PEDiatric Guillain-barré Syndrome in México
Clinical Features Before and During SARS-Cov-2 Pandemic

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Abstract

Introduction: Guillain-Barré Syndrome is the most common cause of acute flaccid paralysis in childhood. It is a post infectious disease immune-mediated with a rapidly progressive course, usually without relapse. The main features are progressive weakness of more than one limb, areflexia or hyporeflexia, which reaches a maximum severity requiring mechanical ventilation.

Objective: We aimed to describe the clinical features of pediatric Guillain-Barré Syndrome in México before and during SARS-CoV-2 pandemic.

Methods: We performed an ambispective, observational, cross-sectional study in a Mexican reference hospital from January 2013 to December 2021. Data were obtained through records: demographic, clinical, laboratories, neurophysiological variants and treatment.

Results: Here we show that amongst 96 patients, 55 were males with average age of 9 years, 72% had history of infection; progressive weakness was present in 97%, areflexia/hyporeflexia in 97%, progress of symptoms in 99%, mean cells of 9/mm3 and mean proteins 88 mg/dL. Admission to Pediatric Intensive Care Unit was 20%. Acute Motor Axonal Neuropathy was the most frequent subtype. Nineteen patients required mechanical ventilation. Immunoglobulin was administered in 88%. Most frequent Disability Score at discharge was bedridden/wheelchair-bound. During 2020-2021 we found two SARS-CoV-2 cases and one associated with BNT162b2 vaccine.

Conclusions: Our results demonstrate that clinical features of pediatric Guillain-Barré Syndrome are similar before and during SARS-CoV-2 pandemic, nevertheless the number of cases associated with SARS-CoV-2 infection did not find increase.

Keywords: Guillain-Barré Syndrome, pediatric, immunoglobulin, SARS-CoV-2, pandemic

Background

During World War I, Guillain, Barré and Stroh reported an acute flaccid paralysis and increased concentration in proteins in the cerebrospinal fluid in two French soldiers, later being described as Guillain-Barré Syndrome (GBS). It is the most common cause of acute flaccid paralysis in childhood. It affects children of all ages, being more frequent in males and varies with seasons. It is a post infectious disease immune-mediated with a rapidly progressive course, usually without relapse. The main features are bilateral weakness, classically described as ascending, beginning in distal lower limbs that worsens progressively over days-to-weeks to potentially life-threatening severity requiring mechanical ventilation, in combination with areflexia or hyporeflexia, which reaches a maximum severity within 4 weeks.

One of the greatest pediatric cohort included 95 children, 53 were males, 77% suffered an infection, GBS was more common in autumn and winter, the main features were progressive weakness and areflexia or hyporeflexia in 100%, 13% required mechanical ventilation, 87 patients were treated with Intravenous Immunoglobulin (IVlg). A retrospective study from northwestern Mexico found 91 patients, 55 were males,
49.8% had history of infection, more common in spring and summer, progressive weakness presented in 100%, 29% required mechanical ventilation, 36 patients received IVIg\(^4\).

The clinical course and prognosis of GBS in children are challenging, especially in children younger than 6-year-old. Some features of GBS are different continent to continent, an example is that Campylobacter jejuni (C. jejuni) is found in 25-50% of adult patients, being most frequently in asian countries and south americans\(^2\).

United States of America, Canada and Australia represent 85-90% of Acute Inflammatory Demyelinating Polyneuropathy (AIDP), meanwhile in China the most common variant is Acute Motor Axonal Neuropathy (AMAN) in 70%\(^2\).

On January 30 2020, World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19), a public health emergency of international concern, being the first two confirmed cases reported in Italy, with travel history to Wuhan, China\(^3\). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) presents with severe respiratory signs and neurological manifestations, one of them being GBS\(^4\).

Ray et al. described a pediatric cohort of neurological or psychiatric features of COVID-19 in United Kingdom, they found 5 patients with GBS associated with SARS-CoV-2, three were males, four with positive PCR test for SARS-CoV-2, one with positive IgG for SARS-CoV-2, one was admitted to Pediatric Intensive Care Unit (PICU), four received IVIg\(^5\).

