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Serum cortisol level in patients with a transient global amnesia.

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Abstract :

Transient Global Amnesia (TGA) could be triggered by a high level of blood cortisol. We assessed whether patients had a higher level of cortisol during the TGA than shortly after. We included 52 patients 21 with blood collected during the TGA and 31 shortly after. We compared these two groups after adjustment on time of blood collection. The cortisol's level was significantly higher in the per-ictal group (p= 0.03) and negatively correlated with the time elapsed from the onset of symptoms (p= 0.005). The results are consistent with of the hypothesis of a hyperreactivity of the hypothalamic–pituitary–adrenal axis.

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Serum cortisol levels in patients with a transient global amnesia.

Abstract :

Transient global amnesia (TGA) can be triggered by a high level of blood cortisol. We assessed whether patients had a higher level of cortisol during the TGA than shortly after. We included 52 patients, 21 with blood collected during the TGA episode and 31 shortly thereafter. We compared these two groups after adjustment for time of blood collection. The cortisol level was significantly higher in the per-ictal group (p= 0.03) and negatively correlated with the time elapsed from symptom onset (p= 0.005). The results are consistent with of the hypothesis of a hyperreactivity of the hypothalamic–pituitary–adrenal axis.

Key Words: Transient Global Amnesia, Cortisol, Stress, Memory

Introduction

Transient global amnesia (TGA) is a benign neurological condition that occurs principally in people between 50 and 70 years and is characterized by a profound memory impairment of sudden onset which lasts up to 24h. The clinical syndrome is now well described. It combines a profound anterograde amnesia, retrograde amnesia, disorientation in time and repetitive questioning, contrasting with spared consciousness and other cognitive functions [1].

The cause of TGA remains unclear, even though the diffusion-weighted magnetic resonance data point to an acute impairment of the CA1 field of the hippocampus [2]. However, the pathophysiology of this impairment is still unknown. One theory assumes the role of stress-related factors in the emergence of TGA. According to this hypothesis [3], the metabolic stress could induce a high blood level of cortisol which, in return, might trigger an impairment of hippocampal functioning. This assumption is backed by several facts: the high prevalence of stressing events occurring before TGA shown by epidemiological studies [4], the high density of glucocorticoid receptors in the hippocampus - especially in the CA1 subfield -, the rise in serum cortisol level in stress situations and the deleterious effect of acute stress or cortisol injection on declarative memory [5]. A recent study in 14 patients, seen during and after TGA [6], found that the salivary cortisol levels were higher during the TGA than after. The aim of our study is to replicate these results on a larger sample of patients with an assessment of serum cortisol levels during the TGA or in the following 24 hours.

Patients, material and methods.

The patients included in this study are part of an ongoing cohort of TGA patients seen at Caen University Hospital between 2000 and 2012. All subjects included in the present study fulfilled the Hodges and Warlow criteria and were enrolled in the emergency department. They had a blood sample collected either during the TGA or the first following twenty-four hours to assess the level of cortisol. The study design was accepted by a local ethics committee and each participant gave written informed consent. The main objective of this

study was to determine whether the level of cortisol was higher during the acute stage of TGA than after it. The secondary objectives were to estimate if this level was associated with stress as trigger factors of TGA or with its severity defined as its total duration. A stress factor was defined either as a physical stress (strengthening exercises, cleaning of the house…) or as an emotional stress (fight with a relative, hospitalization of a granddaughter).

We applied a Student *t* test to compare quantitative data between groups and categorical comparisons were made by the Pearson χ^2test. All statistical analyses were conducted using R software 3.4.0. Results were considered significant at a 2-sided α-level of 0.05.

Fifty-three patients met the inclusion criteria, but one of them was excluded from analysis because the time of blood sampling was missing. Twenty-one patients had a blood sample taken during the acute phase (per-TGA group) and thirty-one after the TGA (post-TGA group).

