Elevated levels of IgA and IgG2 in individuals with chronic spinal cord injury

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Objectives: To determine circulating levels of antibodies (IgA, IgM, IgG1-4) in individuals with SCI as compared to uninjured individuals.

Study Design: Prospective, observational study.

Setting: Outpatient clinic of a Department of Physical Medicine and Rehabilitation and research institute in an academic medical center.

Participants: Individuals with chronic (≥ 1 year from injury) SCI and uninjured individuals.

Outcome Measures: Serum antibody titers were determined by commercial multiplex ELISA.

Results: Blood samples were collected from individuals with chronic SCI (N = 29, 83% males) and uninjured individuals (N = 25, 64% males). Among participants with SCI, the distribution of American Spinal Injury Association Impairment Scale (AIS) grades was: A (n = 15), B (n = 2), C (n = 4), D (n = 8). Neurological levels of injury were: cervical (n = 17), thoracic (n = 10), and lumbar (n = 2). IgA levels were significantly elevated in participants with SCI compared to uninjured participants (median: 1.98 vs. 1.21 mg/ml, P < 0.0001), with levels most elevated in individuals with motor complete injuries compared to uninjured participants (P < 0.0003). IgG2 antibodies were also significantly elevated in participants with SCI compared to uninjured participants (median: 5.98 vs. 4.37 mg/ml, P < 0.018).

Conclusions: To our knowledge, this study provides the first evidence of elevated IgA, the antibody type most prevalent at respiratory, genitourinary and gastrointestinal tracts, common sites of infections in individuals with SCI. IgG2 levels were also elevated in individuals with SCI. These data support further investigations of IgA and other antibody types in individuals with chronic SCI, which may be increasingly important in the context of emerging novel infectious diseases such as SARS-CoV-2.

Keywords: Spinal cord injury, Antibodies, Immune Responses, IgA, Immunoglobulins

Introduction

More than 353,000 Americans and millions globally are living with spinal cord injury (SCI).1 Historically, infections, particularly pneumonia,2-4 have been the leading cause of rehospitalization and death for this population. Individuals living with SCI are more than 80 times more likely to die from sepsis4 than those without an SCI. During the first year after injury, infections in individuals with cervical SCI were associated with poor neurological outcomes.5-7

Increasingly, it is appreciated that the autonomic nervous system regulates multiple organ systems, including the immune system.8 Individuals with neurological level of injuries rostral to T5, as sympathetic nervous system (SNS) fibers begin to exit the spinal cord at T1 and innervate the immune system (as well as other) organs, are the most susceptible to infection
and inflammation. This is clinically relevant, given that the most common extent of injury pattern in the US is incomplete tetraplegia. Chronic systemic inflammation, which is present in more than 75% of individuals with chronic SCI, may contribute to immunosuppression and infection risk via induction of immunosuppressive cell types, a concept known more broadly as “inflamm-aging.”

During an infection, antigen presentation cells of the innate immune system activate the adaptive immune response, including the production of antigen-specific antibodies by B cells that differentiate into plasma cells. When bound to pathogens such as viruses or bacteria, antibodies are critical for clearing infections: they can neutralize pathogens by blocking their entry into cells, promote pathogen opsonization and destruction, and activate the complement system, which also promotes opsonization and pathogen clearance. There are five known main classes of immunoglobulins (Ig), IgA, IgD, IgE, IgG, and IgM, which have different antigen binding properties, kinetics, and prevalence in specific tissues or compartments. IgA is most common at mucosal surfaces such as those lining respiratory, genitourinary and gastrointestinal tracts, common sites of infections for individuals with SCI. IgM is typically the most rapidly produced antibody type during an infection and activates the complement system. IgG is typically of higher affinity and the most common antibody type in plasma. IgD is less well understood, but it is part of the B Cell Receptor (BCR) and activates B cells and other immune cell types. IgE is most commonly found attached to mast cells, where it modulates their responses. In healthy conditions, relative levels of antibody types in sera are (greatest-least): IgG1 > IgG2 > IgA > IgM > IgG3 > IgD > IgE.