This study was realized in Hospital General “Dr. Gaudencio González Garza” Centro Médico Nacional La Raza, which provides medical attention to 9,000,000 people with social security in México City, the Valley of México, Hidalgo, Yucatan, Campeche y Quintana Roo\(^8\).

Objective: Given there is few information about pediatric GBS in México, here we present the clinical features of a pediatric GBS population before and during SARS-CoV-2 pandemic.

Methods

We performed an ambispective, observational, cross-sectional study at UMAE Hospital General CMN La Raza “Dr. Gaudencio González Garza\(^a\)” from January 2013 to December 2021. The study had two phases: a retrospective phase, before SARS-CoV-2, in which medical records of patients treated between January 2013 and June 2019 were reviewed, resulting in 82 patients being included in the study. For the second phase, during SARS-CoV-2, information from 14 patients was collected prospectively from July to December 2021.

All patients were evaluated in the Emergency Department by a pediatric neurologist, later admitted to Pediatric Neurology. We included children and adolescents between 1 to 18 years old with discharge diagnosis as GBS from the Department of Pediatric Neurology.

Patients fullfilled Asbury and Cornblath criteria for GBS: features needed, additional symptoms and features that should raise doubt\(^6\). Miller Fisher Syndrome, variant of GBS, was considered as ophthalmoplegia, ataxia and areflexia, serum anti-GBQ1b antibodies were requested in those cases.

Data were recollected according to International Classification of Diseases, Tenth Revision (ICD-10) G61.0: a) Demographic (age, age group, gender, season), b) Clinical (presence of fever, history of bacterial/viral infection, history of immunization, Asbury and Cornblath criteria, GBS Disability Score at admission, mechanical ventilation), c) Laboratorial (cerebrospinal fluid cells and protein count, serum anti-GBQ1b antibodies, history of Polymerase Chain Reaction confirmed SARS-CoV-2 infection), d) Neurophysiological studies (Acute Inflammatory Demyelinating Polyneuropathy, Acute Motor Axonal Neuropathy, Acute Motor Sensory Axonal Neuropathy), e) Therapeutic (Immunoglobulin 2 g/ kg bodyweight, second course of Immunoglobulin) and e) Outcomes variables (GBS Disability Score at discharge, admission to Pediatric Intensive Care Unit, mortality). We excluded illegible and lost records. All data were recorded on a recollection registry.

Descriptive statistics were realized and stablished two groups in base of gender (male and female) and age groups\(^1\) were realized in categories: <2 years (<2y), 2-5y, 6-11y and 12-18y, making contingency tables, categorical variables were expressed as counts and percentages, differences in proportions for the categorical variables were evaluated using \(\chi^2\) test. Continuous variables were expressed by mean, standard deviations, min and max with difference under the assumption of normality using Student’s t test, in order to demonstrate significance statistics with \(p\) values less than 0.05. Comparative analyses were realized for both phases with the same variables. All analyses were realized using STATA 17.0 BE software.
This study was accepted by the Local Committee of Investigation in Health 3502 and Local Committee of Ethics in Investigation 35028 at Hospital General “Dr. Gaudencio González Garza” Centro Médico Nacional La Raza.

**Results**

**Before SARS-CoV-2**

First, we found 57% (55/96) were males, with mean age 8 years (see Table 1). The most frequent age group was 6-11 years with 38% (36/96), 23 males and 13 females (see Figure 1).

Autumn was the most common season of the year. There was history of respiratory/gastrointestinal infection in 72%. Fever was present in 20%. In relation to previous immunization were present in 13% (13/96), six cases related to Influenza vaccine (6-30 days), two cases related to Oral Polio Vaccine (OPV), three related to Diphtheria, Tetanus, Pertussis (DPT), one related to Pentavalent and one case with Pneumococcal vaccines (1-15 days).

