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SUNCT and high nocturnal prolactin levels: some new unusual characteristics

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Abstract SUNCT is a rare condition characterised by a short-lasting periorbital pain associated with autonomic symptoms and is usually unresponsive to pharmacological treatment. We report a case of SUNCT syndrome linked to a pituitary micro-adenoma, with only nocturnal attacks. The nocturnal levels of prolactin (PRL) were increased, while other hormonal, haematological, serological and biochemical investigations and levels of PRL did not reveal abnormal findings during the day-time. PRL serum secretion after thyrotropin-releasing hormone test was lower than nocturnal secretion, but not enough to induce severe attacks. We suggest that in our patient the rise of nocturnal levels of PRL could have a direct role in the worsening of this headache, perhaps secondarily to an altered regulation of the hypothalamic–hypophysial axis, however the actual influence of sleep and the interaction between all neurotransmitters and hormones needs to be clarified further.

Keywords SUNC · Hyperprolactinaemia · Nocturnal headaches · SUNCT and neuro-endocrine disorders

Introduction

Recurrent short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) were first described by Sjaastad et al. in 1978 as a distinct and rare clinical entity [1]. The typical form is characterised by several attacks of moderate or severe orbital, periorbital or temporal, stabbing or pulsating pain lasting 5–250 s, with ipsilateral conjuctival injection, lacrimation and rhinorrhoea or nasal obstruction. An irregular temporal pattern is the rule, with symptomatic periods alternating with remissions in an unpredictable fashion. During active periods, the frequency of attacks may vary from <1

Table 1 Levels of PRL at 8 a.m. and after 1, 2, 3, 4 hours in basal condition and after TRH-test and at 1 a.m. after 1,2, 3, 4 hours during symptomatic (a) and remission periods (b).

(a) Symptomatic periods						
Diurnal secretion	Time (h)	8	9	10	11	12
	Value (ng/mL)	18±1.2	15±0.9	15±1.1	12±0.6	18±0.7
After TRH test	Time	8	9	10	11	12
	Value	42±2.7	46±2.2	48±1.2	34±1.7	36±1.8
Nocturnal secretion	Time	1	2	3	4	5
	Value	70±2.2	82±2.2	98±2.8	87±2.3	65±1.2
(b) Remission periods						
Diurnal secretion	Time (h)	8	9	10	11	12
	Value (ng/mL)	14±1.3	15±1.1	12±1.1	10±0.9	12±0.2
After TRH test	Time	8	9	10	11	12
	Value	50±2.6	44±2	46±1.1	42±1.4	32±1.4
Nocturnal secretion	Time	1	2	3	4	5
	Value	22±0.9	34±1.2	26±1.2	28±1.3	16±0.5

attack/day to >30 attacks/hour [2]. The attacks predominate during the daytime, nocturnal attacks being seldom reported [3]. The pathophysiology of this headache form is still unknown [4], though functional magnetic resonance imaging (fMRI) studies in spontaneous attacks have demonstrated activation of the ipsilateral hypothalamic grey [5]. We described a new case linked to adenoma pituitary gland with some unusual characteristics which will extend our knowledge of the full spectrum of this disease.

Case report

A 32-year-old woman was admitted to our observation in April 2004 because of recurrent short attacks of severe ocular and periocular pain. Her short-lasting pain episodes had started about two years earlier (April–May, 2002), were strictly on the right side, accompanied by ipsilateral conjuctival injection, tearing and nasal congestion. Her personal history had been positive for oligo-amenorrhoea for about three years. The characteristic of the present case was that headache attacks always occurred during sleeping hours, approximately between 2:00 and 5:00 a.m.. Occasionally a pain-free period of 3–4 months was reported. Duration of the headaches was 30–100 s, with frequency raging from 10–20 attacks per night, interfering with sleep and with quality of life. The general and neurological examination was normal. Cranial and sella-turcica magnetic resonance imaging (MRI) with gadolinium showed a pituitary gland micro-adenoma (Fig. 1). The polysomnographic studies, recorded during nocturnal episodes, did not show any abnormality. The diurnal rhythmicity secretion of serum prolactin (PRL), luteinising hormone (LH), follicle-stimulating hormone (FSH), oestradiol, progesterone, T3, T4, thyrotropin (TSH) and TSH response to thyrotropin-releasing hormone (TRH) test were studied for two consecutive days during active headache period (Table 1a). The patient was admitted to the hospital in the early morning on the 1st day of the study. At least 1 h before the first blood sampling an indwelling catheter was inserted into an antecubital vein. The blood samples at night were drawn in dim light. Blood samples were drawn every 1 h in the 24 h for two consecutive days. The patient was asked to take notes in a diary on time and duration of attacks. The same valuations were effected for two consecutive days two months later, during clinical remission period (Table 1b). The hormonal, haematological, serological and biochemical investigations did not reveal abnormal findings during the daytime; otherwise only in the symptomatic nocturnal period were headache attacks often associated with increased serum PRL levels (Fig. 2). PRL responses increased after TRH test, but did not induce severe attacks. Nocturnal PRL level was higher than maximum values after TRH test, and no significant differences between active period and remission were observed. The patient was given cabergoline 0.5 mg/week. The dopamine-agonist dose was

