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Reactive arthritis attributable to *Shigella* infection: a clinical and epidemiological nation-wide study

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Key words: reactive arthritis, *Shigella flexneri, Shigella sonnei, Shigella dysenteriae*, population-based study.

Running head: *Shigella* and reactive arthritis
ABSTRACT

Objectives. To study the incidence and clinical picture of Shigella-associated reactive arthritis (ReA) and the arthritogenicity of various Shigella species in the population.

Methods. A questionnaire on enteric and extraintestinal, especially musculoskeletal, symptoms went to 278 consecutive patients with Shigella-positive stool culture and to 597 controls. Analysis of self-reported musculoskeletal symptoms was supplemented with clinical examination of those subjects with recent symptoms.

Results. Of the patients, 14 (7%) had ReA, and a further 4 (2%) other reactive musculoskeletal symptoms (tendinitis, enthesopathy, or bursitis). Of the 14 ReA patients, all adults, 10 had S. sonnei, 3 S. flexneri, and one S. dysenteriae infection. HLA-B27 was positive in 36% of the ReA patients. One control subject had ReA. In the patients with Shigella infection, the odds ratio for developing ReA was 16.2 (95% CI 2.1-123.9), P=0.001.

Conclusions. ReA occurred in 7% of patients following Shigella infection, with an annual incidence of 1.3/1 000 000 in Finland. Besides S. flexneri, also S. sonnei and S. dysenteriae are able to trigger ReA.

INTRODUCTION

The genus Shigella comprises four species: S. dysenteriae, S. flexneri, S. boydii, and S. sonnei. In developing countries in general, the most common serogroups are S. flexneri, S. boydii, and S. dysenteriae, whereas in developed countries, the most common is S. sonnei and the least common S. dysenteriae [1, 2].

In Finland, with a population of 5.2 million, the annual number of bacteriologically verified reported Shigella cases, according to the National Infectious Disease Registry (National Public Health Institute [KTL], Helsinki), has varied in recent years between about 50 and 100. Approximately 90% of these infections are imported. The majority, about 60%, of all Shigella cases have been caused by S. sonnei, followed by S. flexneri, S. boydii, and S. dysenteriae (Statistics of the Laboratory of Enteric Pathogens, KTL).

Extraintestinal complications in patients with Shigella infection include erythema nodosum, conjunctivitis, and reactive arthritis (ReA). ReA is a nonpurulent joint inflammation, which can be triggered by infections in the gut or urogenital tract. Most ReA cases specifying the triggering Shigella species have been due to S. flexneri [3, 4], but S. sonnei has been reported in a few cases [5, 6]. One case report also exists in which the triggering species was S. dysenteriae [7].

In the medical literature in English, the few rheumatological surveys on Shigella outbreaks reveal occurrences of ReA between 1.5% and 4% [4, 8-10], but no large population-based study of the incidence of Shigella-triggered ReA has been performed. The aims of our study were to examine the incidence and clinical picture of ReA and other reactive musculoskeletal symptoms in patients with positive stool culture for Shigella, the arthritogenicity of various Shigella species, and the frequency of such symptoms also in age- and sex-matched controls.
PATIENTS AND METHODS

Study design
Between October 1996 and September 2000, a questionnaire on enteric and extraintestinal symptoms was sent to consecutive subjects with a *Shigella*-positive stool culture. The questionnaire also went to age-, sex-, and municipality-matched controls recruited from the Finnish Population Registry. If no response was obtained from a control within 2 weeks, the questionnaire was sent to another matched control. Altogether, the questionnaire was posted to a total of 278 subjects with *Shigella* infection and to 597 controls. *Shigella* findings were submitted from the local microbiology laboratories to the Laboratory of Enteric Pathogens of KTL, the reference laboratory for the whole of Finland, where all *Shigella* findings are verified. In addition to *Shigella*, all stool specimens were cultured in the local microbiology laboratories also for *Salmonella*, *Campylobacter*, and *Yersinia* species, but, unfortunately, we had no access to these local data. Of the 278 *Shigella*-positive subjects and 597 controls, 211 (76%) and 330 (55%), returned the questionnaire, based on which, 190 matched case-control pairs were formed for comparison of musculoskeletal symptoms between *Shigella*-positive patients and those of controls. The study protocol was approved by the Ethics Committees of the Helsinki University Central Hospital (HUCH) and of the KTL, Helsinki.