Days from onset to diagnosis were 8 (Std. Dev 8.06). The main features of GBS were progressive weakness in 97% (90/96), areflexia/hyporeflexia in 97% (93/96), progression of symptoms in 99% (95/96). Symptoms symmetry 71% (68/96), affection of cranial nerves were reported in 52% (50/96); VII cranial nerve with 41% (40/96). Autonomic dysfunctions were reported in 30% (29/96), respiratory muscles involvement and admission to PICU in 20% (19/96). According to gender and age groups we did not find difference in the number of admissions to PICU.

Second, we showed that lumbar puncture was performed in 90%, with mean cells of 9/mm3 (Std desv.17), as a matter of fact 70% presenting less than 10 cells/mm3, mean proteins 88 mg/dl (Std desv. 67) in cerebrospinal fluid (CSF). Only 6.2% (6/96) had positive culture for C. jejuni. AntiGQ1B antibodies were positive in three patients with clinical suspicion of Miller Fisher Syndrome (MFS). The most common neurophysiological variant of GBS was Acute Motor Axonal Neuropathy (AMAN) (see Table 2), also being the most frequent in Pediatric Intensive Care Unit (PICU).

Third, we found the duration of intravenous immunoglobulin (IVig) treatment was 3.0 days. Length of hospital stay was 14.15 (Std. dev. 16.8) days, p 0.069. Eighty-one percent had rehabilitation. The most frequent GBS Disability Score\textsuperscript{10} at discharge was bedridden or wheelchair-bound (see Table 3).

### Table 1. Demographic and Clinical Features

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total (n=96)</th>
<th>Female (n=41)</th>
<th>Male (n=55)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>N mean</td>
<td>N mean</td>
<td>N mean</td>
<td>0.18*</td>
</tr>
<tr>
<td>Age</td>
<td>96 8.3</td>
<td>41 7.6</td>
<td>55 8.9</td>
<td></td>
</tr>
<tr>
<td>Presence history of viral or bacterial infection</td>
<td>N %</td>
<td>N %</td>
<td>N %</td>
<td>0.83</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progressive weakness</td>
<td>92 96.9</td>
<td>39 95.1</td>
<td>53 96.3</td>
<td>0.39</td>
</tr>
<tr>
<td>Areflexia/hyporeflexia</td>
<td>92 96.9</td>
<td>41 100.0</td>
<td>51 94.5</td>
<td>0.12</td>
</tr>
<tr>
<td>Symptom increase</td>
<td>95 99.0</td>
<td>40 97.6</td>
<td>55 100.0</td>
<td>0.24</td>
</tr>
<tr>
<td>Relative symmetry of symptoms</td>
<td>68 70.8</td>
<td>32 78.1</td>
<td>36 65.5</td>
<td>0.18</td>
</tr>
<tr>
<td>Mild sensory symptoms or signs</td>
<td>22 22.9</td>
<td>9 22.0</td>
<td>13 23.6</td>
<td>0.85</td>
</tr>
<tr>
<td>Facial palsy</td>
<td>39 40.6</td>
<td>18 43.9</td>
<td>21 38.2</td>
<td>0.57</td>
</tr>
<tr>
<td>Autonomic dysfunction</td>
<td>29 30.2</td>
<td>14 34.2</td>
<td>15 27.3</td>
<td>0.47</td>
</tr>
<tr>
<td>Respiratory muscles involvement</td>
<td>19 19.8</td>
<td>10 24.4</td>
<td>9 16.4</td>
<td>0.33</td>
</tr>
<tr>
<td>Admission Pediatric Intensive Care Unit</td>
<td>19 19.8</td>
<td>10 24.4</td>
<td>9 16.4</td>
<td>0.33</td>
</tr>
</tbody>
</table>

\textsuperscript{a} T test for mean difference  
\textsuperscript{b} Chi squared test for proportion difference

![Figure 1. Age groups in years and gender](image)
During SARS-CoV-2
First, two GBS cases associated with SARS-CoV-2 infection were found, both confirmed with positive Polymerase Chain Reaction (PCR) test in nasopharyngeal swab. Days from onset to diagnosis of cases associated with SARS-CoV-2 were 18.5 days.

