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Thank you for your assistance.
The influence of age at onset and duration of illness on long-term outcome in patients with obsessive-compulsive disorder: A report from the International College of Obsessive Compulsive Spectrum Disorders (ICOCS)

Bernardo Dell’Osso, Beatrice Benatti, Massimiliano Buoli, A.Carlo Altamura, Donatella Marazziti, Eric Hollander, Naomi Fineberg, Dan J. Stein, Stefano Pallanti, Humberto Nicolini, Michael Van Ameringen, Christine Lochner, Georgi Hranov, Oguz Karamustafalioglu, Luchezar Hranov, Jose M. Menchon, Joseph Zohar, on behalf of the ICOCS group

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Keywords
Obsessive compulsive disorder (OCD); age at onset; duration of illness; long-term outcome

Abstract
Several studies reported a negative effect of early onset and long duration of illness on long-term outcome in psychiatric disorders, including Obsessive-Compulsive Disorder (OCD). OCD is a...
prevalent, comorbid and disabling condition, associated with reduced quality of life and overall well-being for affected patients and related caregivers. The present multicenter naturalistic study sought to assess the influence of early onset and duration of illness on long-term outcome in a sample of 376 OCD out-patients worldwide, as part of the “International College of Obsessive-Compulsive Spectrum Disorders” (ICOCs) network. Binary logistic regressions were performed with age at the onset and duration of illness, as continuous independent variables, on a series of different outcome dependent variables, including lifetime number of hospitalizations and suicide attempts, poly-therapy and psychiatric comorbidity. Correlations in terms of disability (SDS) were analyzed as well. Results showed that a longer duration of illness (but not earlier age of onset) was associated with hospitalization (odds ratio = 1.03, p = 0.01), earlier age at onset with CBT (odds ratio = 0.94, p < 0.001) and both a later age at onset (odds ratio = 1.05, p = 0.02) and a shorter duration of illness (odds ratio = 0.93, p = 0.02) with panic disorder comorbidity. In addition, earlier age at onset inversely correlated with higher social disability (r = −0.12, p = 0.048) and longer duration of illness directly correlated with higher disability in work, social and family life (r = 0.14, p = 0.017; r = 0.13, p = 0.035; r = 0.14, p = 0.02). The findings from the present large, multicenter study indicate early onset and long duration of illness as overall negative predictors of long-term outcome in OCD.

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1. Introduction

Obsessive compulsive disorder (OCD) is a chronic and disabling disorder (Fineberg et al., 2013), with a lifetime prevalence estimated around 1-2% of the general population (Weissman et al., 1994; Kessler et al., 2005). Chronicity and disability of OCD may depend on specific characteristics of the disorder. Several studies showed that the majority of patients suffering from OCD had a continuous and chronic course of illness (Angst et al., 2004). In addition, the mean age at onset of OCD typically ranges between the 20s and early 30s in epidemiological studies (Pollitt, 1957; Weissman et al., 1994; Angst et al., 2004), with two recent large sample studies showing a mean age at onset of 15 years (De Luca et al., 2011) and an infrequent onset after the age of 30 (Grant et al., 2007). Chronic and continuous course may also be related to only partial/poor response to standard pharmacological treatments, as many as half of OCD patients, treated with first-line medications (e.g., an adequate trial of serotonin reuptake inhibitors [SRIs]), fail to fully respond to treatment and continue to exhibit significant symptoms (Koran et al., 2007). Taken as a whole, early age at onset and poor pharmacological response may result in overall longer duration of illness and chronic course, even though understanding the primum movens among such variables is still object of debate. It is more likely, in fact, that they are in a relationship of continuous reciprocity and implication rather than a hierarchical causal disposition. Indeed, a recent Canadian study assessing the age at onset distributions in a large sample of OCD patients reported a negative correlation between age at onset and duration of illness (De Luca et al., 2011), which, in turn, seems to be consistent with previous studies showing that late-onset OCD subjects had a shorter duration of illness before seeking treatment (Grant et al., 2007).

