Could *Helicobacter pylori* play an important role in axonal type of Guillain-Barré Syndrome pathogenesis?

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**Keywords:** Guillain-Barré Syndrome

**Article info**

Article history:
Received 15 March 2009
Received in revised form 7 November 2009
Accepted 13 November 2009
Available online xxx

**Abstract**

In this case-control study, ELISA and Western blot with whole bacterial protein lysate were performed on serum and cerebrospinal fluid (CSF) of 15 controls and 15 patients. According to Griffin subtypes, 10 of our patients were in acute inflammatory demyelinating polyradiculoneuropathy (AIDP) group, 3 in acute motor axonal neuropathy (AMAN) group, and 2 in acute motor sensory axonal neuropathy (AMSAN) subtype. 86.6% of patients were positive for *Helicobacter pylori* (*H. pylori*) IgG. Serum anti-*H. pylori* IgG of patients and controls were significantly different. CSF anti-*H. pylori* IgG was significantly higher in patients than controls. In patients, the titer of anti-*H. pylori* IgG in serum was significantly higher than CSF, which may indicate extra-neural antibody synthesis. CSF IgG titer was higher in patients having axonal pattern. Western blot was positive in CSF of 13 patients and negative in all controls. There was a correlation between the number of antibody types against *H. pylori* particles and the titer of anti-*H. pylori* IgG in CSF and serum. Also, antibody against cytotoxins associated protein (CagA) was associated with primary axonal pattern.

The association between the presence of anti-CagA and primary axonal pattern, is in favor of the relation between axonal neuropathy and *H. pylori* infection.

1. Introduction

Guillain-Barré Syndrome (GBS), an acute monophasic immune-mediated disease, is the most common cause of generalized acute polyradiculoneuropathy worldwide. In a significant part of the patients, there is an antecedent event such as respiratory and/or gastrointestinal infection, vaccination, or surgery several days to weeks before the onset of neurological symptoms [1]. It is probably an autoimmune disease beginning after a molecular mimicry by an infectious agent [2].

*Helicobacter pylori* (*H. pylori*) is a curved or spiral gram negative microorganism, considered as a new genus, related to *Campylobacter* [3]. 50% of all people in the world are affected by this bacterium [4]. Recent reports propose the role of this agent in different diseases such as stroke [5], autoimmune thrombocytopenia [6], and Alzheimer’s disease [7].

Recently an association is suggested between some *H. pylori* antigens, such as urease B (UB) and heat shock protein (HSP), and axonal type GBS [8]. An association is also proposed between Vacuolating cytotoxin A (Vac A), and two subtypes of GBS, i.e. acute inflammatory demyelinating polyradiculoneuropathy (AIDP) and Miller-Fisher Syndrome (MFS) [9,10]. It seems that *H. pylori* infection is a trigger for a cascade of autoimmune events which finally lead to myelin or axonal damage [11].

In previous studies, some important points could be highlighted: (1) some of them have focused on a specific GBS subtype [10,11]. (2) Antibodies against definite *H. pylori* particles were investigated rather than all possible reactive antigens [9,10]. (3) The relation between anti-*H. pylori* antibodies and different subtypes of the disease is not similar in different studies [8–11].

We designed this case-control study on common GBS subtypes and performed ELISA and Western blot using crude *H. pylori* antigens in serum and cerebrospinal fluid (CSF) of patients and controls. Our purpose was to evaluate the potential association between antibodies against different *H. pylori* particles and electrophysiological subtypes of GBS. We tried to show the relation between disease severity and antibody titer.

