

Circadian elevation of IL-6 levels in Muckle–Wells syndrome: a disorder of the neuro-immune axis?

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Summary

Muckle–Wells syndrome (MWS) is a rare autosomal dominant hereditary disorder characterized by chronic recurrent urticaria, arthralgia, sensorineural deafness, and in some cases nephropathy due to amyloidosis (AA type). We report a 21-year-old

woman and her father, both suffering from this syndrome, in whom elevated serum levels of IL-6 could be documented during the flares of urticaria, and discuss the relevance of this finding for MWS.

Introduction

Since the first description of urticaria, deafness and amyloidosis as a hereditary syndrome in nine members of a Derbyshire family by Muckle and Wells 1962,¹ about 100 further cases, partly familial but also sporadic, have been reported in the literature.^{2,3} Though most of them correspond to what has become known as the Muckle–Wells syndrome (MWS), some of the sporadic cases in particular have probably been confounded, mostly with the CINCA (chronic infantile neurological, cutaneous and articular) syndrome;⁴ for example, the patient of Linke *et al.*⁵ MWS is an autosomal dominant hereditary disorder with incomplete penetrance, consisting of chronic recurrent urticaria, often combined with fever, chills, rigors, malaise and aching pains in the limbs. It leads to progressive sensorineural deafness, and in about one third of the patients, to amyloidosis of the kidneys as well as of other organs.³

Methods and results

A 21-year-old woman of Swiss ancestry suffered from chronic recurrent urticaria from her day of birth onwards. Her urticaria predominantly affects the trunk and the limbs, is non-pruritic and seems to follow an 'internal clock', beginning in the early

afternoon, culminating in the late evening, and then fading away during the night. It is often associated with fever, chills, rigors, malaise and aching pains in the limbs, symptoms which are usually most prominent on Mondays. During the morning there are absolutely no symptoms. The patient could not define any triggering factors, apart from fatigue and hot sunny weather. At the age of seven, an audiogram revealed mild sensorineural deafness, but her parents refused further investigations because the father, suffering from identical symptoms and showing a constantly raised ESR, otherwise felt completely healthy. It was not until the age of 19 that she presented at our out-patient clinic searching for an explanation of her chronic urticaria. Based on her personal and family history, MWS was assumed.

Laboratory investigations disclosed a raised ESR (45 mm/h), CRP (58 mg/l), and complement activity (CH 50 = 464 E/ml), mild normo- to hypochromic anaemia with low to normal ferritin and serum iron, leucocytosis of up to $11.7 \times 10^9/l$ with normal differential count, thrombocytosis of up to $453 \times 10^9/l$ and elevated cortisol levels. Lymphocyte subpopulations (B, T and NK cells), as well as the CD4/CD8 ratio, were normal. Of the T cells, 2–3% were activated (CD3⁺ HLADR⁺). Total serum protein levels were 82.4 g/l with elevated α_2 globulins in

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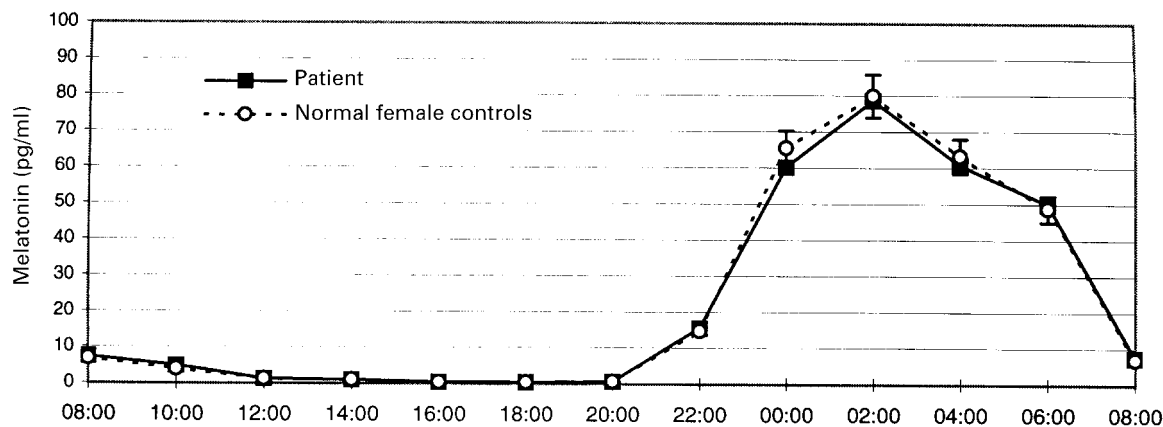


Figure 1. Mean (\pm SE) plasma melatonin sampled at 2-h intervals in the MWS patient and in 10 normal female controls (mean age 22 years, range 18–24).

electrophoresis. In the presence of urticaria, serum fibrinogen was slightly elevated and the reptilase test slightly prolonged, while thrombin time I was shortened. Thromboplastin time and activated partial thromboplastin time were normal. At the climax of the urticaria, cortisol levels were elevated (up to 700 nmol/l) and ACTH levels inversely suppressed (<1.0 ng/l). The dexamethasone suppression test with 1 mg revealed a fasting cortisol level of 42.7 nmol/l, ruling out a Cushing syndrome. The circadian profile of melatonin corresponded to the patient's age (Figure 1). The following laboratory parameters were also within normal limits: urea, creatinine, creatinine clearance (74 ml/min), potassium, liver function tests, triglycerides, total cholesterol, C3, C4, C3dg and the C1q-binding assay. Based on the clinical picture and these laboratory data, our patient fulfilled the criteria of MWS.

