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Neurotoxic Effects Of Childhood And Adolescent Blood Lead Levels

Fiona Farrar Fordyce
Yale University, fionafordyce@gmail.com

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Fiona Fordyce
Environmental Health Sciences Division
Yale School of Public Health
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Abstract

Background: Lead has long been established as a potent neurotoxin, childhood being a key period of exposure due to rapid development at that stage in life. While lead is known to cause harmful health effects in the entire population, it is known to particularly damage the developing nervous system in children and potentially interfere with behavioral development. In 2001 a small cohort of children were identified with elevated blood lead level in Montevideo, Uruguay.

Objectives: This study investigated whether 2001 blood lead levels (BLL's) or current (2011) BLL's have had an effect on the behavioral outcomes in this group of adolescents.

Methods: A cohort study of 60 adolescents (mean age 15.2 years) from Montevideo was identified in 2001. Children with elevated BLL's in 2001 (mean 2001 BLL= 13.2 μg/dL, SD= 5.2) were re-identified and tested for current (2011) BLL's (mean 2011 BLL= 4.2 μg/dL, SD= 2.7) using atomic absorption spectrometry. The Child Behavior Checklist, a standardized assessment of behavioral problems, was administered to the adolescents. Linear regression was used to assess the relationship between 2001 BLL's, current BLL's, and the behavioral outcomes.

Results: 2001 BLL's were found to be significantly associated with total problem behavioral score (β=0.98, 95% CI= 0.12-1.85) as well as the social (β=0.80, 95% CI= 0.20-1.40) and externalizing (β=0.93, 95% CI= 0.08-1.78) problem subscales when controlling for current (2011) BLL's and age. 2011 BLL's were not found to be significantly associated with behavioral outcomes. Additionally, 2011 BLL's were found to be significantly lower than 2001 BLL's (Wilcoxon paired test p= 1.90E-8).

Conclusions: This study confirms evidence that increased childhood exposure to lead is associated with subsequent negative behavioral outcomes, and suggests that childhood lead exposure has a stronger impact on behavioral outcomes than current exposure levels. Additionally, BLL's have been significantly reduced since 2001 in this population.

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Background

Lead is one of the most abundant metals on earth, and has been used by humans since prehistoric times (Tong et al. 2000). In more recent times, however, the use of lead in industry has caused it to become widely used and distributed throughout the earth and our environment. As a result, human exposure to lead has dramatically increased, and has led to serious health problems in developed and developing countries alike. Although massive public health campaigns have been successful in reducing environmental and occupational exposure to lead, much exposure remains, and is a particular problem in the developing world, and among low-income and disadvantaged populations.

As lead is a poisonous metal, exposure at both high and low levels, can cause significant detriment to human health. The most accurate and efficient way to assess one's exposure to lead is to measure the blood lead level, with a level of 10 micrograms/dL considered to be the medical and/or environmental intervention limit (CDC, 2012). Recent research however has shown harmful effects at blood lead levels lower than 10 micrograms/dL, and has prompted a movement to lower the intervention limit (CDC, 2012). Lead can interfere with a wide range of body functions, and can be toxic to many organs and organ systems including the heart, bones, intestines, kidneys, blood, and reproductive system (Tong et al. 2000). Most notably however, exposure to lead is known to cause severe effects on the brain and the central nervous system (Tong et al. 2000), with levels much lower than the accepted 10μg/dL intervention limit having been shown to cause cognitive deficits (Lanphear et al. 2000). In the most severe of cases, lead exposure can cause coma, seizures, stroke and even death.

Although exposure at any age can be detrimental to health, the effect of lead exposure on children is the most notable and severe. Children are particularly vulnerable because the intake of lead per body unit is much higher than that for adults. Furthermore, children are particularly vulnerable because they are still in a state of rapid mental/neural development and exposure to lead has the potential to hinder this development (Winneke, 2011). These neural effects of lead exposure on children are irreversible, and for this reason studying exactly how lead exposure effects children's mental development is of significant importance to public health.