Preclinical studies have shown the importance of autonomic regulation of immune system homeostasis in uninjured or spinal cord injured animals and clinical studies have shown that the autonomic nervous system (ANS) is dysregulated in humans after SCI. Autonomic dysfunction and the significant risk of infection motivated previous studies of antibody levels in individuals with chronic SCI. Popovitch and colleagues measured elevated serum titers of anti-GM1 gangliosides IgM, but not IgG, in individuals with chronic SCI. Debakan and colleagues reported elevated serum titers of anti-GM1 gangliosides IgM and IgG antibodies in individuals with chronic SCI. In a vaccination study, Lynch et al. determined comparable levels of IgM, IgA and IgG antibodies in persons with chronic SCI and in uninjured persons 14 days after vaccination against gram positive bacteria (S. pneumoniae) with Pneumovax 23. Trautner and colleagues investigated vaccine responses to influenza virus (H1N1) and also found comparable responses in persons with chronic SCI and uninjured persons four weeks after vaccination. Here, our goal was to extend these studies to determine levels of IgA, IgM, IgG1-4 in individuals with chronic SCI compared to uninjured individuals and examine relationships of antibody levels to clinical and demographic features of SCI.

**Methods**

**Participants**

Statement of Ethics: We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during the course of this research. This study (#09-026) was performed with approval by the Northwell Health Institutional Review Board. All participants provided written informed consent prior to study enrollment.

All participants were recruited from 2009–2016 and samples were stored at −80C until analysis; additional immune and health related outcomes were reported for some participants previously. Inclusion criteria for participants with chronic SCI were: ≥18 years old, a history of SCI at any level, an initial injury at least one year prior to enrollment, and an injury severity classified as an American Spinal Injury Association Impairment Scale (AIS) grade of A-D (Table 1).

**Table 1 Clinical and demographic features of participants.**

|                              | Uninjured | Chronic SCI |
|------------------------------|-----------|-------------|
| Participants (N)             | 25        | 29          |
| Males N, %                   | 16, 64%   | 24, 83%     |
| Age, years (Mean ± SEM) Range| 47.6 ± 2.3| 53.9 ± 2.8  |
| Mechanism of injury, N (%)   |           |             |
| MVA                          | 6 (20.7)  |             |
| Fall                         | 9 (31.1)  |             |
| Sports                       | 10 (34.5) |             |
| Violence                     | 3 (10.3)  |             |
| Other                        | 1 (3.5)   |             |
| AIS grade, N (%)             |           |             |
| A                            | 15 (51.7) |             |
| B                            | 2 (6.90)  |             |
| C                            | 4 (13.8)  |             |
| D                            | 8 (27.6)  |             |
| Level of Injury, N (%)       |           |             |
| Cervical                     | 17 (58.6) |             |
| Thoracic                     | 10 (34.5) |             |
| Lumbar                       | 2 (6.9)   |             |
| At or rostral to (≥) T5, N (%)| 21 (72.4) |             |
| At or caudal to (≤) T6, N (%)| 8 (27.5)  |             |
| Years from Injury (Mean ± SEM)| 15.3 ± 2.3|             |
Injury level and severity were determined by the International Standards for the Neurological Classification of Spinal Cord Injury (ISNCSCI) exam, performed by a physiatrist board certified in SCI medicine. The neurological level of injury was used to classify injuries as cervical, thoracic, lumbar, or rostral or caudal to thoracic level 5 (T5). Potential participants were excluded if they had any of the following: active urinary tract infection (UTI) supported by lab data (urinalysis, positive culture) and clinical signs such as hematuria, fever, or incontinence between catheterizations; active respiratory or gastrointestinal infections, pressure ulcers, cancer, chemotherapy, neutropenia, or autoimmune disease.

Uninjured participants were: ≥18 years old, without history of SCI, and within an age range similar to the participants with SCI. Blood samples for participants with chronic SCI were collected in an outpatient clinic of a Department of Physical Medicine and Rehabilitation; blood samples for uninjured participants were collected in an outpatient research clinic of an academic medical center. Clinical data was collected from participants with SCI and their medical charts (Table 1).