*Shigella* strains
Identification of all *Shigella* strains was confirmed by standard methods [11].

Questionnaire
The questionnaire covered the presence, severity, and duration of diarrhoea, the presence of concomitant symptoms of infection such as abdominal pain, fever, eye symptoms, skin and urinary symptoms, painful or swollen joints, limitation of joint movement, pain in tendon insertions, low back or neck pain, time of onset and duration of these symptoms, eventual visits to a physician or admittances to hospital and drug therapy for these symptoms during the preceding 6 months, and previous joint or other musculoskeletal complaints or diagnoses. The questionnaire included a graphic representation of the body on which each subject was asked to mark the swollen or painful joints and tendons. Both the patients and controls received analogous questionnaires. The questionnaire was the same used in our earlier study dealing with ReA attributable to *Campylobacter* in the population [12].

Diagnostic criteria
Information on travel history of a patient came from a form that was accompanied a *Shigella* strain submitted to the Laboratory of Enteric Pathogens. The strain was defined as domestic if it was isolated from a patient with no travel history within the month preceding the sampling or without contact with any person returning from abroad and suffering from shigellosis.

ReA was defined as the development of synovitis (either swelling or limitation of joint movement, and pain) in a previously asymptomatic joint, or as inflammatory low back pain (low back pain worse by night) within the first 2 months after a gastrointestinal infection [12]. In the case of any positive history of chronic rheumatic disease, any “de novo” acute arthritis or acute lumbosacral pain was regarded as evidence of ReA. For synovitis, we accepted either the findings of the clinical examination or the description given in the questionnaire. Each affected joint in fingers and toes was counted individually. Tendinitis, enthesopathy, and bursitis were regarded as reactive if occurring within the first 2 months after the infection. Any other forms of joint or back pain during or after the acute infection were also recorded. The appropriate musculoskeletal diagnosis given to all patients and control subjects was based on information from the questionnaire, completed with data from a clinical examination if performed.
Clinical examination
All subjects reporting recent joint complaints (79 in the Shigella-positive and 81 in the control group) were invited to a clinical examination by study rheumatologists (TH, M L-R) at the Outpatient Department of Medicine, HUCH. The clinical examination was performed on Shigella patients within a median of 13 weeks (range 3-40) after the date of the positive stool specimen, and on controls within a median of 11 weeks (range 3-20) after the return of the questionnaire. A detailed study of affected joints and tendons was an essential part of the clinical examination, which was performed without knowledge of Shigella species. In addition, blood was collected for measurement of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and rheumatoid factor (RF), and for antigen HLA-B27 analysis.

Statistical analysis
Proportional data were compared with the Chi-square test or with Fisher’s exact test. The Mann-Whitney U or Student’s t-tests were applied in comparisons of continuous variables. Analysis of case-control pairs was by paired sample t-test and McNemar’s test. For associations between musculoskeletal diagnoses and exposure (Shigella infection) in these case-control pairs, odds ratios (OR) with confidence intervals (95% CI) were computed. Differences at the 5% level were considered statistically significant. Data were analysed by SPSS statistical software system version 10.05 (SPSS, Inc., Chicago, IL, USA).

As all subjects did not answer all items on the questionnaire, figures in Results are, if necessary, given as proportions of positive answers/number of responders.

RESULTS

Shigella-positive patients
The mean age of the 211 Shigella-positive patients was 37.8 years (range 2-76). Of these, 5% were younger than 16, and 63% were females. As symptoms of Shigella infection, 99.5% (210 of 211) reported diarrhoea, 81% (166 of 204) abdominal pain, and 77% (156 of 203) fever (≥37.5 °C). A total of 90% of the Shigella cases were known to be associated with travelling abroad.