Results

The main characteristics of each group are summarised in Table 1. The two groups were similar in age (63.6 years vs 62.5, p = 0.62), gender (Males = 36.5% vs 35%, p = 1) and presence of stress as a trigger factor (38% vs 32%, p = 0.4) but the duration was longer in the per-ictal than in the post-ictal group (5.6 hours vs 4.7 hours, p = 0.02). They also differed by the time of blood sampling (p < 0.001), as a higher proportion of patients in the post-TGA group was tested between 08:00 and 12:00 military time (18 vs 1).

There was no significant difference between the cortisol levels of the two groups (168.5 ng/l vs 163.5ng/l, t= -0.27 p = 0.8). However, after adjustment on time of blood sampling in a

multiple linear regression model, the difference in cortisol levels became significant (p = 0.03, Fig. 1): with a similar time of blood collection, cortisol levels were significantly higher in the per-TGA group than in the post-TGA group. Moreover, in the per-TGA group, cortisol levels were negatively correlated with duration between TGA onset and blood sampling (Pearson's R= -0.6, CI95%: -0.8, -0.2; p = 0.005, Fig. 2). On the contrary, cortisol levels were associated neither with the duration of TGA (cor = 0.08; CI95%: -0.2, 0.3; p = 0.6) nor with the presence of stress as an identified trigger factor (155ng/l vs 169ng/l; p = 0.07). These results were not modified by the adjustment for time of blood sampling.

Discussion

The results presented above are coherent with the metabolic hypothesis as, after adjustment for the time of blood collection, the level of cortisol was higher during the TGA than shortly after. They are also coherent with previous data in the literature. Besides, the levels of cortisol were negatively correlated with the elapsed time since the TGA's beginning, backing the hypothesis that there is a threshold of serum cortisol above which the risk of TGA is increased and under which it is more likely to end. Moreover, the cortisol level during the TGA is not related to the stress as a causative factor, so it seems that the high cortisol level is not only an expression of the level of stress that has triggered the TGA, but could be itself involved in the pathogenesis. As glucocorticoids are highly responsive to stressful events [7], it may be argued that the high level of cortisol during the TGA is only a physiological response that reflects the severe anxiety that is common during it. But it has been shown that patients who recently suffered from TGA had a stronger dexamethasone feedback than healthy controls and a higher cortisol level in anticipation of experimental stress. The results seem to indicate a hyperreactivity of the hypothalamic–pituitary–adrenal

axis (HPPAA) [8]. They are in favor of the hypothesis that the high cortisol level is not associated with the anxiety induced by the TGA but could result, at least in part, from a primary disorder of the HPAA and explain why a stress event could trigger it.

But the HPAA could also play a key part in the psychopathology of TGA. A recent review stressed that the psychiatric symptoms during TGA - such as anxiety and depressive mood - should be considered as a core feature of TGA and are uncommon in other situations of acute anterograde amnesia like transient epileptic amnesia. [9]. It has been shown that cortisol is involved in the pathogenesis of anxiety disorders especially in older adults [10]. A high cortisol level during TGA could trigger both the neuropsychological and the psychiatric symptoms of TGA. Consequently, one of the strengths of the metabolic hypothesis is that it can explain both neurological and neuropsychological symptoms through a common pathophysiological pathway.

New studies are needed to better understand the pathophysiology of TGA, especially to establish correlation between cortisol levels and psychological features at baseline and during the episode.