Lead Exposure in Uruguay

The issue of lead exposure in Uruguay became prominent in 2001 when children from the low income La Teja and other surrounding low-income neighborhoods of Montevideo were found to commonly have blood lead levels higher than 20 μg/dL, with a mean level of almost 14 μg/dL (Kordas et al. 2010). After the economic crisis of the 1980's, many industrial spaces, often including lead handling facilities, were abandoned in La Teja and in surrounding areas. Families lost great portions of their income, and many low-income families settled in these areas without knowing they were polluted with lead, or without understanding the health risks of this exposure (Mañay et al. 2008). Furthermore, to supplement lost income, many families in these areas engaged in informal work collecting recyclables, often including scrap metals and batteries, and burning cables (Mañay et al. 2008), work which resulted in high levels of lead exposure as well as environmental lead contamination.

The finding of such high blood lead levels in these children prompted a significant response from the Uruguayan Health and Environmental authorities, as well as generated a heightened awareness of environmental lead pollution and the resulting human health effects (Mañay et al. 2008). Blood lead levels of pregnant women and children living in La Teja and other surrounding neighborhoods were analyzed, and lead analyses on environmental samples such as drinking water, soil and air were performed at the same time to identify the possible sources of the lead exposure (Mañay et al. 2008). It was found that soil was the principle source of the children's exposure because La Teja and the surrounding areas, where many of these children lived, had been widely contaminated by the collection of lead scrap, the recycling of batteries, as well as the burning of cables, and additionally, because bare soil constituted the floor of most homes in the area (Mañay et al. 2008).

Lead Exposure and Neurodevelopmental Disorders in Children

Children are significantly more vulnerable to the effects of environmental lead exposure than adults, and this effect is largely neurological (Leggett, 1993; Cory-Schlecta and Schaumburg, 2000). As children are smaller than adults, their intake of lead per body unit is much higher than that of adults, the gastrointestinal tracts of children absorb a greater proportion of lead than those of adults and a greater proportion of systemically circulating lead is allowed access to the brain of a child than that of an adult (Lidsky, 2002). Furthermore, studies have consistently shown that lead is a potent neurotoxin (Winneke, 2011), and as children's brains and nervous systems are still in a process of rapid development, lead exposure at both high and low levels can largely hider this development and can cause permanent neurological damage (Lidsky, 2002). This finding has given rise to the idea that childhood lead exposure could be responsible for a whole host of neurodevelopmental disorders including behavioral and emotional problems such as ADHD, lowered IQ, anti-social behavior, depression, and delayed development to name a few, and has prompted a wide range of studies on the subject.

Lead Exposure and Depression

Studies have found a link between developmental lead exposure and depressive-like behavior in rats (de Souza Lisboa et al. 2005) as well as in young adults in the United States (Bouchard et al. 2009). It was found that in young adults, increasing blood lead levels were associated with a significantly higher risk of major depressive disorder: when compared with persons with a blood lead level of less that 0.7 μg/dL, those with a level greater than 2.1 μg/dL had a 2.3 fold increased risk of meeting the DSM-VI criteria for major depressive disorder (Bouchard et al. 2009). However, other studies have failed to find consistent evidence that environmental lead exposure measured by blood lead level was associated with depression (Golub et al. 2009).

Lead Exposure and Somatic Complaints

Various studies have found a relationship between elevated lead body burden in children and sleep issues (Needleman, 1996; Kordas, 1997; Owens-Stively, 1997). This finding has been replicated in adolescents (Olimpio, 2009), however similar findings have not been made in adults. One study found that children with even moderately elevated blood lead levels experiences a higher incidence of sleep disturbances such as restlessness, night waking, sitting up in bed, trouble falling asleep, or trouble waking up to four years after exposure (Owens-Stively, 1997). Another study done on Mexican children aged 6 to 8 found that blood lead levels above 10 μg/dL were associated with later waking time and shorter duration of sleep (Kordas, 2007). However these same results have not been found in adults: a study done on adult lead smelting workers found that the incidence of sleep disturbances and fatigue were not higher in the group of opposed workers when compared with a control group of non-lead exposed worker (Kirkby, 1983).

Lead Exposure and Social Problems

The effects of increased lead exposure on social problems has not been widely studied, however an association between lead exposure and social problems has been found in both children and adolescents (Roy, 2009; Olympio, 2010). A study on children between three and seven done in India found that higher blood lead levels were associated with social problems as measured by the Conner's Teacher Rating Scales-39 (Roy, 2009), and a study done on Brazilian adolescents found that a higher surface dental enamel lead levels was associated with an increased risk of social problems (Olympio, 2010).