**Biochemical analysis**

A multiplex ELISA-based bead assay was used to measure IgA, IgM, IgG1, IgG2, IgG3, IgG4 (Bio-plex Pro Human Isotyping Panel #171-A3100M, 2000 Alfred Nobel Drive, Hercules, CA 94547, USA) using the Bio-Plex 200 plate reader and Bio-Plex Manager software. The assay was performed according to the manufacturer’s recommendations; each plasma sample was diluted 40,000 fold and assayed in duplicate. The working range for each antibody type was defined by the manufacturer (lower–upper, ng/ml): IgA (0.114-2,075.873), IgM (0.682-11,312.463), IgG1 (0.096-1,745.794), IgG2 (2.135-31,003.815), IgG3 (0.055-864.386), IgG4 (0.015-240.630). All participants had detectable levels of antibodies. IgD and IgE, which were not included in this multiplex assay, were not measured.

**Statistical analysis**

Statistical analyses were performed using Prism GraphPad 8 Software for Mac OSX. Descriptive statistics are presented for each group (Tables 1–4). Antibody levels in uninjured and SCI participant groups were compared using the Mann Whitney U test, with significance set to P < 0.05. Secondary analyses with participant subgroups were performed to examine relationships between levels of each antibody type to clinical and demographic features, using the Kruskal Wallis test, with significance set to P < 0.05 (Tables 2–4). Dunn’s multiple comparisons test was performed for comparisons of more than two groups, with significance set to P < 0.05 (Figs. 2–3).

**Results**

We determined levels of antibodies in sera from individuals with chronic SCI (N = 29) and uninjured individuals (N = 25). Demographic and clinical features of participants are shown in Table 1. Most participants in both groups were male and of comparable average age (53.9 vs. 47.6 years old, SCI vs. uninjured respectively, Table 1). Among participants with SCI, mechanisms of injury were: sports (34.5%), falls (31.1%), motor vehicle accidents (20.7%), or violence (10.3%). The distribution of AIS grades was: A (51.7%), B (6.9%), C (13.8) and D (27.6%). Neurological levels of injury were cervical (58.6%) and thoracic (34.5%) and lumbar (6.9%); most participants (72.4%) had injuries rostral to thoracic level 5 (≥T5).

**Participants with chronic SCI have significantly elevated levels of IgA and IgG2**

We measured levels of IgA, IgM and IgG1-4 in sera from participants with chronic SCI and uninjured participants.
Levels of IgA were significantly elevated in participants with chronic SCI compared to uninjured participants (1.98 vs. 1.21 mg/ml, respectively; P < 0.0001, Fig. 1(A), Table 2). IgM levels were not significantly different between the groups (Fig. 1(B), Table 2). For IgG isotypes 1–4 (Fig. 1(C–F)), only IgG2 levels were significantly elevated in participants with chronic SCI compared to uninjured participants (5.981 vs 4.375 mg/ml respectively, P < 0.018, Fig. 1(D), Table 2).

**Relationships of IgA levels to clinical and demographic features of participants**

We next examined relationships between elevated IgA antibodies and specific demographic or clinical features.

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**Table 3** Clinical and demographic features of individuals with chronic SCI with elevated IgA antibodies and uninjured participants.

| AIS Grade | AB | CD | Uninjured |
|-----------|----|----|-----------|
| Median    | 2.070 | 1.700 | 1.207,000 |
| IQR       | 0.730 | 0.822 | 773,000   |
| Min, Max  | 1.240, 3.270 | 1.080, 3.250 | 0.574, 2.176 |

**Neurological level of injury (I)**

| AIS Grade | Cervical | Thoracolumbar | Uninjured |
|-----------|---------|---------------|-----------|
| Median    | 1.832 | 2.098 | 1.207 |
| IQR       | 0.787 | 0.913 | 0.773 |
| Min, Max  | 1.076, 3.252 | 1.243, 3.271 | 0.574, 2.176 |

**Neurological level of injury (II)**

| AIS Grade | ≥ T5 | ≤ T6 | Uninjured |
|-----------|-----|-----|-----------|
| Median    | 1.960 | 2.070 | 1.207 |
| IQR       | 0.860 | 0.895 | 0.773 |
| Min, Max  | 1.080, 3.270 | 1.240, 2.340 | 0.574, 2.176 |

**Time from injury (Years)**

| AIS Grade | <10 | >10 | Uninjured |
|-----------|-----|-----|-----------|
| Median    | 1.790 | 2.100 | 1.207 |
| IQR       | 1.130 | 0.687 | 0.773 |
| Min, Max  | 1.080, 3.250 | 1.240, 3.270 | 0.574, 2.176 |