**ARTICLE IN PRESS**

**Clinical Neurology and Neurosurgery**

**Contents lists available at ScienceDirect**

**Clinical Neurology and Neurosurgery**

**journal homepage:** www.elsevier.com/locate/clineuro

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2. Method

2.1. Patients

In this case-control study, according to Asbury Cornblath Criteria, 15 patients suffering from GBS (8 male, 7 female, mean age 40.27 ± 4.80) were chosen as the case group [12]. They, electrodiagnostic studies were performed 2–4 weeks after beginning of the disease. These studies included: nerve conduction study of median, ulnar and peroneal motor nerves; median, ulnar and sural sensory nerves; f wave of median, ulnar and tibial nerves; bilateral tibial H reflex and needle electromyography of tenar, tibialis anterior, vastus lateralis and deltoid. The patients were categorized based on Ho et al. criteria [13]. Finally, the patients were grouped to GBS subtypes based on Griffin classification [14].

In order to confirm the diagnosis, lumbar puncture was performed after 2 weeks of the disease onset.

The control group included 15 patients suffering from pseudotumor cerebri in which lumbar puncture (LP) was done as a diagnostic and therapeutic procedure (male: 7, female: 8, mean age: 34.53 ± 2.64).

All these patients represented signs and symptoms of raised intracranial pressure (RICP). Brain MRI and serum and CSF analysis were normal.

Serum and CSF frozen samples were sent to reference laboratory in order to evaluate IgG antibodies against H.pylori and Western blotting to detect antibodies against H. pylori particles in CSF and serum.

All ethical issues were considered. Informed consent was obtained from all subjects. Patients were observed throughout the study period and the severity of illness was determined for all cases on the basis of the case and control status of each sample. The optical density readings obtained in the IgG tests were converted into antibody concentrations with a standard curve that was performed for each run. Results were interpreted according to Wisdom [16].

3. Methods

3.1. ELISA

An indirect enzyme linked immunosorbent assay (ELISA) was performed in this study in order to specific detection of H. pylori IgG antibody in human sera and CSF. ELISA polystyrene microplates coated with bacterial H. pylori antigens were used (Disease, Enzymewell Helicobacter Pylori IgG ELISA kit, Italy).

The serum and CSF samples were thawed to room temperature and mixed. Then 10 μl serum or 100 μl CSF aliquots were diluted 1:100 and 1:20, respectively, in the dilution buffer provided by the manufacturer. All procedures including incubations and washing steps were performed according to instruction manuals provided by the manufacturer (Diesse, Enzymewell Helicobacter Pylori IgG ELISA kit, Italy). All samples were analyzed in duplicate with positive and negative controls and calibrator samples on each ELISA plate. The assay laboratory was blind with respect to the case or control status of each sample.

3.2. SDS-PAGE and Western blotting

Sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE) and immunoblots were run according to standard methods. 5% stacking gel and a 12% separating gel were used for SDS-PAGE. Pellet of bacteria (H. pylori/Campylobacter jejuni/Escherichia coli) was boiled for 3 min in mixed (1:1) with sample preparation buffer [0.125 M Tris–HCl, pH 6.8, 4% (v/v) sodium dodecyl sulfate, 20% (v/v) glycerol, 10% (v/v) mercaptoethanol, 0.2% (w/v) bromophenol blue] before being loaded in the gels. HP/C. jejuni/E. coli lysate supernatants containing 10 g of protein were applied to each lane. Proteins were separated using SDS-PAGE. Samples were loaded on a discontinuous gel (5% stacking gel, 12% resolving gel) and electrophoresed in vertical slab gel electrophoresis unit (Mini-PROTEIN 3 Cell apparatus, Bio-Rad) using Tris-glycine buffer system (0.025 M Tris base, 0.192 M glycine, 0.1% SDS) at 120 V gel for 2 h. Western blotting procedures were performed at room temperature. The proteins were transferred onto a PVDF membranes (0.45-mm pore size) (Roche, Laboratories) by the semidy method (Semi Dry Blottter, Cleaver, UK) at 15 V for 35 min. Membranes were cut into strips and blocked with 3% bovine serum albumin (BSA) in Tris-buffered saline (TBS) (0.02 M Tris base–0.385 M NaCl–0.1%) and washed with Tris-buffered saline containing 0.05% Tween 20 (TTBS). After washings, the membranes were incubated separately with human serum samples diluted 1:100 or CSF samples diluted 1:10 in TTBS–BSA (TBS 0.02% Tween 20 and 3% BSA) at 37°C during 2 h and washed again. Protein G recombinant–proxidase labeled (1:500) (Sigma, Germany) was used in place of secondary antibody for human antibodies. Membranes were incubated with protein G for 1 h at 37 °C, and washed three times with TTBS. The reaction was developed with 0.3 mg α-chloronapthol (Sigma, Germany) in 100 ml of TBS containing 30 μl of 30% H2O2, placing the sheet paper membranes in running tap water for 5 min to stop the reaction.