The aforementioned variables have been investigated in relation to outcome and long-term course. A meta-analytic study on the long-term outcome of child/adolescent-onset OCD, including 22 studies (n = 521) with follow-up periods ranging between 1 and 15.6 years, found that earlier age at onset and increased duration of illness predicted persistence of OCD (Stewart et al., 2004). An association between early onset and higher symptom severity has been reported in previous studies as well (Rosario-Campos et al., 2001; Fontenelle et al., 2003). In addition, higher rates of obsessions of superstition (Millet et al., 2004), repetitive compulsions (Geller et al., 1998), co-occurring tic disorders (Eichstedt and Arnold, 2001), hair pulling (Stewart et al., 2005), poor insight (Ravi Kishore et al., 2004) and multiple anxiety disorders (Geller et al., 2001a, 2001b) have been associated with early onset OCD. Furthermore, a greater familiar contribution (Waltita et al., 2010), a higher incidence of OC personality disorders (Maina et al., 2008) and male gender (Zohar et al., 1997; Fontenelle et al., 2003) have been associated with early onset OCD. Patients with OCD and early onset, moreover, were generally found to respond more poorly to treatment (Erzegovesi et al., 2001), as well as to monotherapy with antiobsessional agents (Rosario-Campos et al., 2001), although other studies have not reported any difference in final treatment outcome among patients with either early and late onset (Fontenelle et al., 2003; Millet et al., 2004). Long duration of illness was found, in turn, to be associated with very early onset OCD (Nakatani et al., in press), non-response to SRIs (Storch et al., 2006) and overall poor outcome (Catapano et al., 2006).

Beyond early onset and duration of illness, duration of untreated illness (DUI) - expressing the latency to first adequate pharmacological treatment - has recently become object of investigation in OCD, given the well-established reluctance, for different reasons, of OCD patients to seek help (Goodwin et al., 2002; Fullana et al., 2009; Altamura et al., 2010). For instance, among other variables, familial OCD was associated with earlier age at onset and longer DUI in a recent study (Viswanath et al., 2011), while another study found a worse treatment response/outcome in patients with a longer latency to pharmacological treatment (Dell’Osso et al., 2010).

In order to further investigate the influence of early onset and duration of illness in relation to outcome and long-term...
course, the present study was conducted on behalf of the International College of Obsessive Compulsive Spectrum Disorders (ICOCS). The ICOCS, which is primarily aimed at advancing, promoting and facilitating research into the causes and consequences of OCD and OC (http://www.icoocs.org/), includes a multisite collaborative network of OCD experts which generated a large database of patients, collecting their main socio-demographic and clinical variables.

2. Experimental procedures

2.1. Sample

The sample included 376 consecutive OCD out-patients of either gender and any age, afferent to different psychiatric departments worldwide participating to the “international college of obsessive-compulsive spectrum disorders” (ICOCS) network. In particular, centers participating to the network database that was analyzed in the present study were: University Hospitals of Milan (Fondazione IRCCS Ca’ Granda) and Florence (Institute of Neuroscience) for Italy, Grupo Medico Carracci of Mexico City for Mexico, Bellvitge University Hospital in Barcelona for Spain, Mount Sinai School of Medicine of New York for USA, Chaim Sheba Medical Center in Israel, University Hospital of Neurology and Psychiatry St. Naum of Sofia for Bulgaria, McMaster University (St Joseph’s Healthcare Hamilton) in Ontario for Canada, Sigi Efsal Teaching and Research Hospital of Istanbul for Turkey and University of Stellenbosch for South Africa.

After obtaining patients’ written informed consent and approval from local Ethics Committee/Institutional Review Board for using patients’ information for research purposes, the main socio-demographic and clinical variables were collected and included in a common web-database. Main socio-demographic features included: age, gender, nationality, marital status, family status, educational status, current profession and income. For the purposes of this experiment, the a-priori clinical variables included: age of OCD onset, smoking status, presence of insight and medical illness, current pharmacological and psychotherapeutic interventions, lifetime history of suicide attempts and hospitalizations (i.e., due to OCD), disability and comorbidity.