**Table 4** Clinical and demographic features of individuals with chronic SCI with elevated IgG2 antibodies and uninjured participants.

| AIS Grade | AB | CD | Uninjured |
|-----------|----|----|-----------|
| Median    | 5.440 | 6.360 | 4.375 |
| IQR       | 5.095 | 5.937 | 3.945 |
| Min, Max  | 3.260, 15.300 | 2.670, 16.300 | 1.828, 11.330 |

**Neurological level of injury (I)**

| AIS Grade | Cervical | Thoracolumbar | Uninjured |
|-----------|---------|---------------|-----------|
| Median    | 6.743 | 4.778 | 4.375 |
| IQR       | 5.704 | 4.654 | 3.945 |
| Min, Max  | 2.767, 16.260 | 2.671, 10.720 | 1.828, 11.330 |

**Neurological level of injury (II)**

| AIS Grade | ≥ T5 | ≤ T6 | Uninjured |
|-----------|-----|-----|-----------|
| Median    | 6.140 | 5.050 | 4.375 |
| IQR       | 5.820 | 4.575 | 3.945 |
| Min, Max  | 2.670, 16.300 | 3.260, 9.590 | 9.590, 11.330 |

**Time from injury (Years)**

| AIS Grade | <10 | >10 | Uninjured |
|-----------|-----|-----|-----------|
| Median    | 5.980 | 5.790 | 4.375 |
| IQR       | 5.845 | 4.760 | 3.945 |
| Min, Max  | 2.670, 16.300 | 3.260, 10.900 | 1.828, 11.330 |

**4B: Age of participants**

| Age Group | SCI | Uninjured |
|-----------|-----|-----------|
| Median    | 5.981 | 6.335 |
| IQR       | 3.363 | 6.066 |
| Min, Max  | 2.67, 9.594 | 2.671, 16.260 |

| Age Group | SCI | Uninjured |
|-----------|-----|-----------|
| Median    | 5.981 | 6.335 |
| IQR       | 3.363 | 6.066 |
| Min, Max  | 2.67, 9.594 | 2.671, 16.260 |
of participants with SCI (Table 3). IgA levels were significantly elevated in participants with SCI whose injuries were classified as motor complete (AIS A or B) compared to uninjured participants (Fig. 2(A), P < 0.0003, Table 3(A)). IgA levels were higher in participants with SCI with cervical (Fig. 2(B), P < 0.01) or thoracolumbar (Fig. 2(B), P < 0.01) level injuries than uninjured participants. Since pre-ganglionic sympathetic innervation of immune organs occurs at the level of T5, it was also of interest to observe that compared to uninjured participants, IgA levels were highest in participants with SCI with injuries rostral to T5 compared to uninjured participants (Fig. 2(C), P < 0.0007) but also significantly elevated in individuals with injuries caudal to T6 (Fig. 2(C), P < 0.04). Compared to uninjured participants, IgA was most significantly elevated in participants with SCI who were living with SCI for more than 10 years (Fig. 2(D), P < 0.0004), but was also elevated in participants with SCI who were living with SCI for less than 10 years (Fig. 2(D), P < 0.04). When examining...
Figure 2  Clinical and demographic features of individuals with chronic SCI with elevated IgA antibodies and uninjured participants. Panels A-E compare IgA levels in uninjured participants to those in participants with SCI by: (A) AIS grade, (B) Neurological level of injury: cervical or thoracolumbar, (C) Neurological level of injury: rostral or caudal to T5, (D) Time from initial injury: less or more than 10 years, (E) Age: younger or older than age 50. Bar indicates median levels. Square symbols indicate a sample from a participant with chronic SCI. Round symbols indicate a sample from an uninjured participant. Asterisks indicate significance compared with uninjured controls: NS: Not significant $P$ values were determined by Kruskal-Wallis test followed by Dunn's Multiple Comparison's test.
IgA levels in participant groups older or younger than age 50, participants with SCI who were older than age 50 had significantly higher IgA levels than any other subgroup (Fig. 2(E)).