In the 211 Shigella-positive patients, stool culture was positive for S. sonnei in 161 (76%), for S. flexneri in 36 (17%), for S. boydii in 9 (4%), and for S. dysenteriae in 5 (2%) (Figure 1).

Reactive musculoskeletal symptoms
Recent joint or other musculoskeletal symptoms were reported by 39% (79 of 204) of the Shigella-positive patients and by 25% (81 of 325) of the controls (P <0.0001). Of these 79 Shigella-positive patients and of these 81 controls, 35 (44%) and 18 (22%) were clinically examined. Of the 211 patients with Shigella infection, 14 patients (6.6%) fulfilled the criteria for ReA and additional 4 (1.9%) for reactive tendinitis, enthesopathy, or bursitis (=ReTEB). Thus, in total, of the Shigella patients clinically examined, 18 (8.5%), all adults, showed reactive musculoskeletal symptoms. (In addition, one patient described symptoms suggestive of ReA and one other patient of ReTEB on the questionnaire but neither participated in the clinical examination; adding these patients to the calculations would have increased ReA frequency to 7.1% and of all the reactive musculoskeletal symptoms to 9.5%.) Based on clinical examination and/or questionnaire, one subject (0.3%) in the control group (n=330) had symptoms suggestive of acute ReA attributable to urological infection.

Among Shigella-positive patients, those 18 with reactive musculoskeletal symptoms had significantly higher frequencies of ocular symptoms (18% vs. 6%; P = 0.023), but not of urinary
(9% vs. 7; P=0.748) or of skin symptoms (9% vs. 8%; P=1.0) than did patients without reactive symptoms (n=193). No statistically significant differences existed related to gender or to age distribution between these two groups (data not shown), although the former group (mean ± SD; 43.6 ± 13.6 years) tended to be older (37.2 ± 14.1; P = 0.67). Neither did the duration of diarrhoea, fever or abdominal pain differ statistically significantly between these two groups (data not shown).

**Patients with Shigella-triggered ReA**

Among the 14 patients with ReA, the *Shigella* infection was imported in all (Egypt and India, 3 each; Turkey, 2; Kenya, Congo, Thailand, the Philippines, Dominican Republic, and Spain, 1 each). Of these patients, 10 had positive stool culture for *S. sonnei*, three for *S. flexneri*, and one for *S. dysenteriae* (Figure 1). Occurrence of ReA did not differ statistically significantly between the *S. sonnei* (6%), *S. flexneri* (8%), *S. dysenteriae* (20%), and *S. boydii* (0%) groups (P=0.492; Chi-square test).

Four of the ReA patients had only inflammatory low back pain without peripheral arthritis (Table 1). The peripheral arthritis was monoarticular in two, oligoarticular (2 to 4 affected joints) in three, and polyarticular in five patients. The most frequently affected joints were wrists (60%), followed by the distal interphalangeal joints of the hands (40%), metatarsophalangeal joints, metacarpophalangeal joints, and the proximal interphalangeal joints of the hands (30% for each), knees and elbows (20% for each), and ankles (10%). The size of joints affected was large in one and small in six patients; three (30%) had both large and small joints affected. Both upper and lower extremities were affected in four patients (40%); only the upper extremities in five, and only the lower in one. As a pre-existing inflammatory rheumatic disease, two men had ankylosing spondylitis (AS) and one woman seronegative rheumatoid arthritis.

The arthritis in most cases was mild. Eight of the 14 ReA patients (57%) had visited a physician because of arthritis, but only two suffered arthritis severe enough to require hospitalisation. Duration of acute ReA could be determined for the half of patients who had fully recovered from the arthritis by the clinical examination: ≤ 1 month in four patients, 1 to 2 months in one patient, and 2 to 3 months in two. In the rest, ongoing arthritis was still evident at the time of clinical examination; in these patients, the longest duration of acute ReA was 6 months.