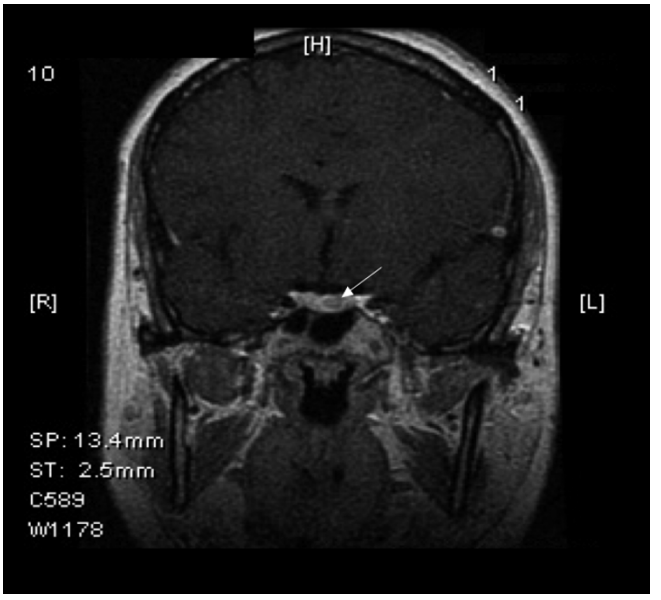

Fig. 1 MRI scan with contrast of the brain showing a micro-adenoma pituitary gland

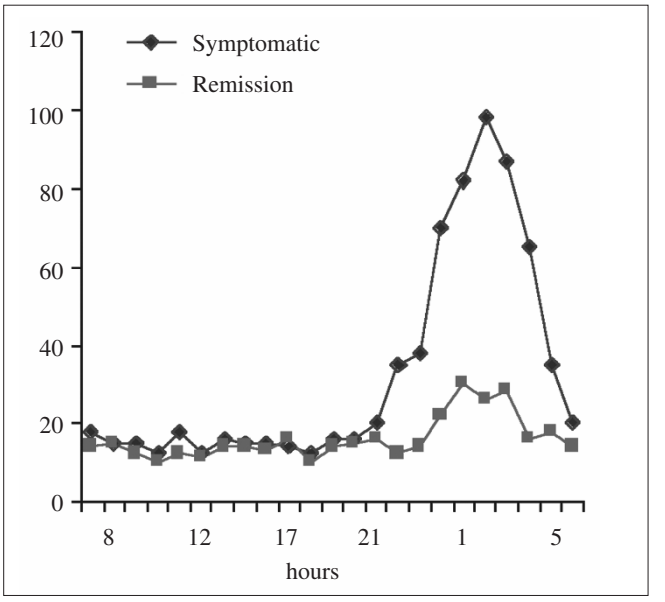

Fig. 2 Mean values of PRL in the 24 h during symptomatic and remission periods

thereafter elevated to 1 mg/week. The headaches were resolved completely within 4 months.

Discussion

Among the neuro-endocrinological alterations, disorders of the hypothalamic–hypophysial axis are believed to be implicated in the pathogenesis of several headache syndromes [6]. PRL was first measured in patients already suffering from chronic headaches. Here we present a woman with SUNCT linked to pituitary micro-adenoma, who was found to have increased nocturnal levels of PRL. We found that the rise of serum PRL during attacks was not accompanied by a TSH rise. This case, along with other similar reports in the literature, supports the hypothalamic connection to this trigeminal autonomic cephalalgia [7]. The pathophysiology of SUNCT is unknown, though fMRI studies in attacks have documented activation of the ipsilateral hypothalamic grey [5]. Some authors suggest a hypersensitivity of dopamine receptors based on the observation that some headaches showed higher PRL after taking dopaminergic agents [8]. Reduced responsiveness of pituitary lactotroph cells to the action of dopaminergic agents has also been postulated [9]. Other authors suggested a serotoninergic hyperfunction rather than dopaminergic dysfunction. Serotonin is known to increase PRL secretion and decrease TSH secretion [10]. Therefore, dopaminergic hypofunction could be the consequence of serotoninergic hyperfunction, because of the inhibitory effect of serotonin on dopamine neurons. In fact, in patients with SUNCT the treatment with dopamine-agonists can determine various responses, with worsening in some cases [7] and improvement in others [11, 12]. Most cases of SUNCT syndrome are primary but several cases of SUNCT are secondary and occur in patients with pituitary tumours, further supporting involvement of the hypothalamic–hypophysial axis. There are seven cases reported of SUNCT syndrome secondary to pituitary adenomas in the medical literature, of which four cases had prolactinomas [10–12], two non-secreting macro-adenoma [13, 14] and one case had micro-adenoma linked to acromegaly [15]. In all the case reports with prolactinoma, the tumour was ipsilateral to the side of the attacks, producing a possible mass effect or mechanical mode of action, which may have played a role in SUNCT onset. Nevertheless, even if a mechanical mode may be a plausible mechanism for the headache in the cases of pituitary macro-adenomas and cavernous sinus invasion, it is not an acceptable explanation for the attacks in micro-adenomas.