Table 1
Clinical and laboratory findings of the patients.

<table>
<thead>
<tr>
<th>Number</th>
<th>Age/sex</th>
<th>Clinical syndrome</th>
<th>Serum IgG Au/ml</th>
<th>CSF IgG Au/ml</th>
<th>Antibody against HP particles (kDa)</th>
<th>Western blot profile</th>
<th>Electrodiagnostic type</th>
<th>ICU admission</th>
<th>Severity score</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>M/25</td>
<td>AMSAN</td>
<td>68.47</td>
<td>2.13</td>
<td>31, 36, 38, 47</td>
<td>4</td>
<td>Equivocal</td>
<td>–</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>F/34</td>
<td>AIDP</td>
<td>91.67</td>
<td>2.58</td>
<td>31, 36, 47, 5667, 128</td>
<td>6</td>
<td>Axonal</td>
<td>–</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>M/74</td>
<td>AIDP</td>
<td>32.38</td>
<td>0.43</td>
<td>67</td>
<td>2</td>
<td>Demyelinating</td>
<td>+</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>M/66</td>
<td>AIDP</td>
<td>133.37</td>
<td>2.54</td>
<td>31, 36, 38, 47, 4767, 86, 128</td>
<td>5</td>
<td>Demyelinating</td>
<td>–</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>F/55</td>
<td>AMAN</td>
<td>131.86</td>
<td>2.51</td>
<td>31, 36, 38, 47, 4767, 86, 128</td>
<td>5</td>
<td>Axonal</td>
<td>–</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>M/34</td>
<td>AMAN</td>
<td>133.42</td>
<td>2.52</td>
<td>31, 36, 47, 56, 67, 128</td>
<td>6</td>
<td>Axonal</td>
<td>–</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>M/55</td>
<td>AIDP</td>
<td>81.03</td>
<td>1.34</td>
<td>67, 86</td>
<td>3</td>
<td>Axonal</td>
<td>+</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
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<td>AIDP</td>
<td>3.52</td>
<td>1.22</td>
<td>67, 86</td>
<td>3</td>
<td>Demyelinating</td>
<td>+</td>
<td>4</td>
</tr>
<tr>
<td>9</td>
<td>F/32</td>
<td>AMAN</td>
<td>13.98</td>
<td>0.14</td>
<td>67, 86</td>
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<td>Intractable</td>
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<td>M/32</td>
<td>AIDP</td>
<td>15.21</td>
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<td>–</td>
<td>1</td>
<td>Demyelinating</td>
<td>–</td>
<td>3</td>
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<tr>
<td>12</td>
<td>F/45</td>
<td>AIDP</td>
<td>133.55</td>
<td>0.73</td>
<td>67</td>
<td>2</td>
<td>Demyelinating</td>
<td>+</td>
<td>4</td>
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<tr>
<td>13</td>
<td>M/15</td>
<td>AIDP</td>
<td>87.97</td>
<td>0.37</td>
<td>67, 86</td>
<td>3</td>
<td>Demyelinating</td>
<td>+</td>
<td>4</td>
</tr>
<tr>
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<td>F/30</td>
<td>AIDP</td>
<td>53.33</td>
<td>0.0</td>
<td>–</td>
<td>1</td>
<td>Demyelinating</td>
<td>–</td>
<td>3</td>
</tr>
<tr>
<td>15</td>
<td>F/17</td>
<td>AIDP</td>
<td>95.78</td>
<td>0.0</td>
<td>67, 86</td>
<td>3</td>
<td>Demyelinating</td>
<td>+</td>
<td>4</td>
</tr>
</tbody>
</table>


