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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.

1 Serum cortisol levels in patients with a transient global amnesia.

2

3 **Abstract :**

4 Transient global amnesia (TGA) can be triggered by a high level of blood cortisol. We

5 assessed whether patients had a higher level of cortisol during the TGA than shortly after.

6 We included 52 patients, 21 with blood collected during the TGA episode and 31 shortly

7 thereafter. We compared these two groups after adjustment for time of blood collection.

8 The cortisol level was significantly higher in the per-ictal group ($p= 0.03$) and negatively

9 correlated with the time elapsed from symptom onset ($p= 0.005$). The results are consistent

10 with of the hypothesis of a hyperreactivity of the hypothalamic–pituitary–adrenal axis.

11

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

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16 **Introduction**

17 Transient global amnesia (TGA) is a benign neurological condition that occurs principally in

18 people between 50 and 70 years and is characterized by a profound memory impairment of

19 sudden onset which lasts up to 24h. The clinical syndrome is now well described. It combines

20 a profound anterograde amnesia, retrograde amnesia, disorientation in time and repetitive

21 questioning, contrasting with spared consciousness and other cognitive functions [1].

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

36

37

38 **Patients, material and methods.**

39

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

46 study was to determine whether the level of cortisol was higher during the acute stage of
47 TGA than after it. The secondary objectives were to estimate if this level was associated with
48 stress as trigger factors of TGA or with its severity defined as its total duration. A stress
49 factor was defined either as a physical stress (strengthening exercises, cleaning of the
50 house...) or as an emotional stress (fight with a relative, hospitalization of a granddaughter).
51 We applied a Student *t* test to compare quantitative data between groups and categorical
52 comparisons were made by the Pearson χ^2 test. All statistical analyses were conducted using
53 R software 3.4.0. Results were considered significant at a 2-sided α -level of 0.05.

54

55

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

60

61 **Results**

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

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

70 multiple linear regression model, the difference in cortisol levels became significant ($p =$
71 0.03 , Fig. 1): with a similar time of blood collection, cortisol levels were significantly higher in
72 the per-TGA group than in the post-TGA group. Moreover, in the per-TGA group, cortisol
73 levels were negatively correlated with duration between TGA onset and blood sampling
74 (Pearson's $R = -0.6$, $CI_{95\%}: -0.8, -0.2$; $p = 0.005$, Fig. 2). On the contrary, cortisol levels were
75 associated neither with the duration of TGA ($cor = 0.08$; $CI_{95\%}: -0.2, 0.3$; $p = 0.6$) nor with
76 the presence of stress as an identified trigger factor (155ng/l vs 169ng/l ; $p = 0.07$). These
77 results were not modified by the adjustment for time of blood sampling.

78

79 **Discussion**

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

94 axis (HPPAA) [8]. They are in favor of the hypothesis that the high cortisol level is not
95 associated with the anxiety induced by the TGA but could result, at least in part, from a
96 primary disorder of the HPAA and explain why a stress event could trigger it.
97 But the HPAA could also play a key part in the psychopathology of TGA. A recent review
98 stressed that the psychiatric symptoms during TGA - such as anxiety and depressive mood -
99 should be considered as a core feature of TGA and are uncommon in other situations of
100 acute anterograde amnesia like transient epileptic amnesia. [9]. It has been shown that
101 cortisol is involved in the pathogenesis of anxiety disorders especially in older adults [10]. A
102 high cortisol level during TGA could trigger both the neuropsychological and the psychiatric
103 symptoms of TGA. Consequently, one of the strengths of the metabolic hypothesis is that it
104 can explain both neurological and neuropsychological symptoms through a common
105 pathophysiological pathway.
106 New studies are needed to better understand the pathophysiology of TGA, especially to
107 establish correlation between cortisol levels and psychological features at baseline and
108 during the episode.