A few studies reported how patients with micro-adenoma may suffer from severe headache, while patients with macro-adenoma may not have headache. This suggests that mass effect of the tumour is not correlated to the presence or intensity of the headache [11], but rather the headache syndromes may result from alterations in the neuro-endocrine system. Recently, in the case reported by Rozen, the complete cessation of headaches after the

removal of an acromegalic micro-adenoma was documented, suggesting a potential role also for GH in SUNCT pathogenesis [15]. Indeed, the neuro-endocrine mechanism could be an important factor in triggering and aborting headaches, supported by the result of studies regarding the analgesic effect of somatostatin analogues [16]. Moreover, a study documented low levels of serum testosterone in a case of SUNCT, in which clomiphene citrate therapy induced a significant rise of testosterone values and led to a remarkable decrease of the SUNCT attacks [17].

In the present case, as the tumour was located in the pituitary left side while the pain affected the right side and in view of the relatively small size of lesion, a mechanical origin for headaches is not plausible [18], so the neuro-humoral mechanism influence can be suggested. The mean observed values of the nocturnal serum PRL, evaluated on two consecutive days, were significantly higher during the symptomatic period and lower during remission phases. It is supposed that prolactinomas have abnormal secretory behaviour associated with lactotrope neoplastic transformation and/or isolation of tumour cell mass from normal hypothalamic controls, with a consequent irregular PRL secretion pattern [19, 20]. Nocturnal attacks have been described in patients with SUNCT [3], nevertheless attacks exclusively during the night-time are an unusual expression, never before described in other papers. Basal serum levels of LH, FSH, progesterone, oestradiol, cortisol, ACTH, GH, T3, T4, TSH and TRH test were normal and there were no difference between active and remission period. Moreover, excluding amenorrhoea, there were no documented clinical signs related to other endocrine disorders. It is difficult to establish a clear relation between the high levels of PRL and triggering headache attacks. One hypothesis is that PRL could contribute to the development of certain pain disorders, possibly including neuro-modulation processing of sensory neurons in the trigeminal ganglia [21]. Indeed it is documented that receptors of PRL are also situated in trigeminal ganglia in rats [22]. Moreover, as the increased secretion of PRL after the TRH test is not linked to pain, we suppose the occurrence of a PRL critical value above which headache attacks occur. Nevertheless, a larger number of patients would be necessary to confirm this hypothesis. Therefore in this case even sleep could play a role in the manifestation of the attacks. A temporal connection between attacks and REM sleep has also been suggested, but no formal data are available to correlate the attacks with REM or other stages of sleep. It has been shown that serum PRL levels tend to rise with the cessation of REM and they are higher during non-REM sleep [23]. In our case, the attacks occur with variable frequency and polysomnographic studies showed these attacks occurred during all sleep stages, including REM sleep. There was a clear temporal relation between headache attacks and REM in only 8 out of 42 attacks. As the headache and amenorrhoea were almost coincident in our patient and considering that medical treatment of the prolactinoma led to a resolution in headache symptoms, this strongly indicates that the hyperprolactinaemia plays a central role in triggering the headache, rather than being a coincidental pathology. We propose that nocturnal PRL levels should be evaluated in all patients who suffer from nocturnal SUNCT attacks, even in the presence of average basal values or normal PRL values after TRH test. In addition, a larger screening of patients with SUNCT by basal hormone measurements could be useful, including LH, FSH, oestradiol, progesterone, T3, T4, TSH, cortisol, ACTH, testosterone and GH. The possible influence of altered regulation of PRL, of sleep, of serotoninergic and dopaminergic mechanism, and the influence and interactions of all the hormones would provide further clarity.

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