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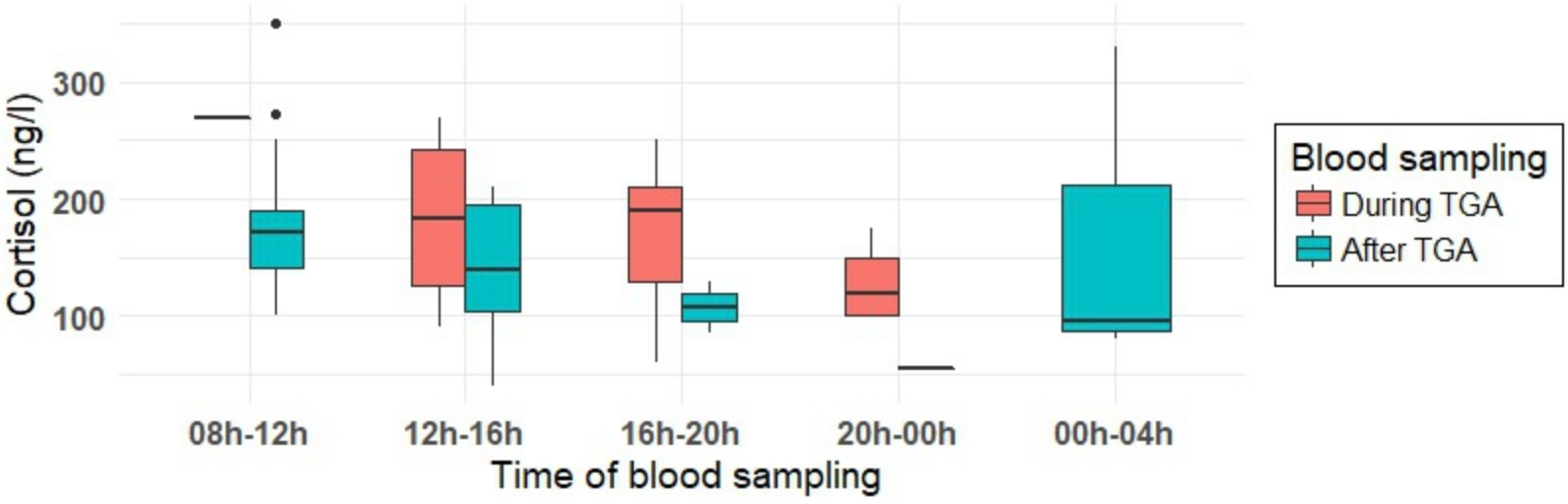
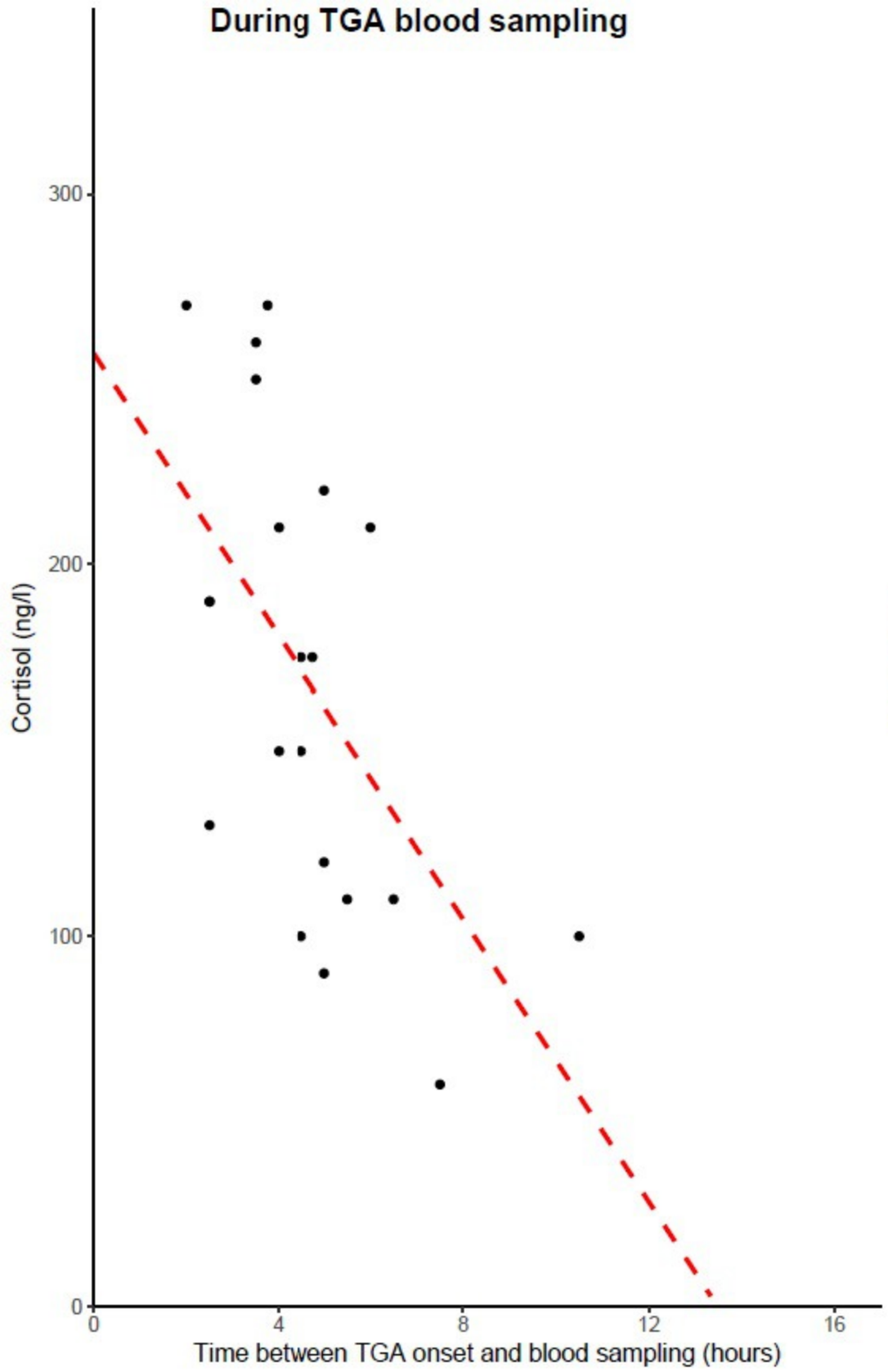
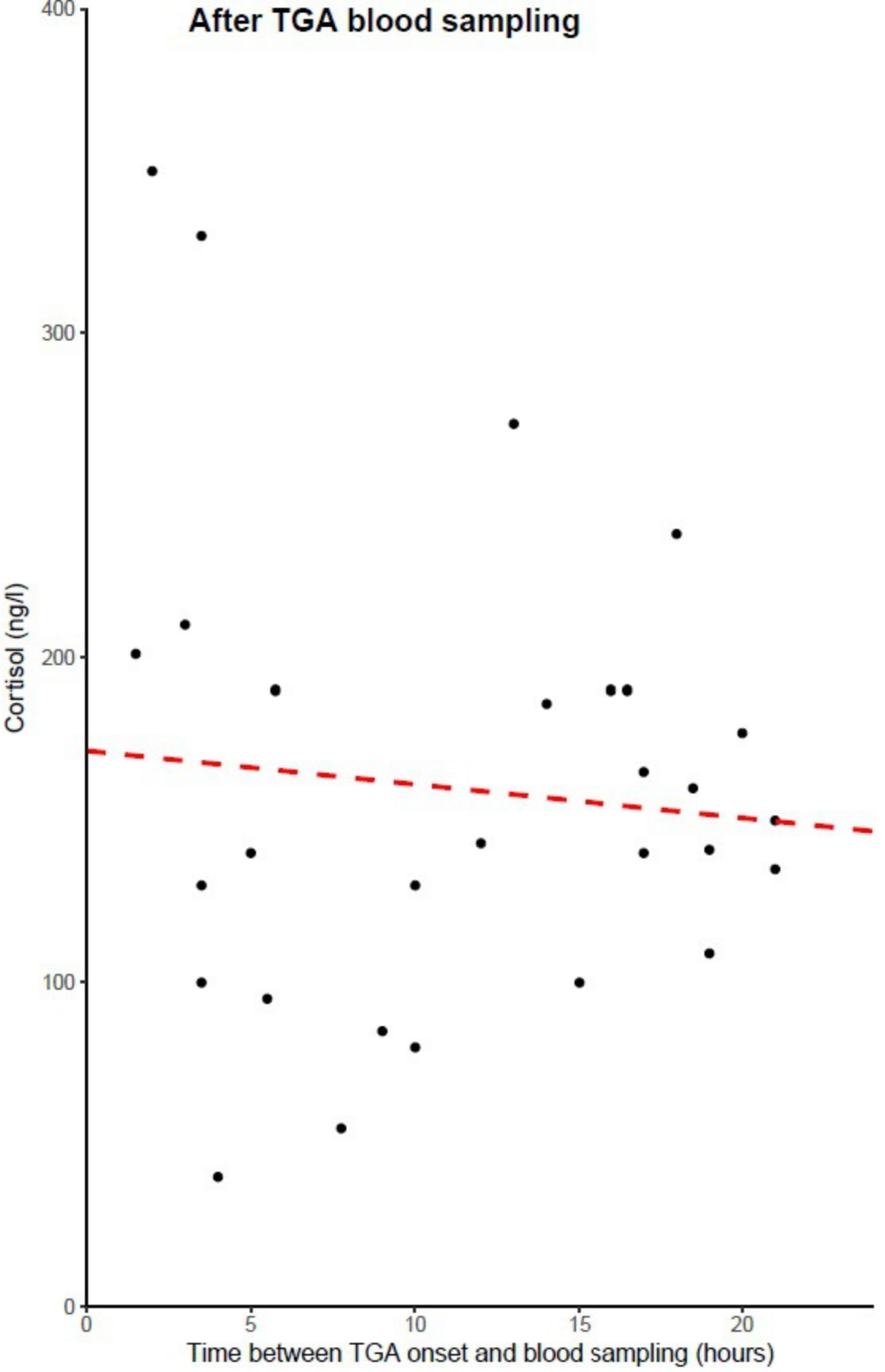
Figure 1: Boxplots of cortisol level after or during transient global amnesia (TGA) by time of blood sampling. With a similar time of blood collection, cortisol levels were significantly higher during TGA than after it was over.