2.2. Psychopathological assessment

In order to have their clinical charts reviewed, patients had to be diagnosed as affected by OCD through the administration of the Mini-International Neuropsychiatric Interview (M.I.N.I.; Sheehan et al., 1998), which was used to diagnose psychiatric comorbidity as well. If a comorbid disorder was present, OCD had to be the primary diagnosis, i.e. causing the most distress and dysfunction and providing the primary motivation to seek treatment. Furthermore, psychometric evaluations of OCD and related severity of illness were performed through the Yale-Brown obsessive-compulsive scale (Y-BOCS; Goodman et al., 1989), the dimensional Y-BOCS (Rosario-Campos et al., 2006), the Y-BOCS symptoms checklist (Feinstein et al., 2003), the clinical global impression scale (CGI; Guy, 1976), the Sheehan disability scale (SDS; Sheehan et al., 1996), the compulsive personality assessment scale (CPAS; Fineberg et al., 2007) and the Montgomery and Asberg depression rating scale (MADRS; Montgomery and Asberg, 1979).

2.3. Statistical analyses

Binary logistic regressions were performed considering age at onset and duration of illness as independent continuous variables and the following outcome variables as dependent ones: lifetime history of suicide attempts and hospitalizations, current need of poly-therapy (including cognitive-behavioral therapy [CBT] or other forms of psychotherapy) and presence of psychiatric comorbidity. Furthermore, Pearson’s correlation analysis was performed to assess any relationship between age at onset and duration of illness with disability levels in the area of family, work and social life, as measured through the SDS. The level of significance was set at 0.05 for all the analyses, performed using SPSS 19 for Windows software.

3. Results

The main demographic and clinical variables of the total sample are provided in Table 1. Mean age of OCD onset of the whole sample was 20.6 years (SD = 10.93, median 18) and mean duration of illness was 21.9 years (SD = 12.83, median 19.5). In particular, with respect to possible gender-related differences, no statistically significant difference was found in terms of age at onset (F = 0.41, p = 0.522) and duration of illness (F = 0.63, p = 0.803).

A longer duration of illness was found to be predictive of hospitalization (odds ratio = 1.03, p = 0.01) (Table 2). The goodness-of-fit test results (Holmser and Lemeshow Test: \( \chi^2 = 10.47, df = 8, p = 0.23 \)) showed that the model including age at onset and duration of illness as possible predictors of hospitalization was adequate, allowing for a correct classification of 84.3% of the cases. In addition, the model was overall significant (Omnibus test: \( \chi^2 = 6.25, df = 2, p = 0.04 \)).

Earlier age at onset (odds ratio = 0.94, p < 0.001) was found to be predictive of receiving CBT in combination with pharmacological treatments (Table 2). The goodness-of-fit test results showed that the model including age at onset as a predictor of treatment choice was overall adequate, allowing for a correct classification of 82.1% of the cases. In addition, the model was overall significant (Omnibus test: \( \chi^2 = 6.17, df = 2, p = 0.04 \)).

Table 1 Main socio-demographic and clinical features of the study sample.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total sample (n=376)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>150 (39.9%)</td>
</tr>
<tr>
<td>Females</td>
<td>226 (60.1%)</td>
</tr>
<tr>
<td>Age</td>
<td>42.7 (± 12.8)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>142 (37.7%)</td>
</tr>
<tr>
<td>Married</td>
<td>161 (42.8%)</td>
</tr>
<tr>
<td>Divorced</td>
<td>25 (6.8%)</td>
</tr>
<tr>
<td>Age at onset</td>
<td>20.6 years (± 10.9)</td>
</tr>
<tr>
<td>Duration of illness</td>
<td>21.8 years (± 12.8)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>219 (52.6%)</td>
</tr>
<tr>
<td>Yes</td>
<td>70 (16.8%)</td>
</tr>
<tr>
<td>In the past</td>
<td>87 (20.9%)</td>
</tr>
<tr>
<td>Suicide attempts:</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>305 (81.1%)</td>
</tr>
<tr>
<td>Yes</td>
<td>29 (7.7%)</td>
</tr>
<tr>
<td>Number of suicide attempts</td>
<td>0.2 (± 0.8)</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>282 (75%)</td>
</tr>
<tr>
<td>Yes</td>
<td>54 (14.3%)</td>
</tr>
<tr>
<td>Number of hospitalizations</td>
<td>0.4 (± 0.9)</td>
</tr>
<tr>
<td>Current cognitive behavioral therapy (CBT)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Please cite this article as: Dell’Osso, B., et al., The influence of age at onset and duration of illness on long-term outcome in patients with obsessive-compulsive disorder, European Neuropsychopharmacology (2013), http://dx.doi.org/10.1016/j.euroneuro.2013.05.004
and duration of illness as possible predictors of CBT allowed for a correct classification of 63.2% of the cases. In addition, the model was overall significant (Omnibus test: $\chi^2 = 25.89$, df = 2, $p < 0.001$).