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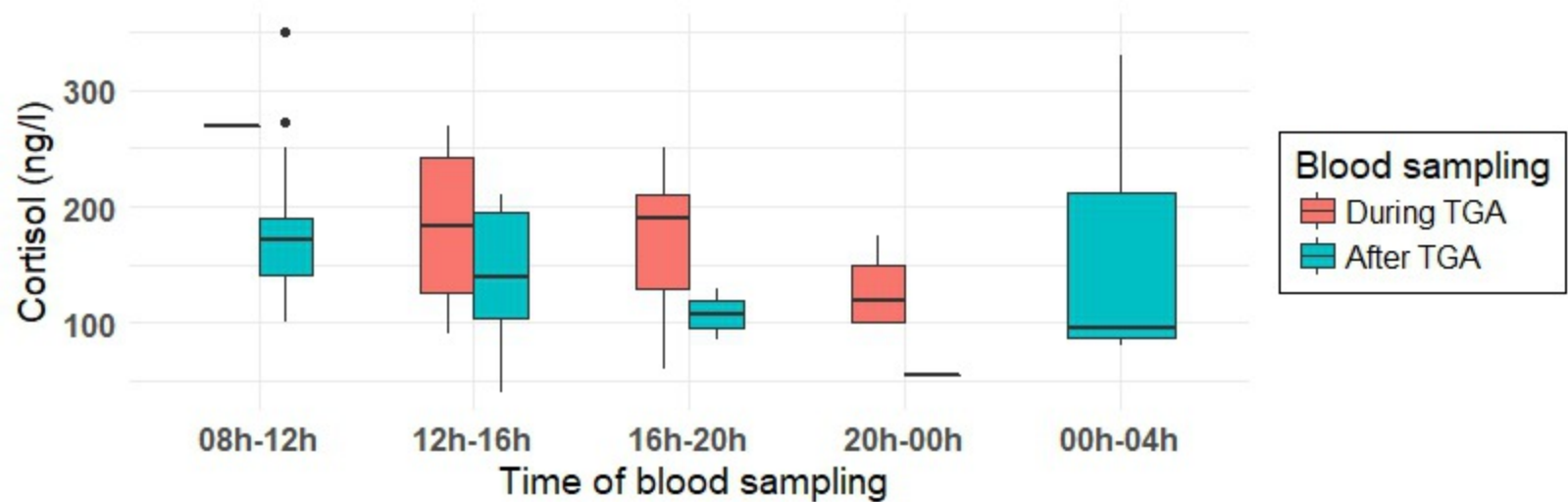
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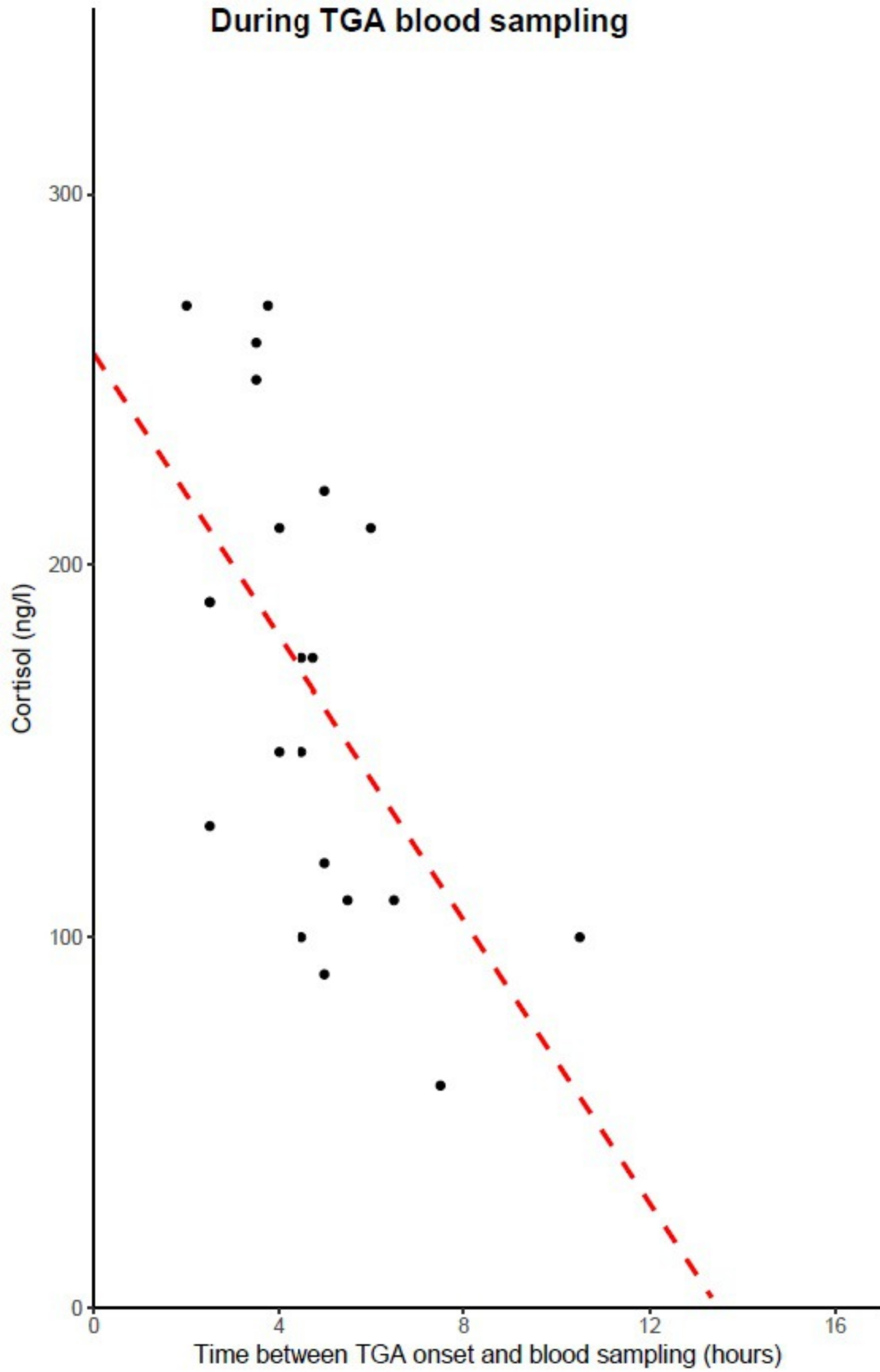
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Figure 1: Boxplots of cortisol level after or during transient global amnesia (TGA) by time of blood sampling. With a similar time of blood collection, cortisol levels were significantly higher during TGA than after it was over.