Figure 2: Correlations between cortisol level after or during transient global amnesia (TGA) and time between beginning of the episode and blood collection.


Cortisol (ng/l)
300
200
100
08h-12h
12h-16h
16h-20h
20h-00h
00h-04h
Time of blood sampling
Blood sampling
During TGA
After TGA


During TGA blood sampling
Cortisol (ng/l)
0
100
200
300
0
4
8
12
16
Time between TGA onset and blood sampling (hours)


After TGA blood sampling
Cortisol (ng/l)
0
100
200
300
400
0
5
10
15
20
Time between TGA onset and blood sampling (hours)

	All patients(n=52)	Per-TGA (n=21)	Post-TGA (n=31)	p *
Cortisol ng/l (sd)	169 (72.6)	168,6 (73,2)	163.5 (71)	0.7
Age (sd)	63.6 (8.8)	63.8 (7.7)	62.5 (9.6)	0.62
Sex : male (%)	19 (36.5%)	8 (38%)	11 (35%)	1
TGA duration hours (sd)‡	5.6 (3.3)	6.8 (2.7)	4.7 (3.5)	0.02
Stress as trigger factor♣ (%)	20 (38%)	10 (48%)	10 (32%)	0.4
Time between TGA and blood collection in hours (sd)	8.6 (6.1)	4.6 (1.2)	11.4 (6.6)	<0.001
Time of blood collection				
00h-4h	3	0	3	
4h-8h	0	0	0	
8h-12h	19	1	18	<0.001
12h-16h	13	6	7	
16h-20h	11	9	2	
20h-00h	6	5	1	

Table 1 : Main characteristics of TGA patients.

‡ Missing data for 6 patients; * t. tests for quantitative variable, Fischer test or Chi-Square for qualitative data between the per-ictal and post-ictal groups. ♣ Examples of stress factor in our cohort: medical procedure, fight with a relative…