Lead Exposure and Attention Problems

The relationship between childhood lead exposure and attention problems has long been studied. A wide range of older studies comparing elevated lead exposure in children to the incidence of attention problems such as ADHD, inattention, and distractibility have consistently found a positive relationship (Needleman, 1979. Yule, 1984. Thomson, 1989. Bellinger, 1994.) More recent studies have used a clinical diagnosis of ADHD as a proxy for attention problems. Two recent studies using NHANES data found that children in the fifth quintile and third tertile were 4.1 and 2.3 times, respectively, as likely to have been diagnosed with ADHD (Braun, 2006. Froehlich, 2009). Additional more recent studies have consistently found that increased blood lead levels are significantly associated with an increased risk of ADHD diagnosis (Wang, 2008. Nigg, 2010. Nicolescu, 2010).

Lead Exposure and Delinquent/Rule Breaking Behavior

The relationship between lead exposure and antisocial or delinquent behavior has been widely studied, and research has consistently found a relationship between increased bone or blood lead levels and an increased incidence of delinquent behavior in childhood and adolescence alike (Needleman, 1996; Dietrich, 2001). One study found that youths with high bone lead levels are twice as likely to be delinquent, after controlling for confounders (Needleman, 2003). Furthermore, in a survey of Philadelphia youths, it was found that a history of lead poisoning was the strongest predictor of criminality in males (Denno, 1990). More recently, the idea that childhood lead exposure could increase the risks of delinquency later in life has sparked a myriad of studies on the subject. One study conducted in nine different countries found that preschool blood lead levels were very strongly associated with subsequent crime rate trends over several decades, and concluded that preschool lead exposure has a significant effect on delinquent behavior later in life (Nevin, 2006).

Lead Exposure and Aggressive Behavior

The association between childhood lead exposure and violent and aggressive behavior was first noted in 1943 in a study that observed that children with higher levels of lead exposure exhibited explosive tempers and poor impulse control (Byers, 1943). This association however, was not explored in more depth until many years later. A study examining the bone lead level of 301 primary school children in 1996 found that those children with higher lead levels were significantly more likely to score in the clinical range for aggression on the standardized CBCL assessment questionnaire (Needleman, 1996), and additional studies have found that prenatal lead exposure is associated significantly with parental reports of aggression (Dietrich, 2001).

Child Behavior Checklist (CBCL) 6-18

The Child Behavior Checklist (CBCL) 6-18 was used in this study to assess the presence of behavioral and emotional problems in the study subjects. The CBCL has been widely used in a variety of studies involved with psychopathological diagnoses and assessments

(Achenbach, 2001), and has been translated into Spanish and validated for use in South America and specifically in Uruguay (Viola, 2011). The CBCL is a questionnaire containing 113 items each scored on a three point scale, 0 indicating "never", 1 indicating "sometimes", and 2 indicating "often." These 113 items consist of eight specific syndrome scales: withdrawn/depressed, anxious/depresses, somatic complaints, delinquent or rule-breaking behavior, aggressive behavior, social problems, thought problems, and attention problems. Additionally two broader problems scales exist, internalizing and externalizing, the internalizing being comprised of withdrawn/depresses, somatic complaints, and anxious/depressed, and the externalizing comprised of delinquent behavior and aggressive behavior. Finally, a total behavior score is a summation of the scores of all 113 items, with a higher score indicating a higher level of problem. A scoring template is used to obtain normalized T-scores for all eight behavior subsections, both the internalizing and externalizing broader subsections, as well as the final behavior score, normalized to a general population by age and gender.