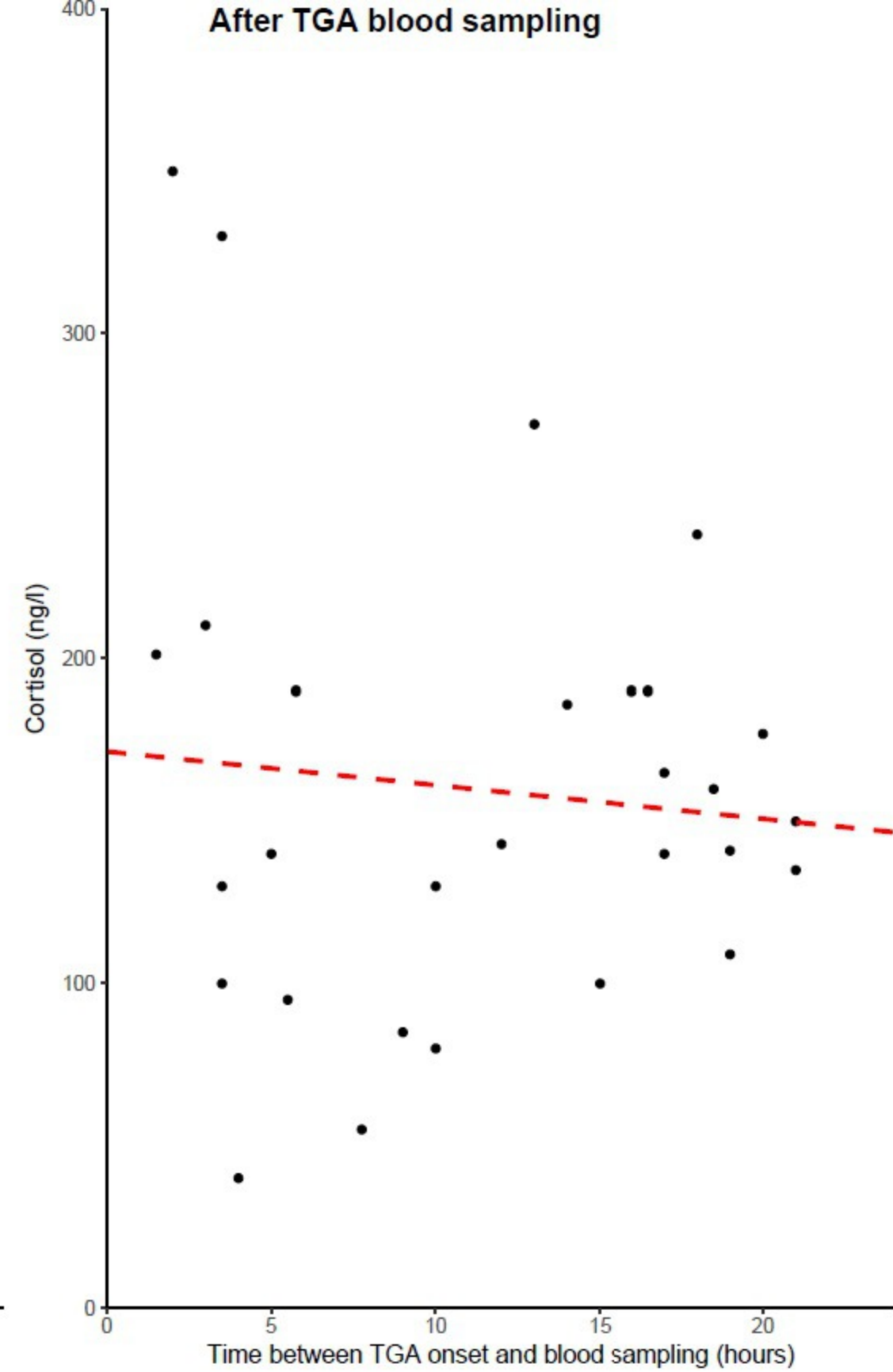
Figure 2: Correlations between cortisol level after or during transient global amnesia (TGA) and time between beginning of the episode and blood collection.



During TGA blood sampling



After TGA blood sampling



	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...