**Relationships of IgG2 levels to clinical and demographic features of participants**

We next examined relationships of specific clinical and demographic features to IgG2 levels (Table 4). IgG2
levels were not significantly elevated in participants grouped by motor completeness of injury (Fig. 3(A)), by time from injury (Fig. 3(D)) or by age group (Fig. 3(E)). Compared to uninjured participants, IgG2 levels were significantly higher in participants with cervical level injuries (Fig. 3(B), P < 0.02) and were significantly higher in participants with injuries at or rostral to T5 (Fig. 3(C), P < 0.046).

Discussion

The ANS is thought to play an important role in regulating immune system function, in able-bodied populations, and in clinical populations including individuals with SCI.8,9

In the clinical setting, the immunological phenotype of heightened infection risk and persistent inflammation in persons with SCI is likely to result from multiple factors, including anatomical injuries to the central and peripheral nervous systems, nutritional deficiencies, heightened stress, metabolic changes, and reduced mobility.9 Previously, we demonstrated that inflammatory mediators and the beta-2 adrenergic receptor are elevated, while B cell related genes are reduced, in individuals with chronic SCI.17,19,20 We and others showed changes in T cell populations in persons with chronic SCI, including reduced CD3+T cells and expansion of activated CD4+ T regulatory cells.21-24 Others have shown changes in specific antibody populations (IgM or IgG) and an expansion of molecular mediators associated with B cell activation or signs of autoimmunity.13-16,25

Here, we investigated serum titers of IgA, IgM, and IgG1-4 in persons with chronic SCI compared to uninjured persons. We discovered elevated levels of IgA in persons with chronic SCI, which is the antibody class most prevalent at mucosal surfaces of respiratory, genitourinary and gastrointestinal tracts, typical sites of infection for this population. Consistent with ANS disruption in more severe SCI, in the present study, IgA levels were highest in participants with motor complete injuries and in participants with injuries rostral to T5.9 As described earlier, the elderly are considered to have diminished immune function, a concept referred to as “inflamm-aging”.9,10 SCI is often considered to be a condition of accelerated aging.21 Consistent with this concept, in this study, IgA levels were highest in participants with SCI older than age 50. Compared to uninjured participants, IgA levels were highest in individuals who were living with SCI for more than 10 years (P < 0.001).

We also discovered elevated levels of IgG2 in persons with chronic SCI, which also plays a role in neutralizing mucosal-associated pathogens. For example, low IgG2 levels were shown to be an independent prognostic factor for mortality in hospitalized patients with community-acquired pneumonia.26 While we did not take an infection history from participants, individuals with chronic SCI are at increased risk of pneumonia, especially those with cervical, motor complete injuries.

For the past twenty years, the mechanisms by which the ANS regulates immune system function in an intact (non-injured, non-SCI) setting, including antibody production, has been a topic of intense investigation. Starting with a pioneering publication in 2000 describing the cholinergic anti-inflammatory pathway, Tracey and colleagues have demonstrated regulation of innate and adaptive immunity by the vagus nerve, which belongs to the parasympathetic arm of the ANS.8,27 In mice, Tracey and others have shown that vagus nerve innervation of the spleen regulates T and B lymphocyte functions and antibody responses.28-30 IgA, IgM and IgG have all been shown to be regulated by the ANS in intact animals using different experimental paradigms. One of the earliest studies to show this used lipopolysaccharide (LPS), a portion of Gram negative bacterial cell wall used to elicit inflammation in preclinical models, to activate splenic-projecting pre-autonomic neurons in the brain and to activate IgM antibody production in the spleen.28 Activation of the cholinergic anti-inflammatory pathway via nicotine administration or electrical stimulation of the vagus nerve reduced immunization-elicited IgM antibody production by decreasing splenic B cell migration.31

The vagus nerve has also been shown to regulate intestinal immune responses through regulation of the splanchnic nerves.32 In mice, anterior subdiaphragmatic vagotomy led to decreased IgA, but increased IgM levels in intestinal fluid.33 In another study, anterior subdiaphragmatic vagotomy led to decreased IgA in intestinal fluid.34 Vagus nerve stimulation has already been translated into the clinic in the context of chronic inflammatory diseases, as a recent clinical trial showed that it improved rheumatoid arthritis in patients refractory to other therapies.35 The clinical relevance of vagus nerve stimulation in the context of SCI is currently unknown, as many individuals with SCI have complex functional alterations in the ANS.36