**Patients with Shigella-triggered ReTEB**

Among the four patients with ReTEB, the *Shigella* infection was imported in all (one each from the Baltic countries, Nigeria, Thailand, and Dominican Republic). Of these ReTEB patients (Table 1), three had a positive stool culture for *S. sonnei* and one for *S. dysenteriae*. Two ReTEB patients had visited a physician for their musculoskeletal complaints. The duration of acute ReTEB could be determined in one patient; it was 1 to 2 months.

**Laboratory findings for patients with ReA and ReTEB at the clinical examination**

Frequency of HLA-B27 was 36% (five of 14) among ReA patients, including two patients with pre-existing AS. In these ReA patients, the frequency of HLA-B27 was three of 10 (30%) with *S. sonnei*, two of three (67%) with *S. flexneri*, and 0 with *S. dysenteriae* (P=0.331; Chi-square test). None of the patients in the ReTEB group were HLA-B27-positive. In the ReA patients, the presence of the HLA-B27 antigen had no statistically significant effect on duration of ReA or on size of the joints affected (data not shown). All the ReA and ReTEB patients were negative for RF. The mean
± SD ESR and CRP values were 15 ± 14 mm/h and 5 ± 7 mg/L in the ReA subgroup and 9 ± 4 mm/h and 3 ± 2 mg/L in the ReTEB subgroup, respectively.

**Matched 190 patient-control pairs**

Because joint symptoms are frequent in the community, we compared musculoskeletal symptoms in the *Shigella*-positive patients and age-, sex- and municipality-matched controls (Table 2). The mean age of 190 patient-control pairs was 38.0 years (range 2-73). Of these pairs, 3% were under 16 years of age, and 64% were female.

Joint or other musculoskeletal symptoms during the last 6 months were reported by 40% (74 of 184) of patients and by 27% (51 of 184) of control subjects (OR 1.74 [95%CI 1.13-2.68], *P*=0.021).

ReA occurred mainly in the *Shigella* patient group (OR 16.2 [95% CI 2.12-123.93], *P*=0.001); only one control subject had ReA attributable to urological infection. Chronic joint complaints or previous musculoskeletal disease (especially degenerative symptoms or chronic joint pain) were more frequent in the controls than in the *Shigella* group (Table 2).

**DISCUSSION**

This is the first population-based study on the frequency of joint symptoms in patients with a positive stool culture for *Shigella*. Based on calculations at the clinical examination, occurrence of *Shigella*-triggered ReA was 6.6%. This figure is somewhat higher than in outbreak studies with reported occurrences between 1.5% and 4% [4, 8-10]. When we included the other reactive musculoskeletal symptoms (tendinitis, enthesopathy, or bursitis) the total rose to 8.5%. Including questionnaire data with no clinical examination ReA occurrence rose to 7.1%, and with other musculoskeletal symptoms, to 9.5%. In Finland, with about 100 identified *Shigella* infections annually (National Infectious Disease Registry), the actual minimum incidence of reactive musculoskeletal symptoms after shigellosis is 1.6/1 000 000 population per year and of ReA 1.3/1 000 000. Moreover, we could estimate the risk for developing ReA in association with *Shigella* infection; this risk was high (OR = 16.2). Although the corresponding 95% confidence interval was broad, indicating that the study series was epidemiologically small, this association was statistically highly significant.

