariate analysis.
Unfortunately, a convenient clinical assessment of the outcome probability based on the six levels of the tree was not found to be optimal, as the lower leaves offered low improvement of the probability of accurately predicting the outcome, increasing instead the number of steps to be performed when classifying. Hence, we analyzed the top three leaves with the highest number of instances covered (no neuroleptics prescribed, no lentiform nucleus involvement and age within the third tertile: ≥78 years). In the sample assessed, patients who did not require neuroleptics for the control of their HCB symptoms, who were not diagnosed with a lesion in the lentiform nucleus, and whose age was within the third tertile: ≥78 years had an odds ratio of 6.6 (CI95% 1.18-141.10) for a complete clinical recovery. These three conditions were fulfilled in five patients, all of whom had a successful outcome.

Discussion

Several key features of HCB have been described previously in the literature, including its predominance in elderly and female patients, higher frequency in NKH, and good prognosis. However, to our knowledge, specific data regarding differences between patients in relation to types of hyperglycemia, clinical laterality, and prognosis based on clinical presentation have never been analyzed, likely due to the low frequency with which this syndrome is observed. In addition to informing the clinical care of these patients, the results of our systematic review may be useful to elucidate the potential pathophysiological mechanisms of the disease.
As stated previously in the literature, the present study showed that patients with HCB were frequently elderly women, mainly with an Asian ethnic origin and with NKH. Interestingly, we found that in one in every five cases, the HCB was the debut symptom of diabetes mellitus, a finding that may support the need for a higher level of suspicion of this syndrome in the clinical setting, or that may reflect barriers to utilization of preventive care.
Only one recent review has analyzed the clinical data of HCB patients, reporting that KH patients tended to be younger and were more likely to have negative neuroimaging tests than NKH patients – however, this was a small study that included only 15 patients with KH (Chen et al., 2014). We found the same trend in our analysis, which included a much larger number of cases (n= 286 patients). We herein report additional differences between these groups, including higher levels of glucose and Hb1Ac observed in KH patients, highlighting the poorer metabolic control in these cases, and also a predominance of bilateral basal ganglia involvement in this group when compared with the NKH patients, who instead were more likely to show unilateral involvement. Correlated with this finding, cases with bilateral lesions reported a significantly higher serum osmolarity, supporting the potential role of the hyperosmolar state derived from hyperglycemia in disease pathogenesis and severity. Hyperglycemia-related hyperviscosity has been hypothesized to lead to blood-brain barrier dysfunction and an abnormal brain autoregulation process, causing local hypoperfusion. Supporting this mechanism, single-photon emission computed tomography studies have shown decreased perfusion of the striatum in patients with HCB compared with controls, directly impacting regional neuronal metabolism, a situation that could lead to subthalamic nucleus disinhibition as the potential cause of the abnormal movements (Nabatame et al., 1994; Shimomura et al., 1995; Lai et al., 1996; Oh et al., 2002). Also in favor of this metabolic hypothesis, PET studies have shown decreased metabolism in the affected basal ganglia; however, this hypometabolic state has been proven to be a late change, as all the PET studies that have reported this alteration were done after 30 days following symptom onset and the ones that were performed in an earlier period (<10 days) showed no metabolic alterations or even a hypermetabolic state.
These findings suggest that metabolic changes in the basal ganglia may not have particular relevance in the pathogenesis of HCB, but be, rather, a direct result of histological changes related to its development, as hypometabolism in the late HCB stages may reflect cellular ischemia and ensuing gliosis (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). Finally, this hypothesis may explain the typical neuroimaging findings of HCB (Figures 4 and 5), as the ischemia may alter the functioning of GABAergic neurons in the putamen and caudate nucleus, leading to impairment of the indirect neuronal pathway of this region, with preservation of the integrity of the direct pathway, whose neurons are activated because of the

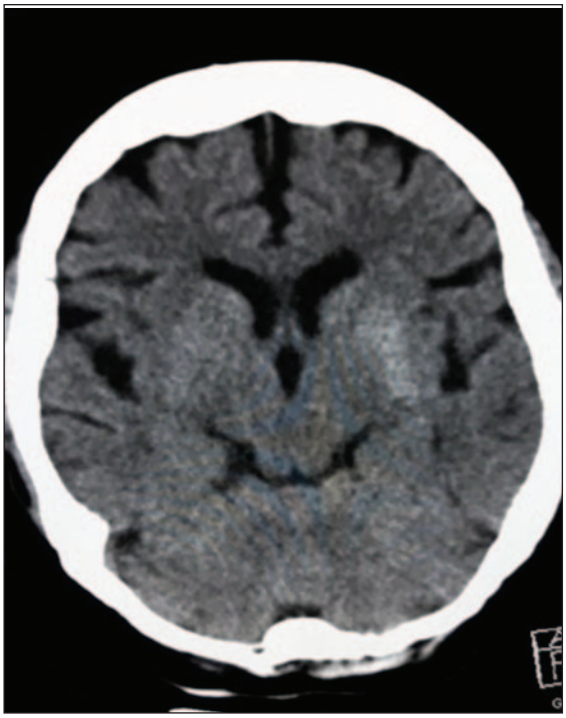

Figure 4 - CT study showing a hyperdense lesion in the left basal ganglia in a patient with NK-HCB.