2. Table 2: Clinical and laboratory findings of the controls.

<table>
<thead>
<tr>
<th>Number</th>
<th>Age/sex</th>
<th>Serum IgG Au/ml</th>
<th>CSF IgG Au/ml</th>
<th>CSF Western blot for HP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F/44</td>
<td>26.03</td>
<td>0.18</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>F/31</td>
<td>40.38</td>
<td>0.00</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>M/54</td>
<td>0.00</td>
<td>0.00</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>F/23</td>
<td>35.67</td>
<td>0.00</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>F/29</td>
<td>0.64</td>
<td>0.00</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>M/21</td>
<td>38.95</td>
<td>0.09</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>F/35</td>
<td>0.00</td>
<td>0.00</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>F/34</td>
<td>0.00</td>
<td>0.00</td>
<td>–</td>
</tr>
<tr>
<td>9</td>
<td>M/42</td>
<td>37.73</td>
<td>0.00</td>
<td>–</td>
</tr>
<tr>
<td>10</td>
<td>F/38</td>
<td>8.97</td>
<td>0.00</td>
<td>–</td>
</tr>
<tr>
<td>11</td>
<td>F/20</td>
<td>23.48</td>
<td>0.00</td>
<td>–</td>
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<tr>
<td>12</td>
<td>M/37</td>
<td>45.35</td>
<td>0.00</td>
<td>–</td>
</tr>
<tr>
<td>13</td>
<td>M/22</td>
<td>25.54</td>
<td>0.04</td>
<td>–</td>
</tr>
<tr>
<td>14</td>
<td>M/42</td>
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</tr>
<tr>
<td>15</td>
<td>M/46</td>
<td>0.00</td>
<td>0.00</td>
<td>–</td>
</tr>
</tbody>
</table>

3. 3. Statistical methods

For statistical analysis, we used SPSS version 15. Statistical tests including independent samples t-test, paired samples t-test, one-way ANOVA test, Pearson correlation coefficient test were used in different parts of our study.

4. Results

(1) Fifteen patients fulfilling Asbury and Corn Bluth diagnostic criteria for GBS were categorized according to Griffin subtypes as: 10 AIDP (female: 5, mean age: 39.3 ± 6.9), 3 acute motor axonal neuropathy (AMAN) (female: 2, mean age: 40.33 ± 7.4), 2 acute motor sensory axonal neuropathy (AMSAN) (male: 2, mean age: 45 ± 10). Based on Ho TW et al. criteria, 9 patients were demyelinative, 4 patients were primary axonal, 1 patient was unexcitable and 1 was equivocal.

The data of patients and controls are summarized in Tables 1 and 2, respectively.

(2) Thirteen out of 15 patients were positive for H. pylori IgG (86.6%), while only 8 out of 15 controls were serologically positive (53.3%). Serum anti-H. pylori IgG titer of patients and controls were significantly different (P < 0.001) based on independent samples t-test (Fig. 1).

CSF anti-H. pylori IgG was detected in 12 patients and 3 controls (80% and 20%, respectively). Furthermore, the difference of CSF anti-H. pylori IgG titer between cases and controls was significant (P < 0.002) based on independent samples t-test (Fig. 2).

CSF IgG titer was higher in patient having axonal pattern in electrodiagnostic studies (P < 0.018) based on one-way ANOVA test (Table 3).