On the basis of outbreak studies, it has been suggested that, unlike *S. flexneri*, *S. sonnei* is not arthritogenic [4, 13]. This finding has been attributed to a sampling error [14]. Another reason could be that the particular strains causing those epidemics were not arthritogenic. On the other hand, *S. sonnei*-associated ReA has been documented in some case reports [5, 6], with also one case report of ReA in association with *S. dysenteriae* infection [7]. In the present series, the frequency of ReA attributable to *S. sonnei* (6%) and to *S. flexneri* (8%) was of the same magnitude. Moreover, one of the 5 patients with *S. dysenteriae* infection developed ReA. Because we could not obtain the results of stool specimens for other ReA-associated microbes (*Salmonella*, *Campylobacter*, and/or *Yersinia*) in our patients, it can be reasoned that we cannot with certainty exclude the possibility that ReA was co-triggered by some of those microbes. However, none of the *Shigella* patients reported in the questionnaire or at the clinical examination any concurrent intestinal infections. Our findings thus confirm the evidence of previous case reports that *S. sonnei* and *S. dysenteriae* are triggering agents in ReA.
In addition to ReA, four patients had reactive tendinitis or enthesopathy or bursitis (ReTEB). The concept of reactive enthesitis (ReE) was first used by Thomson et al in association with Salmonella-triggered ReA [15]. ReE and ReTEB are analogous concepts of ReA and describe patients with these musculoskeletal manifestations but without synovitis of the peripheral joints. Tendinitis or enthesopathy have been previously reported in association with Shigella-induced ReA [6, 8, 16], but, to our knowledge, not bursitis. In the present series, the ReTEB frequency was about 2%, a result much in line with our previous population-based finding regarding Campylobacter-triggered ReA [12].

The clinical picture of Shigella-triggered ReA was, in half our cases, polyarticular, with frequent arthritis in the small joints of the hands or the feet. This clinical manifestation of ReA has previously been reported in ReA attributable to Shigella [4, 10] and was also noticed in our earlier community-based study of Campylobacter [12].

A longer duration of enteritis has occurred in patients with ReA triggered by Salmonella [17] and by Campylobacter [12] than with uncomplicated patients, while the reverse has occurred in yersinosis [18]. We found no statistically significant difference in duration of diarrhoea in Shigella patients with reactive musculoskeletal complications than in those with an uncomplicated course.

Shigella-triggered ReA in children is infrequent [3, 16, 19]. We observed no child with ReA. Therefore, in agreement with previous studies, ReA seems to be a rare complication of enteritis in children, as observed also in association with Salmonella [20], Yersinia [21], and Campylobacter [12] infections.

In our ReA patients, occurrence of antigen HLA-B27 was 36%, a figure lower than reported in outbreak studies, where HLA-B27 has been positive in 86% (18 of 21) of patients tested [4, 9, 10, 22]. This figure, however, is higher than the frequency of HLA-B27 (14%) in the general Finnish population [23]. In our study, interestingly, the positivity of antigen HLA-B27 was 67% with S. flexneri and 30% with S. sonnei, whereas, in those above-mentioned epidemics, the Shigella species involved was S. flexneri. Our results thus may indicate that the presence of HLA-B27 plays a more important role as a marker of ReA attributable to S. flexneri than to S. sonnei.

The following factors indicate the reliability of our data and the diagnostic accuracy of our study. First, because our material was based on a nation-wide recording of patients with a positive stool culture for Shigella, no selection bias occurred, and confirmation of the triggering infection was certain. Second, we based our diagnosis of ReA on a questionnaire we successfully used previously [12]. Third, our response rate was high. Fourth, our results were based not only on questionnaire data, but patients with reactive musculoskeletal symptoms were also studied clinically. Finally, because joint complaints are frequent in the community, we used age- and sex-matched controls to validate diagnoses of patients with reactive symptoms.

In summary, ReA occurred in about 7% of patients with Shigella infection, with other reactive musculoskeletal symptoms (tendinitis, enthesopathy, bursitis) also observed. In addition to S. flexneri, S. sonnei and S. dysenteriae should be included among the triggering agents of ReA.
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This manuscript has neither been published previously nor is simultaneously submitted elsewhere. No portion of the data has been or will be published in proceedings or transactions of meetings or symposium volumes. The study has been supported by grants, but we have neither applied for nor received any financial support or other benefits from commercial sources. Neither is there any financial interest.