Methods

Study Population and Recruitment

This study was conducted between June and October of 2011 in Montevideo, Uruguay. All study subjects were from, and still live in Montevideo or closely surrounding areas. All subjects had had their blood previously tested for lead in 2001 and all had blood lead levels in 2001 above 5 μg/dL. Subjects were identified through medical records from the Clinicas Hospital Department of Toxicology. The parents of potential subjects were telephoned by doctors from the Pediatric Environmental Unit of the Filtro Hospital and asked if they were interested in enrolling their children in a lead exposure follow-up study in which their children's blood would be tested for lead, they would be asked to fill out a questionnaire and answer several questions, and they would be given a physical exam by a physician. Most parents were very receptive and a total of 60 subjects were recruited for the study. The subjects came with a parent or guardian to the Pediatric Environmental Unit at the Filtro Hospital for the study visit, and were reimbursed for bus fare to and from the hospital. The parents or guardians of all study subjects provided informed consent and the study protocol was approved by the Yale University Human Investigation Committee.

Subject Interviews

At the Pediatric Environmental Unit, the parent or guardian was given the Child Behavior Checklist (CBCL) to complete in regards to their child. To ensure accuracy in the case of low levels of comprehension or literacy of the parent or guardian, an interviewer read the questions from the questionnaire out loud and the respondent followed along by reading a copy of the questionnaire. The answers were given in a clear and audible voice and were recorded by the interviewer. This process was adopted to avoid embarrassment or confusion and is recommended by the creators of the questionnaire (Achenbach and Rescorla, 2001). Responses to the questionnaire were scored and translated into T-scores by hand using the ASEBA Hand Scored Profiles. In addition, the parent or guardian was asked to answer several questions from a separate questionnaire regarding lead exposure in their home and neighborhood.

Blood Collection and Analysis

Blood was collected from the subjects at the time of interview at the Filtro Hospital. After cleaning the skin, blood was obtained from the cubital vein in heparin-moistened evacuated disposable syringes found to contain no detectable amounts of lead (corresponding to less than 3.2 μg/dL). Samples were transported within 8 hours of collection to the Clinicas Hospital Department of Toxicology were they were frozen at -20 °C until their analysis. Blood was analyzed at the Laboratory of the Department of Toxicology and Environmental Hygiene of the Chemistry Department of the University of the Republic, Montevideo, Uruguay using flame atomic absorption spectrophotometry with a limit of detection of 3.2 μg/dL.

Statistical Analysis

Data were analyzed using SAS software (version 9.2; SAS Institute Inc., Cary, NC, USA). Population characteristics were calculated for the total sample as well as for the total sample stratified by sex. A T-test was used to test the statistical difference between 2001 and 2011 blood lead levels. Linear regression was used to analyze the relationship between 2001 blood lead levels, current (2011) blood lead levels and T-scores relating to all Child Behavior Checklist outcomes including the eight subsections withdrawn/depressed, anxious/depresses, somatic complaints, delinquent or rule-breaking behavior, aggressive behavior, social problems, thought problems, and attention problems, as well as the broader problem scales internalizing and externalizing and finally total behavioral outcome. This regression was performed for the entire study population as well as the study population stratified by sex. Half the limit of detection was used for those blood lead levels below detection limit. Correlation was assessed between 2001 blood lead level and current (2011) blood lead level to ensure the appropriateness of the model. Linear regression was used to analyze the relationship between 2001 blood lead levels, current (2011) blood lead levels and the raw score of each of the 113 questions of the Child Behavior Checklist.

Results

The total sample size was 60- 35 males (58.3%) and 25 (41.7%) females. Mean and standard deviation of age, 2001 blood lead level, 2011 blood lead level, total behavioral T-score, social problem behavioral T-score and externalizing problems behavior T-score are presented for the study population as a whole as well as stratified by male and female in table 1.

Table 1

	Total	Male	Female	P-Value
N (%)	60 (100)	35 (58.3)	25 (41.7)	
Age Mean (SD)	15.2 (2.8)	14.8 (2.4)	15.8 (3.2)	.1490
2001 BLL µg/dL Mean (SD)	13.2 (5.2)	13.5 (6.0)	12.8 (3.9)	.6092
2011 BLL µg/dL Mean (SD)	4.2 (2.7)	4.7 (3.1)	3.4 (1.9)	.1153
Total Behavior T-Score Mean (SD)	58.7 (9.8)	57.7 (9.7)	60.1 (10.0)	.4012
Social Behavior Problem T-Score Mean (SD)	60.2 (8.1)	58.9 (7.3)	61.8 (8.8)	.2171
Externalizing Behavior	56.3	56.4 (9.4)	56.1	.9142

Problem T-Score Mean (SD)	(9.8)	(10.5)

There was no significant difference between males and females in terms of mean age, mean 2001 blood lead level, mean 2011 blood lead level, total behavioral outcome T-Score, any of the eight problem behavior subsection T-scores, or internalizing or externalizing problem behavior T-score.