(3) On the other hand, the difference of IgG in serum and CSF was statistically significant both in case and in control groups (P < 0.001), based on paired samples t-test.

(4) In Western blot with total lysate of H. pylori, antibodies against different H. pylori particles ranging from 20 to 120 kDa were detected in the serum of cases and controls, with a similar pattern (Fig. 3).

Western blot was positive in the CSF of 13 patients and negative in all the controls (Fig. 4). In two patients with negative CSF Western blot, H. pylori ELISA was also negative. It is shown in our evaluation that these two patients were affected by demyelinating type of GBS. No cross-reaction was found with E. coli and C. jejuni antibodies in the CSF of patients.

(5) In Western blot analysis, CSF antibodies against H. pylori particles ranging from 31 to 120 kDa were detected including 31 kDa (UreaseA), 47 kDa (Urease H), 56 kDa (Flagellin), 67 kDa (HSP),

Fig. 1. Comparison of anti-Helicobacter pylori IgG titer in the serum of patients and controls.

Fig. 2. Comparison of anti-H. pylori IgG titer in the CSF of patients and controls.

Table 3

<table>
<thead>
<tr>
<th>EDX Statistic</th>
<th>Minimum</th>
<th>Mean ± S.E., n</th>
<th>Maximum</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demyelinative</td>
<td>0.00</td>
<td>0.59 ± 0.28, 9</td>
<td>2.54</td>
<td>2.54</td>
</tr>
<tr>
<td>Primary axonal</td>
<td>1.34</td>
<td>2.24 ± 0.30, 4</td>
<td>2.58</td>
<td>1.24</td>
</tr>
<tr>
<td>Equivocal</td>
<td>2.13</td>
<td>2.13 ± 0.00, 1</td>
<td>2.13</td>
<td>0.00</td>
</tr>
<tr>
<td>In excitable</td>
<td>0.14</td>
<td>0.14 ± 0.00, 1</td>
<td>0.14</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Based on one-way ANOVA test, P = 0.018.
Fig. 3. Pattern of Western blotting assay of CSF or serum antibodies to *H. pylori* (*Hp*), *Campylobacter jejuni* (*Cj*), and *Escherichia coli* (*Ec*). (A) CSF or serum of controls. (B) CSF or serum of patient with Guillain-Barré Syndrome. Right hand figures refer to molecular weight standards (in kilodaltons).

Fig. 4. Western blot of CSF antibodies to *H. pylori*. Lane 1: CSF of controls; lanes 2–6: different patterns for CSF of patients with Guillain-Barré Syndrome, positive for different *H. pylori* particles. M refers to molecular weight Marker (Fermentas, Germany).

86 kDa (VacA), and 120 kDa which corresponds with cytotoxin associated protein (CagA) [17] (Fig. 4). The most common antibodies were against 67 and 86 kDa particles (80% and 53.3%, respectively) (Fig. 5). Antibodies against 36 and 38 kDa particles were also detected in CSF of the patients; however, the nature of them has not been identified.

There was a correlation between the number of antibody types against *H. pylori* particles and the titer of anti-*H. pylori* IgG in CSF and serum (r = 0.91, P < 0.001 and r = 0.6, P = 0.10, respectively).

(6) Antibody against 120 kDa particle (CagA) was associated with primary axonal electrodiagnostic pattern.

(7) There was an association between the presence of antibody against HSP and severity of the disease (P = 0.0439).

5. Discussion

(1) As in the studies in North America and Europe, our study shows that AIDP is the commonest observed subtypes of GBS [11].

(2) In our study, 86.6% of patients were infected by *H. pylori*, which is obviously greater than our controls. The rate of infection in our controls (53.33%) was similar to what some researches report in general population [18].