A later age at onset was found to be predictive of PD comorbidity (odds ratio = 1.05, $p = 0.02$) (Table 2). The goodness-of-fit test results (Hosmer and Lemeshow Test: $\chi^2 = 5.27$, df = 8, $p = 0.73$) showed that the model including age at onset as possible predictor of PD comorbidity subsequent to OCD onset was adequate, allowing for a correct classification of 91.2% of the cases. In addition, the model was overall significant (Omnibus test: $\chi^2 = 5.54$, df = 1, $p = 0.02$).

A shorter duration of illness was found to be predictive of PD comorbidity (odds ratio = 0.93, $p = 0.02$) (Table 2). The goodness-of-fit test results (Hosmer and Lemeshow Test: $\chi^2 = 3.46$, df = 8, $p = 0.84$) showed that the model including duration of illness as possible predictor of PD comorbidity subsequent to OCD onset was adequate, allowing for a correct classification of 84.3% of the cases. In addition, the model was overall significant (Omnibus test: $\chi^2 = 6.81$, df = 1, $p = 0.009$).

Finally, the correlation analysis showed an inverse relationship between age at onset and social disability ($r = -0.12$, $p = 0.048$), as well as a direct relationship between duration of illness and disability in all the domains measured through the SDS (family, work and social life: $r = 0.14$, $p = 0.017$; $r = 0.13$, $p = 0.035$ and $r = 0.14$, $p = 0.02$, respectively).

### 4. Discussion

The mean age at onset and duration of illness of the study sample seem to be consistent with literature data (Koran et al., 2007), hence confirming the onset of OCD in the early adulthood (early 20s in the present study), as well as its chronic course (>20 years of duration of illness, on average).

One of the most relevant finding from this study in relation to outcome is the presence of an association between a longer duration of illness and hospitalization. On the other hand, an association between a longer duration of illness and/or an earlier onset of OCD with a lifetime history of suicide attempts was not found. Both results may be interpreted in the light of previous studies dealing with hospitalized patients (Angst et al., 2004). These authors reported that hospitalized OCD patients had a clearly worse outcome, with chronicity, but, over the years, the disorder tended to gradually wane (Ingram, 1961; Lo, 1967). According to Berrios and Chiu follow-up study, over 11 years, symptoms usually persisted but became less impairing (Berrios and Chiu, 1989). The longest 47-year follow-up study of hospitalized patients convincingly demonstrated an improvement in 83% of cases, comprising 20% of complete recovery, 28% of recovery with clinical symptoms and 35% of improvement with symptoms. Only 9% were found to be unchanged and 8% worse (Skog and Skoog, 1999). A more recent naturalistic follow-up study of OCD subjects, who had not responded to at least 2 adequate trials of SRIs, reported significant full and partial remission rates (39% and 11%, respectively), after 4.5 years, suggesting that a substantial proportion of patients with proven SRI non-response may subsequently improve over the long-term, possibly because of continued efforts to treat them (Reddy et al., 2010). On this basis, it could be argued that suicide risk in OCD might be more related to specific symptom dimensions, such as aggressive obsessions, sexual/religious and symmetry/ordering subtypes (Alonso et al., 2010; Torres et al., 2011), as well as specific patterns of comorbidity, such as impulse control disorders, bipolar disorder and major depressive disorder comorbidity (Alonso et al., 2010; Torres et al., 2011), than to a longer duration of illness. Taken as a whole, present findings would suggest that OCD patients with a long duration of illness are at high risk of hospitalization, but not suicide. Nevertheless, suicidality was exclusively measured on the basis of lifetime suicide attempts and it is possible that early phase suicidal ideation might follow a different trajectory.