Sympathetic innervation has been shown to regulate immune system function has in many mechanistic preclinical studies in uninjured, intact animals. Immune cells are regulated by the neurotransmitter noradrenaline and changes in catecholamines modulate immune cell function, both directly and indirectly.5 In SCI research, sympathetic nervous system regulation of the
immune system has been the topic of intense investigation. Elevated catecholamines promote splenic atrophy, B cell apoptosis and reduced antibody production in mice injured at T3, but not T9.\(^{37,38}\) In mice, this was partly mediated by beta-2 adrenergic receptors.\(^{23,38}\) In a mouse model of SCI, animals injured at thoracic level T3, but not thoracic level T9, had autonomic dysreflexia after SCI accompanied by elevated cortisol and splenic noradrenaline, as well as reduced numbers of total splenic B cells.\(^{23}\) In that study, both marginal zone B cells, which are pre-activated and quickly differentiate into antibody-producing plasma cells, as well follicular B cells, which differentiate into memory B cells, were reduced in animals injured at T3, but not T9. In that study, immunization elicited antibody (IgG1) production in T9, but not in T3 injured mice. Popovich and colleagues later showed that high level SCI in mice induces plasticity of sympathetic innervation of the spleen, which promotes immunosuppression, and restoration of sympathetic innervation boosted B cells and other lymphocyte populations.\(^{39}\) In mice, Schwab and colleagues showed that acutely after SCI, a deleterious sympathetic-adrenal reflex promoted immunosuppression.\(^{40}\) Tom and colleagues showed that T3 injury leads to splenic atrophy, which can be reversed by inhibition of soluble TNF-alpha, an inflammatory cytokine that promotes sympathetic hyperreflexia after SCI.\(^{41,42}\) Inhibition of TNF increased survival of animals injured at T3 who were subsequently infected with in a lethal model of \(S.\) pneumoniae infection, accompanied by reduced bacterial load in the lung.\(^{42}\)

While this was a pilot study with a sample size of convenience, we also explored correlations between antibody levels and specific demographic or clinical features. Preclinical studies have shown that due to reduced innervation of lymphoid organs by ANS and reduced supraspinal control, SCI causes dysregulation of the immune system.\(^{8,9}\) Extensive preclinical studies by the Popovich, Schwab labs and others have demonstrated aberrant B cell activation and/or antibody production in a lesion severity- and level-dependent manner, where intact SNS innervation was critical for adaptive immunity. More recently, Andreansky and colleagues showed that mice with high thoracic level SCI had a reduced ability to mount a primary immune response to a new viral challenge, but retained their memory responses established prior to SCI.\(^{43}\)

**Study limitations**

There were many limitations to this study. First, this was a pilot study with a sample size of convenience, thus we were not powered to determine differences by specific clinical and demographic features examined, including injury severity, neurological injury level, time from injury, or age. Due to the sample size, data here may not be applicable to the general SCI population. Second, the mechanism of injury most common among participants with SCI was sports, which does not mirror the national population, where MVA and falls are most common. Third, while we did determine that participants did not have active infections at study visits, there are many factors that can impact adaptive immunity that we did not control for in either participant group, including body composition or physical activity level.\(^9\) We did not perform studies of antibody function or antigen specificity in this study. We also did not measure levels of noradrenaline or cortisol, both of which have been correlated with changes in adaptive immunity after SCI. This study was restricted to sera and did not examine antibody levels at relevant tissues, such as IgA at mucosal surfaces.

**Conclusions**

Despite these limitations, this study provides novel data on adaptive immunity in individuals with chronic SCI. To our knowledge, this is the first report of elevated IgA in persons with chronic SCI. IgA responses are critical for viral infections and interestingly, *in vitro* experiments showed that serum IgA can promote signs of autoimmunity as well as inflammation, two known signs of immune dysregulation observed in chronic SCI.\(^{44}\) Furthermore, while we do not yet understand the impact of COVID-19 on individuals with chronic SCI, or have a complete understanding of humoral responses to COVID-19 in any population, a recent publication reported high IgA levels were associated with disease severity.\(^{45}\) Additional studies are needed to investigate IgA responses in persons with chronic SCI in response to viral and other antigens.

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