A 2-year-old female had history of respiratory/gastrointestinal infection 7 days earlier, fever was present; main features were the same as the 2-year-old except for affection of bulbar nerves that required mechanical ventilation, admission to PICU presenting autonomic dysfunctions; albumino-cytologic dissociation was present. GBS Disability Score\textsuperscript{9} at admission and discharge was requiring assisted ventilation for at least part of the day.

In the context of immunization, one case was associated with first dose of BNT162b2 vaccine (Pfizer–BioNTech) in a 17-year-old female within 6 days of administration: she had history of respiratory infection 7 days earlier, no fever was present; the main features were progressive weakness, areflexia/hyporeflexia, progression of symptoms, symmetry, affection of bulbar nerves. She had pneumonia and pleural effusion, autonomic dysfunction with respiratory muscles involvement requiring admission to PICU. Albumino-cytologic dissociation was present. GBS Disability Score\textsuperscript{9} at admission was able to walk 10 m across an open space with help and discharge was requiring assisted ventilation for at least part of the day. No antibodies tests for SARS-CoV-2 were measured. These three cases had AMAN variant.

No differences were found before and during SARS-CoV-2 for age groups, gender, admission to PICU, length of hospital stay.

Table 2. Neurophysiologic Studies

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total (n=96)</th>
<th>Female (n=41)</th>
<th>Male (n=55)</th>
<th>p value \textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Inflammatory Demyelinating Polyneuropathy (AIDP)</td>
<td>4 (4.2)</td>
<td>2</td>
<td>2</td>
<td>0.94</td>
</tr>
<tr>
<td>Acute Motor Axonal Neuropathy (AMAN)</td>
<td>60 (62.5)</td>
<td>26</td>
<td>34</td>
<td>61.8</td>
</tr>
<tr>
<td>Acute Motor Sensory Axonal Neuropathy (AMSAN)</td>
<td>7 (7.3)</td>
<td>2</td>
<td>5</td>
<td>9.1</td>
</tr>
<tr>
<td>Normal</td>
<td>10 (10.4)</td>
<td>4</td>
<td>6</td>
<td>10.9</td>
</tr>
<tr>
<td>Not realized\textsuperscript{b}</td>
<td>15 (15.7)</td>
<td>7</td>
<td>8</td>
<td>14.6</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Chi squared test for proportion difference
\textsuperscript{b} Patients did not present to their studies, some lost social security.

Table 3. Guillain-Barré Syndrome Disability Score

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total (n=96)</th>
<th>Female (n=41)</th>
<th>Male (n=55)</th>
<th>p value \textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disability Score at Admission</td>
<td></td>
<td></td>
<td></td>
<td>0.34</td>
</tr>
<tr>
<td>Able to walk 10m across an open space with help</td>
<td>20</td>
<td>6</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>Bedridden or chair bound</td>
<td>66</td>
<td>28</td>
<td>38</td>
<td>64</td>
</tr>
<tr>
<td>Requiring assisted ventilation for at least part of the day</td>
<td>10</td>
<td>5</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Disability Score at Discharge</td>
<td></td>
<td></td>
<td></td>
<td>0.74</td>
</tr>
<tr>
<td>Able to walk 10m across an open space with help</td>
<td>31</td>
<td>14</td>
<td>17</td>
<td>27</td>
</tr>
<tr>
<td>Bedridden or chair bound</td>
<td>46</td>
<td>16</td>
<td>30</td>
<td>49</td>
</tr>
<tr>
<td>Requiring assisted ventilation for at least part of the day</td>
<td>14</td>
<td>6</td>
<td>8</td>
<td>11</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Chi squared test for proportion difference

Discussion

Before SARS-CoV-2
In our study, 55 patients were males with mean age of 9 years. 72% had history of infection, the main features were progressive weakness present in 97%, areflexia/hyporeflexia in 97%, progression of symptoms in 99%.

GBS was more common in males in our findings, which is consistent with other series\textsuperscript{3,4,12}. Korinthenberg found the mean age was 6.2 years; Nachamkin’s results were like Korinthenberg with mean age of 6.3 years, however our results contrast to those findings, with mean of 8 years\textsuperscript{3,12}.