REFERENCES


Table 1. Clinical characteristics of patients with reactive arthritis (ReA) and with reactive tendinitis, enthesopathy, or bursitis (ReTEB)

<table>
<thead>
<tr>
<th></th>
<th>ReA</th>
<th>ReTEB</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>Age, mean (range) years</td>
<td>43.9 (25-73)</td>
<td>42.7 (33-50)</td>
</tr>
<tr>
<td>Gender, male/female</td>
<td>5/9</td>
<td>1/3</td>
</tr>
<tr>
<td>No. (%) of patients with peripheral arthritis</td>
<td>10 (71)</td>
<td>0</td>
</tr>
<tr>
<td>No. (%) of patients with inflammatory low back pain</td>
<td>4 (29)</td>
<td>0</td>
</tr>
<tr>
<td>Onset of musculoskeletal symptoms, days from onset of diarrhoea, median (range)</td>
<td>3 (0-40)</td>
<td>33 (4-44)</td>
</tr>
<tr>
<td>No. (%) of patients with other musculoskeletal symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low back pain</td>
<td>11 (79)</td>
<td>1 (25)</td>
</tr>
<tr>
<td>Neck pain</td>
<td>7 (50)</td>
<td>1 (25)</td>
</tr>
<tr>
<td>Heel pain</td>
<td>3 (21)</td>
<td>1 (25)</td>
</tr>
<tr>
<td>Bursitis</td>
<td>0 (0)</td>
<td>2 † (50)</td>
</tr>
<tr>
<td>Tendinitis</td>
<td>1 † (7)</td>
<td>1 † (25)</td>
</tr>
<tr>
<td>Achilles tendon pain</td>
<td>1 (7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Enthesopathy</td>
<td>1 (7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other</td>
<td>2 § (14)</td>
<td>1 ¶ (25)</td>
</tr>
</tbody>
</table>

* Bursitis of the knee in one and of the trocanter bursitis in the other.
† Tendinitis of the wrist.
‡ Tendinitis of the supraspinatus tendon.
§ Pain in the thoracic spine in one, and pain and swelling of the palm of one hand in the other.
¶ Lateral epicondylitis.
Table 2. Comparison of musculoskeletal diagnoses of the 190 matched case-control pairs based on questionnaire or on clinical examination

<table>
<thead>
<tr>
<th>Musculoskeletal diagnoses</th>
<th>Patients</th>
<th>Control subjects</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute musculoskeletal symptoms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reactive arthritis</td>
<td>15</td>
<td>1</td>
<td>16.2</td>
<td>2.12-123.93</td>
<td>0.001</td>
</tr>
<tr>
<td>Reactive tendinitis, enthesopathy, or bursitis</td>
<td>4</td>
<td>0</td>
<td>†</td>
<td>†</td>
<td>0.125</td>
</tr>
<tr>
<td>Postinfective arthralgia or lumbar pain</td>
<td>23</td>
<td>0</td>
<td>†</td>
<td>†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Arthralgia or lumbar pain during infection</td>
<td>9</td>
<td>3</td>
<td>3.10</td>
<td>0.83-11.63</td>
<td>0.146</td>
</tr>
<tr>
<td>Other acute musculoskeletal symptoms</td>
<td>7</td>
<td>11</td>
<td>0.62</td>
<td>0.24-1.64</td>
<td>0.332</td>
</tr>
<tr>
<td><strong>Chronic/past musculoskeletal diseases</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Degenerative musculoskeletal disease</td>
<td>6</td>
<td>10</td>
<td>0.59</td>
<td>0.21-1.65</td>
<td>0.549</td>
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<tr>
<td>Other chronic symptoms</td>
<td>5</td>
<td>24</td>
<td>0.19</td>
<td>0.07-0.50</td>
<td>0.001</td>
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<tr>
<td><strong>Unclassified</strong></td>
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<td></td>
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</tr>
<tr>
<td><strong>Total number of patients/controls with musculoskeletal symptoms</strong></td>
<td>74</td>
<td>51</td>
<td>1.74</td>
<td>1.13-2.68</td>
<td>0.021</td>
</tr>
</tbody>
</table>

*Data presented as pairs from McNemar’s test. OR = odds ratio; 95% CI = 95% confidence interval. † Non-calculable.

Figure 1. Occurrences of *Shigella* species and reactive arthritis (ReA) among the 211 stool-culture positive *Shigella* patients.
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