Another significant finding from the present study was related to patients’ current therapeutic regimen in relation to early onset. In particular, it was found that an earlier age at onset predicted subsequent treatment implementation with CBT. Unfortunately, it was not possible to assess other forms of augmentation - pharmacological treatment, in particular - given that such variable was lacking in the database for the majority of the sample (87.7%). With

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**Table 2** Summary of the statistics for the best-fit logistic regression models applied: 1. hospitalization, 2. current CBT, 3a. PD comorbidity (age at onset), 3b. PD comorbidity (duration of illness).

<table>
<thead>
<tr>
<th>Dependent dichotomic variables</th>
<th>Independent continuous variables</th>
<th>B</th>
<th>S.E.</th>
<th>Wald</th>
<th>df</th>
<th>P</th>
<th>Exp (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hospitalization</td>
<td>Age at onset</td>
<td>0.012</td>
<td>0.016</td>
<td>0.55</td>
<td>1</td>
<td>0.46</td>
<td>1.01</td>
</tr>
<tr>
<td></td>
<td>Duration of illness</td>
<td>0.032</td>
<td>0.01</td>
<td>6.29</td>
<td>1</td>
<td>0.01</td>
<td>1.03</td>
</tr>
<tr>
<td>2. Current CBT treatment</td>
<td>Age at onset</td>
<td>0.64</td>
<td>0.016</td>
<td>16.36</td>
<td>1</td>
<td>&lt;0.001</td>
<td>0.94</td>
</tr>
<tr>
<td></td>
<td>Age at onset</td>
<td>0.05</td>
<td>0.02</td>
<td>5.37</td>
<td>1</td>
<td>0.02</td>
<td>1.05</td>
</tr>
<tr>
<td>3a. PD comorbidity</td>
<td>Age at onset</td>
<td>0.05</td>
<td>0.02</td>
<td>5.37</td>
<td>1</td>
<td>0.02</td>
<td>1.05</td>
</tr>
<tr>
<td>3b. PD comorbidity</td>
<td>Duration of illness</td>
<td>−0.07</td>
<td>0.03</td>
<td>3.53</td>
<td>1</td>
<td>0.02</td>
<td>0.93</td>
</tr>
</tbody>
</table>

Legenda: B = coefficient; S.E. = standard error of B; Wald = Wald statistics; df = degree of freedom; p = significance; Exp (B) = odds ratio.
Influence of age at onset and duration of illness on long-term outcome in patients with obsessive-compulsive disorder

In the context of cognitive behavioral therapy (CBT), along with selective serotonin reuptake inhibitors (SSRIs), such form of psychotherapy is considered the first-line treatment option for patients with obsessive-compulsive disorder (OCD) according to major treatment guidelines (Koran et al., 2007). Previous studies have, in fact, widely documented the efficacy of different cognitive and/or behavioral treatments in OCD. The results of previous behavioral studies have, for instance, supported the efficacy of exposure in vivo and response prevention in the treatment of chronic ritualizers (Rasmussen and Tsuang, 1984). More recently, a study by the Cochrane group confirmed that patients receiving any variant of CBT exhibited significantly fewer symptoms post-treatment than those receiving treatment as usual (Gava et al., 2007). In the attempt to establish a correlation between early onset OCD and subsequent need of CBT, it is worth mentioning a previous study reporting that only 31% of the patients with early onset OCD responded to mono-therapy with an antiobsessional agent (Rosario-Campos et al., 2001). In addition, it has already been reported that chronic OCD patients usually need additional therapeutic support, after effective inpatient treatment, to maintain their improvements over long periods (Rufer et al., 2005). On the other hand, there was recently reported that not having received CBT, along with a later age at onset and other variables, predicted poor outcome in OCD patients (Reddy et al., 2010). On the basis of the aforementioned studies, it may be argued that early onset patients with long-lasting history of OCD - like most of those examined in the present study - might be less responsive to sole medications and would particularly benefit from CBT augmentation.