The Wilcoxon paired test confirmed that there was a significant difference between the mean 2001 blood lead level and the 2011 blood lead level with a highly significant p-value for the test of 1.90E-8.

Multivariate linear regression showed that 2001 blood lead levels were significantly associated with total problem behavioral T-score (β=0.98, 95% confidence interval= 0.12-1.85, p-value= 0.0276), social problem subscale T-score (β=0.90, 95% confidence interval= 0.20-1.40, p-value=0.0106), and externalizing problem subscale T-score (β=0.93, 95% confidence interval= 0.08-1.78, p-value=0.0338) when controlling for current (2011) blood lead levels and age. These results are presented in table 2.

Table 2.

CBCL Subgroup	β	P-Value	95% CI
Total T-Score	0.98	.0276	0.12-1.85
Social Problem T-Score	0.90	.0106	0.20-1.40
Externalizing T-Score	0.93	.0338	0.08-1.78

Multivariate linear regression showed that 2011 blood lead levels were not significantly associated with total behavioral problem T-score or any of the eight behavioral problem subsection T-scores, or with the two internalizing and externalizing problem behavior subscales.

Lastly, seven of the 113 individual questions from the CBCL were identified through regression analysis as being significantly associated with 2001 blood lead levels when controlling for current, 2011, blood lead levels and age. These results are presented in table 3.

Table 3

Variable	β	P-Value	95% CI
Too Dependent	0.09	.0157	0.02-0.16
Nervous Movement/Twitching	0.08	.0011	0.03-0.12
Fearful/Anxious	0.06	.0494	0.00-0.12
Vomits	0.04	.0440	0.00-0.07
Clumsy	0.07	.0201	0.01-0.13
Prefers being w/ older kids	0.06	.0272	0.00-0.10
Unusually loud	0.06	.0318	0.01-0.11

Discussion

Lead contamination in Montevideo as well as the resulting exposed population have been studied in depth since the discovery of the problem in 2001 (Mañay, 2003). Additionally, the effects of lead exposure on child development and subsequent neurological problems has been the topic of much research over the past 30 years (Needleman, 2009). The findings of this study, that childhood lead exposure is associated with subsequent negative behavioral and emotional problems, is congruent with many previous findings on the subject. However, given the unique population and circumstances of this study, several novel findings were made.

After the 2001 discovery of elevated blood lead levels in this population of children, significant efforts were undertaken by Uruguayan health and environmental authorities to reduce both environmental lead contamination and exposure (Mañay et al. 2008). Until December of 2003, the primary gasoline used in Uruguay contained tetraethyl lead (Uruguayan Legislative Power, 2004), a significant source of lead exposure. Furthermore, many older buildings and houses still contain plumbing made of lead pipelines (Cousillas, 2011). After the 2001 discovery of elevated blood lead levels, the use of leaded gasoline was gradually phased out, leaded pipes supplying drinking water were progressively substituted, children were increasingly educated in areas of exposure reducing habits, and an official inter-institutional committee was created (Cousillas, 2011). This committee included delegates from an array of institutions including the Ministry of

Public Health, Ministry of the Environment, Labor Ministry, Industry, Energy and Minerology Ministry, the Municipality of Montevideo, as well as researchers from the Departments of Chemistry, Science, and Medicine from the University of the Republic of Uruguay, the State Potable Water Administration, the Social Security Administration, the WHO, as well as delegates from the community at large (Cousillas, 2011). The primary task of this committee was to "study corrective actions to be taken, identify the sources of contamination, investigate community claims, evaluate blood lead levels from people living in contaminated areas and to propose national regulations to control and prevent the exposure of the population (Cousillas, 2011)." Additionally, beginning in 2001, home visits were made to the homes of children who had been identified as having blood lead levels over 20 µg/dL (Mañay, 2003). During these visits data were collected from each individual regarding age, house, school, and playground addresses, intensity of traffic near the houses and smoking habits of the parents (Mañay, 2003). These children were visited by a multidisciplinary team of physicians, toxicologists, chemists and social workers who studied their residential environment, possible sources of lead exposure as well as socioeconomic and housing conditions. Subsequently, educational and preventative initiatives concerning hygienic and dietary habits were instituted to reduce further exposure (Mañay, 2003). The comparison in this study of 2001 blood lead levels with 2011 levels, and the finding of a significant reduction in mean levels, validates the efforts undertaken by Uruguayan Health and Environment officials and confirms that these efforts have been successful in reducing environmental lead exposure in this population.