Durán discovered that spring and winter were the most frequent season of onset, meanwhile we found autumn season, similar findings to those of Korinthenberg which is consistent with higher risk of infections during cold months including respiratory tract or gastrointestinal infections\textsuperscript{3,4,12}.

In GBS 75% of adult patients have history of respiratory or gastrointestinal tract infection for 4 weeks before the onset of
symptoms. In our patients, 73% had history of respiratory or gastrointestinal infection, Korinthenberg had similar findings with 74%; in contrast, Durán reported 49.8%\textsuperscript{3,4}. About half patients with GBS have Campylobacter jejuni infection, which causes at least one-third of infections by molecular mimicry\textsuperscript{2}. We only found 6/96 patients with positive culture for Campylobacter; however not in all patients, stool culture was taken. Nachamkin found 20/121 patients with positive culture\textsuperscript{11}. González reported 13/60 patients positive for Campylobacter\textsuperscript{13}.

Regarding immunization, in our study most cases were related to Influenza vaccine. During 1976, influenza immunization was associated with an increased risk of developing GBS in 6–8 weeks after the administration. In 2020, Grave et al. analyzed all cases of GBS in France through the time of immunization; they did not find evidence of higher risk of GBS within 42 days following seasonal influenza immunization\textsuperscript{14,15}. The rest of our cases were related to OPV, DPT, Pentavalent and Pneumococcal vaccines (1-15 days). Durán reported five patients received previous immunization less than 1 month, related to OPV, BCG; none related to Influenza vaccine\textsuperscript{4}. In 1985, Findland immunized its population with OPV for 5 weeks during an outbreak of wild type poliovirus, the number of GBS cases increased significantly, this was the first time the OPV was associated with GBS. However, Kinnunen suggested that the number of cases started to increase previous to immunization with OPV, this suggested that the increased in cases of GBS might have been associated with the wild type poliovirus\textsuperscript{16}.

Nasiri reported 2.07 days from onset to diagnosis, in contrast with our results that were 5.54 days; this might suggest that patients arrived at the hospital later\textsuperscript{17}.

Korinthenberg found that the main features were progressive weakness and areflexia/hyporeflexia in 100%; Durán discovered that progressive weakness was present in 100%; all these findings were consistent with ours\textsuperscript{3,4}.

GBS is characterized by albumino-cytologic dissociation; Korinthenberg reported it in 80%, with mean cell 4/mm\textsuperscript{3} and mean proteins 89 mg/dL, we found 90% cases had lumbar puncture with mean cells of 9/mm\textsuperscript{3}, mean proteins 88 mg/dL. Durán found 68% had albumino-cytologic dissociation\textsuperscript{3,4}.

Neurophysiological studies can help to support the diagnosis and demonstrate variations in countries, Acute Inflammatory Demyelinating Polyneuropathy (AIDP) is more common in Europe, United States, Canada, and Australia in 85-90%, meanwhile in north China and México Acute Motor Axonal Neuropathy (AMAN) variant is in 70%. AMAN was the most common variant in our study. In 1969, Ramos-Alvarez reported an autopsy study of children with acute lower motor neuron paralysis, in which AMAN was the most frequent subtype\textsuperscript{18}. González found 35 patients had AMAN and 14 AIDP; meanwhile Nasiri reported 31 patients with AIDP and 18 with axonal subtypes\textsuperscript{13,17}.

AntiGQ1B antibodies are present in at least 90% of patients with MFS. We found it positive in three with clinical suspicion of MFS. Durán found sixteen patients presented clinical features of MFS, with greater positivity of antiGQ1B\textsuperscript{4}.

IVIg is currently the cornerstone for GBS treatment. Eighty-eight percent (84/96) of our patients received IVIg, twelve of them required a second course of IVIg and none received plasmapheresis, only one patient presented treatment-related fluctuations. Nasiri treated 53/57 patients with IVIg, seven patients received a second course of IVIg, two of them also received plasmapheresis previous second course of IVIg\textsuperscript{17}.

Durán reported the length of hospital stay was 34.6 days, more days than our study which was 14 days (Std. Dev 16.79)\textsuperscript{4}. GBS Disability Score at discharge was bedridden or wheelchair-bound, consistent with our results\textsuperscript{10}. No mortality was present in our study.