Another result deserving further appreciation is represented by the association between PD comorbidity and shorter duration of illness/later age at onset. This specific result seems to be consistent with a previous study of Goodin and coworkers, who reported that comorbid PD in OCD was associated with previous use of mental health treatment and increased readiness to seek treatment (Goodwin et al., 2002). Previously, it was found that women with late onset OCD had higher rates of associated panic attacks, after the onset of OCD (Lensi et al., 1996). A possible connection amongst a later onset of OCD, a shorter duration of illness and comorbidity with PD is also supported on the basis of recent studies in the field of DU in anxiety disorders, pointing out a shorter latency to treatment in subjects with PD versus other anxiety disorders (Altamura et al., 2010). In this perspective, it may be argued that the presence of panic attacks and PD might reduce the overall duration of illness by decreasing the latency for seeking help and receiving effective treatment.

It is worthwhile to note that other types of comorbidity, in particular with Tic/Tourette’s disorders, did not show any specific association with early onset and/or long duration of illness in the present study. Gender differences in this regard were not found either. The lack of a specific association between early onset OCD and comorbid Tic/Tourette’s disorders may be in contrast with some literature data (Eichsted and Arnold, 2001), even though certain studies reported that only specific symptom dimensions (i.e., the presence of symmetry/hoarding) were significantly related to a lifetime history of Tourette’s syndrome or chronic tic disorder (Baer, 1994).

The last relevant finding of the present study is represented by the correlation between age at onset and duration of illness with disability levels. In particular, both shorter age at onset and longer duration of illness correlated with higher disability levels: in terms of social life for early age at onset and across all domains of disability (social, work and family) for long duration of illness. Such correlations ultimately provide further support to the hypothesis that patients with early onset and long duration of illness tend to present greater functional impairment. Nevertheless, it needs to be taken into account that the strength of the observed correlations was overall weak, allowing to hypothesize that such patients, in spite of showing a significant functional impairment caused by the illness, could nevertheless develop sufficient adaptability.

In the interpretation of study results, the following methodological limitations need to be taken into account. The present study benefited from including a significant number of patients from widely different countries, mitigating possible selection biases, cultural and clinical attitudes toward treatments (e.g., possibility to offer psychotherapy), service organization and assessment. Nevertheless, the retrospective assessment of variables such as age at onset implied the need to trust the reliability of the patient or of other available information sources and information, in such regard, may have been not always precise. Besides, it needs to be taken into account that centers participating to the ICOCS initiative and database, have well-established expertise in the field of diagnosis and treatment of OCD and it may be that patients attending such services do not necessarily reflect the standard of care usually observed elsewhere. Reported data, moreover, may only apply to patients seeking treatment, and such population may not adequately represent the entire population of OCD patients. In addition, it should be taken into account that large naturalistic studies, like the present one, investigating the prognostic role of some variables over the outcome and clinical course of psychiatric disorders, often report multiple associations with potential confounders, making it hard to establish what comes first. Furthermore, it has been previously stressed by some authors that specific clinical associations, in relation to age at onset, might be indeed related to a chronic age per se (Geller et al., 2001a, 2001b). Finally, the present study just focussed on the analysis of few specific variables in relation to outcome, without considering other clinically relevant parameters (e.g., 121 familiarity, phenotype, psychometric evaluations, long-term treatment response, etc.), which are currently under investigation by other members of the ICOCS.

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Contributors

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Disclosure

Each author will provide his/her specific disclosure over the manuscript revision process.

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Dr Lorrin Koran, M.D., Stanford University, Stanford, CA; Dr Chiara Arici, M.D., Fondazione IRCCS Policlinico, Milan.

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