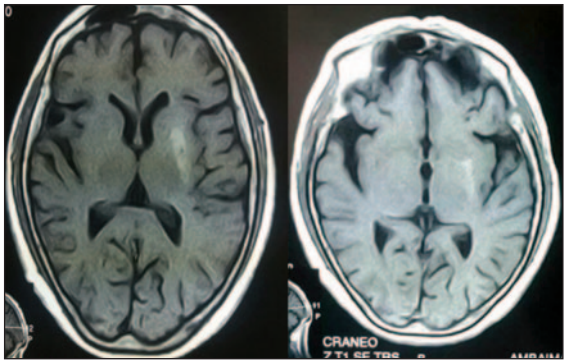

Figure 5 - T1-weighted MRI that shows a hyperintense lesion in the left globus pallidum in a patient with NK-HCB 2 weeks after symptom onset (left) and persistence of the pallidal hyperintense lesion in the same patient at 5 months of follow-up (right).

reduced threshold observed in hyperosmolarity. Shan et al. (1998) proposed that this could cause astrocyte stimulation and the appearance of gemistocytes (swelled reactive astrocytes) and gliosis, explaining the hyperintense lesions observed on MRI and the hypometabolism shown by PET studies (Nath et al., 2006).

Hyperglycemia may also play a role in neurotransmitter physiology, given that, in the presence of high blood glucose levels, a process of anaerobic metabolism develops at the cerebral level with inactivation of the Krebs cycle (tricarboxylic acid). In this situation, the brain begins to metabolize GABA, converting it into succinic acid, however, this will supply only 10 to 40% of the energy needs of the basal ganglia, favoring a process of metabolic acidosis, in which a rapid depletion of acetate occurs. This simultaneous reduction of GABA and acetylcholine at the level of the basal ganglia in conjunction with metabolic acidosis and lack of energy production have been postulated as the main cause of the basal ganglia dysfunction and associated abnormal movements. However, this hypothesis presents a problem, since it is difficult to explain why there are cases in which chorea persists even after appropriate metabolic control. Moreover, patients can develop these abnormal movements in contexts of hypoglycemia or ketotic hypoglycemia, making it difficult to generalize this pathophysiological mechanism, since in the latter context the GABA can be resynthesized (Honda et al., 1998; Boychuk et al., 2015).

As regards the clinical approach to this disease, two main conclusions can be drawn from our analysis, the first of which is related to the laterality of involvement. Only 60% of the patients with bilateral movements showed bilateral imaging involvement on the CT/MRI, suggesting that even if there is only unilateral damage to the neuronal network, this may still cause bilateral symptoms. Second, three variables were identified to be potentially associated with a favorable clinical outcome: patients who did not require neuroleptics, who were not found to have a lesion in the lentiform nucleus, and who were 78 years or older had a significantly higher probability of a complete clinical recovery (OR 6.6 CI95% 1.18-141.10) when compared with those without these characteristics. Therefore, quick and easy assessment of the patient for these features could provide the clinician with additional information for prognostication (an aspect not previously explored in this syndrome). However, a higher number of patients may be necessary in order to create a reliable scoring system, able to predict clinical outcomes more accurately, and this supports the need for continued reporting of HCB cases in the literature (and, ideally, a prospective outcomes study).

The main limitation of our study was the way the patients were included; indeed, literature cases may be described in detail but they can present some significant issues from an analytical perspective, including ethnic differences, different social and cultural characteristics between regions, and missing information. These issues may have affected the analysis and the construction of the classification tree model. Moreover, the small number of patients showing an incomplete clinical recovery could have limited the analysis of the factors related to this outcome. Finally, the use of neuroleptics could be a confounder in the prediction model, as these agents are associated with development of tardive dyskinesia, which could explain why some of these patients had longstanding symptoms (Waln and Jankovic, 2013); moreover, the decision to initiate a neuroleptic may be influenced by the neurologist's expectations about the clinical evolution of the patient, although the need of a neuroleptic may still serve as an indirect marker of a negative clinical evolution. The strengths of this study include its breadth, as the sample included almost all the cases reported in the literature, making this the most comprehensive review available for this neurological syndrome. The inclusion of a large number of cases also permitted exploration of variables not previously described in the literature. Finally, the development of a clinical prediction model increases the applicability of our findings to clinical practice.

In conclusion, chorea/ballism is an important neurological symptom with a wide variety of possible etiologies. Hyperglycemia is associated with a small, but nevertheless important proportion of these cases (given that this condition can be resolved quickly and effectively if diagnosed appropriately). Significant differences in clinical and imaging laterality features were identified between types of hyperglycemia. Furthermore, certain variables (the need of neuroleptic use, lentiform involvement and age) proved to be useful when assessing the prognosis of HCB patients. All of these findings may serve for further research on the underlying pathophysiology of this syndrome.

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Supplementary material

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