Fig. 5. Frequency of antibodies against *H. pylori* particles in CSF of patients.
Our results show that serum IgG of patients is significantly higher than controls. Moreover, CSF anti-\textit{H. pylori} IgG is positive in 80% of patients and in 20% of controls. CSF IgG titer was also significantly higher in patients than controls. Such comparison has not been presented in other studies between CSF and serum of patients and controls \cite{8–11}. It can be concluded from our results that anti-\textit{H. pylori} IgG may have an important role in GBS.

3. Significantly higher titer of anti-\textit{H. pylori} IgG in serum compared to CSF may indicate peripheral antibody synthesis and its later passage from damaged blood-nerve barrier into the endoneurial space. In other words, it seems that the sequence of events in GBS is as follows:

(a) A preceding infection may trigger an autoimmune response through molecular mimicry in which the host generates an immune response against an infectious organism that shares epitopes with the host’s peripheral nerves.

(b) As it is mentioned in the criteria of Asbury and Cornblath, albumino-cytologic dissociation is a hallmark in GBS. Since albumin is not synthesized in the CSF, it is concluded that the damage of blood-nerve barrier takes place in this disease.

(c) Damaged and leaky blood-nerve barrier allows the passage of the antibodies into endoneurial space. Consequently, immunological reactions occur between these antibodies and the epitopes of myelin or axon.

This is against Chiba et al. \cite{9} which state that “local immune responses may be easily facilitated in the intra-endoneurial space of the peripheral nervous system”. Our results are in accordance with GBS pathogenesis model proposed by Bosch \cite{1,19}.

4. As it is shown in Table 3, CSF antibody titer is significantly higher in patients and in 20% of controls. CSF IgG titer was also significantly higher in patients than controls. Such comparison has not been presented in other studies between CSF and serum of patients and controls \cite{8–11}. It can be concluded from our results that anti-\textit{H. pylori} IgG may have an important role in GBS.

5. Western blot analysis was carried out using total lysate of \textit{H. pylori} in the serum and CSF of patients and controls. This analysis showed that: (a) serum antibody patterns were relatively similar in controls and patients. (b) CSF was positive in 80% of patients, but all the controls were negative. These results may be a clue for the role of \textit{H. pylori} in GBS and the extra-neural synthesis of antibodies in this syndrome.

6. Our results showed that the more diversity in antibodies against \textit{H. pylori} particles according to Western blot results, the more IgG in serum and CSF. This is a strong evidence for the role of \textit{H. pylori} in GBS pathogenesis.

7. The association between the presence of anti-CagA and primary axonal pattern are in favor of the relation between axonal neuropathy and \textit{H. pylori} infection. It is worthy noting that anti-CagA was not already reported in GBS patients.

8. In our results, the association between the presence of antibody against HSP and severity of the disease is an important finding. This is in accordance with Chiba et al. research \cite{98} which showed a relation between anti-HSP antibody and axonal type GBS \cite{8}.

9. Anti-CagA which is recently found to be related to gastric adenocarcinoma \cite{20} and chronic idiopathic thrombocytopenic purpura \cite{21}, is seen in the CSF of four patients in our study.

6. Future prospect

1. Antibodies against the 36 and 38 kDa particles which are seen in our study are not identified completely. Since low molecular weight \textit{H. pylori} particles are now proposed to have a role in some diseases such as gastric cancer \cite{22} and idiopathic thrombocytopenic purpura \cite{23}, we suggest that they may be studied in future works in GBS. It seems that using whole bacterial protein lysate has advantages such as obtaining these low molecular weight particles.

2. Since the CSF antibodies are more important than serum antibodies in the pathogenesis of GBS, It may be a good idea to inject the CSF of patients (rather than serum) to rat sciatic nerve, in order to investigate the structure and the exact location of antigens in the nerve.

3. We found CagA in the CSF of some GBS patients and showed its association with axonal type. Other studies are still needed to confirm this finding.

Acknowledgement

We would like to thank patients for their collaborations in this study. This study was supported by a research grant from Tehran University of Medical Sciences (Grant N 1678).

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