During SARS-CoV-2

COVID-19 and vaccines can trigger GBS by molecular mimicry or nonspecific immune response\textsuperscript{19}. Xu et al reported an increased risk of neurologic disorders in people who presented COVID-19, one of them being Guillain-Barré Syndrome\textsuperscript{20}. The first case of pediatric GBS associated with SARS-CoV-2 infection was from a 15-year-old male from Brazil\textsuperscript{21}. We found two GBS cases associated with confirmed preceding SARS-CoV-2 infection during 2020-2021. Luijten reported 16.6 days from onset to diagnosis in confirmed or probable preceding SARS-CoV-2 infection cases, meanwhile...
we reported 18.5 days\textsuperscript{22}. In our study, the clinical features were consistent with GBS before SARS-CoV-2, except for one case that did not present albumin-cytologic dissociation, one patient required mechanical ventilation and was admitted to PICU. Luijten identified eleven confirmed/probable preceding SARS-CoV-2 infection in GBS adult patients, seven presented autonomic dysfunction, four required mechanical ventilation; Ray reported five patients, one was admitted to PICU; López-Hernandez described seven patients, two of them required mechanical ventilation\textsuperscript{7,22,23}. In our cases associated with SARS-CoV-2 infection, PCR in CSF was not taken. Luijten reported eight cases with AIDP; López-Hernández described two patients with AIDP, one with AMAN and one with AMSAN; Frank found the AMAN variant, which is consistent with our findings. These results show that the neurophysiological variant of GBS associated with SARS-CoV-2 in México is the same as the one in north China, although more research is needed to evaluate correlation between demyelinating or axonal variant with SARS-CoV-2. Luijten administered IVlg in all patients except one that received plasma exchange, Ray administered IVlg in four patients, meanwhile López-Hernández and Frank administered in all patients IVlg like us\textsuperscript{21–23}.

In a Mexican cohort of 3,890, 250 recipients of BNT162b2 vaccine, seven cases were reported with GBS associated with first dose of this vaccine within 30 days of administration, this cohort only reported adult patients; four cases had history of infection, the main features of GBS were progressive weakness, progression of symptoms and areflexia/hyporeflexia, only two patients presented albumino-cytologic dissociation, the most common neurophysiological variant was AIDP, all cases were treated with IVlg, two required mechanical ventilation and one patient died\textsuperscript{24}. Malamud reported a case in a 14-year-old male associated within one month of administration of second dose of BNT162b2; the main clinical features were progressive weakness, progression of symptoms and areflexia, albumino-cytologic dissociation was present, the neurophysiological variant was ADPI, he was also treated with IVlg\textsuperscript{25}. To our knowledge, our study is the first pediatric research associated with SARS-CoV-2 vaccines. We only found one case in a 17-year-old female within 6 days of administration of first dose of this vaccine, presenting similar clinical features including albumino-cytologic dissociation, she had AMAN variant, received IVlg but presented treatment-related fluctuations, requiring a second dose of IVlg, she was admitted to PICU.

In our study, the clinical features before and during SARS-CoV-2 pandemic did not increase, which is consistent with our findings\textsuperscript{22}.

This study has limitations: lumbar puncture was not realized in 10 patients due to the fact the attending physician did not approve it or the patient was hemodynamically unstable. Campylobacter stool culture was not ordered for all patients before the beginning of this study, however, nowadays every patient in whom GBS is suspected, Campylobacter stool culture is requested. Neurophysiologic studies are not available at our hospital, the studies need to be done at other facilities and some patients did not present to their studies, some lost social security. SARS-CoV-2 PCR in cerebrospinal fluid was not available at the beginning of the pandemic at our institution.

Conclusions

The clinical features of pediatric GBS are similar in both periods of time, nevertheless the number of cases associated with SARS-CoV-2 infection did not increase.

Funding

This study received no funding from any commercial, academic or governmental entity.

Declaration of conflict of interest

Authors of the present study have no conflict of interest to disclose.

References


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Manuel Velasco Suárez