This study found no significant difference between boys and girls in mean 2001 blood lead level, mean 2011 blood lead levels, or the total behavioral T-score or any of the ten behavioral subsection T-scores. Generally boys have higher exposure to environmental lead due to more sport and outside activities, however this was not the case in this population. The findings of no difference in behavioral outcomes is congruent with the Port Pririe Cohort Study as well as the Bellinger et al. study which found that there were no differences in behavioral abnormalities in relation to lead levels (Bellinger, 1994; Burns, 1999).

The multivariate regression analysis found significant associations between 2001 blood lead levels and the total problem behavior outcomes as well as the social and externalizing problems subscales. These findings were closely corroborated by the Olympio et al. (2010) study which found that the CBCL subsections somatic problems, social problems and externalizing problems were significantly associated with the high surface dental enamel lead group (Olympio et al., 2010). These findings suggest that the CBCL problem subscales which are most closely associated with lead exposure are the social and externalizing subsections.

Multivariate regression analysis comparing 2001 blood lead levels, 2011 blood lead levels, and age with total behavioral problem T-score as well as the eight problem behavior subsections and the two larger, internalizing and externalizing, problem behavior subsections found that while 2001 blood lead levels were associated with total behavioral outcome, as well as the social and externalizing subsections, current (2011) blood lead levels were not associated with total behavioral outcomes or any other the other ten behavioral subsections. This finding is of particular interest because it suggests that early childhood exposure to lead has a greater impact on behavioral and emotional problems than current exposure levels and suggests that younger children are more susceptible to the harmful neurological effects of lead exposure than older children.

There are several limitations to this study. The most significant limitation being the lack of covariates such as related socio economic status data, parental education level, IQ, or psychopathy, or child's IQ - variables commonly used in similar studies as confounders between the relationship of lead exposure and CBCL outcomes (Burns, 1999; Bellinger, 1994). Socioeconomic status is a well known and important confounder in the relationship between lead exposure and children's neural development (Bellinger, 2008) and has often played a central role in efforts to characterize the magnitude of the risk that lead poses to children's neural development. Although this study's population is generally uniform in socioeconomic status, omitting it in analysis allows for the potential of considerable error. Furthermore, as maternal IQ is an important predictor of child's IQ, it is an important and widely accepted covariate used when assessing the relationship between lead exposure and subsequent behavioral outcomes (Burns, 1999; Bellinger, 1994, Baghurst, 1992). Furthermore, the limit of detection, 3.2 μg/dL, being so close to the estimated mean 2011 blood lead level, could reduce the accuracy of the 2011 mean blood lead level.

On the other hand, this study has a great strength in that blood lead level measurements from two different points in time are used to assess the association between lead exposure and CBCL outcomes. This allowed for the analysis of how blood lead levels over a range of time affect behavioral and emotional outcomes.

Conclusions/Implications

The results from this study show that blood lead levels in this population have been significantly reduced since 2001. Furthermore this study finds that 2001 (younger childhood) blood lead levels are significantly associated with total problem behavior outcomes, social problems and externalizing problem behavior outcomes, while current (2011) blood lead levels are not associated with total problem behavior outcome or any of the ten behavioral outcome subsections. This finding suggests that younger children are more susceptible to the harmful neural-developmental effects of environmental lead exposure than older children and corroborates previous evidence that environmental lead exposure has harmful effects on subsequent behavioral outcomes in children.

These findings suggest that efforts undertaken by Uruguayan Health and Environment officials have been successful at reducing environmental lead exposure and thus should be continued. Furthermore, these findings suggest that interventions world-wide should be put in place to prevent childhood exposure to environmental lead and that while these interventions should be aimed at all children, preference should be given to those younger rather than older.

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