Because MWS has features of an inflammatory disorder, and to gain insight into the pathogenesis of the disease, we measured several cytokines, i.e. IL-1 α , IL-4, IL-6, IL-12, TNF- α , interferon- α ,

MIP-1 α and SCF (R&D Systems) in serum samples taken on three consecutive days at 7.30, 12.00 and 18.00 h. Among the cytokines quantified, only IL-6 was elevated. Most striking was the fact that high levels of IL-6 (up to 91 pg/ml) were found in the evening samples, but not in the samples taken in the morning and at noon. We therefore monitored IL-6 levels over 24 h in samples taken at 2-h intervals, clearly confirming the circadian elevation of IL-6 (Figure 2). During this period the patient exhibited unusually few symptoms, and the IL-6 levels were accordingly low. Unfortunately, she refused a second session of continuous blood sampling. Her father exhibited a similar isolated IL-6 elevation (up to 20 pg/ml) in the evening.

Discussion

IL-6 is a pleiotropic cytokine produced by a large variety of cell types and acting on a wide range of tissues.⁶ In our patient the increase in IL-6 levels

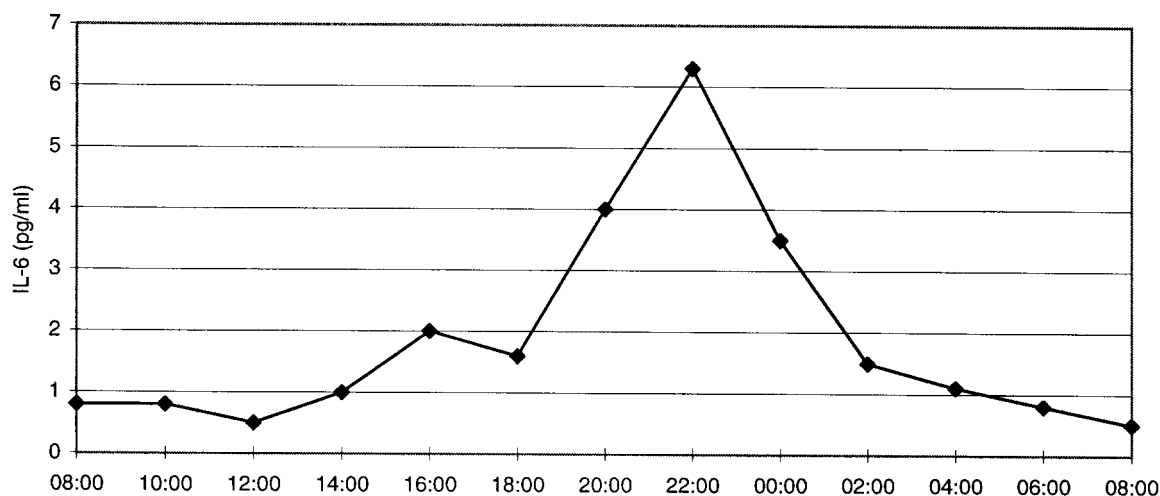


Figure 2. Circadian profile of IL-6 levels in the MWS patient.

could explain the increase in acute-phase proteins such as CRP and fibrinogen with associated raised ESR, as well as leucocytosis and thrombocytosis.⁷ Since IL-6 is known to function as an osteoclast activating factor,⁸ it is conceivable that the sensorineural deafness results from the destruction of the Corti-organ, as reported by Muckle and Wells in two patients.¹ However, fever, chills, aching limb pains and probably also urticaria may be due to an indirect effect of IL-6 or an additional unknown mediator. Little is known about the effect of cytokines on mast-cell function and mediator release and accordingly, the pathogenesis of most forms of chronic urticaria is unknown. Among a large number of cytokines, including IL-6, tested *in vitro*, only SCF was able to activate mast cells.⁹ We also tested whether intradermal injection of autologous serum, collected in the morning and evening, could elicit a weal and flare reaction, but the results were negative. Although the elevated levels of IL-6 may be involved in the pathogenesis of amyloidosis through the chronic induction of acute-phase proteins, the fact that only about one third of patients with MWS develop amyloidosis could point to additional causative factors.

The production of IL-6 is part of the stress response of many cell types and is triggered by immunological, chemical and physical stimuli as well as by several proinflammatory cytokines. The fact that MWS is a hereditary disorder and that the symptoms of this patient were present since birth indicates that the elevation of IL-6 is due to an endogenous factor (or factors). Furthermore, the striking circadian pattern suggests a disturbance in the neuro-endocrine-immune axis. The melatonin rhythm is produced by the vertebrate pineal gland and is thought to be generated by a biological (circadian) clock in the suprachiasmatic nuclei of the anterior hypothalamus. The rhythm is entrained to the 24-h period by the daily light-dark cycle, with hormone levels increased at night (Figure 1). Interestingly, exogenously administered melatonin can entrain circadian rhythms, can change the phase of the endogenous melatonin rhythm, and facilitate reentrainment of circadian rhythms.¹⁰ Thus, melatonin may modulate the entrainment process in humans and be useful for treating circadian rhythm disorders. In our patient, however, the 24-h melatonin profile presented a normal circadian pattern for an adult female (Figure 1) and the administration of melatonin for 1 week (5 mg per day, given at breakfast) did not influence the time pattern of symptoms. Therefore the mechanism inducing the diurnal elevation of IL-6 could not be identified. An attractive candidate linking the neuro-endocrine system with the innate immune system would be the migration inhibitory factor (MIF). MIF is known to

be stored and released in the pituitary gland and induces the production of proinflammatory cytokines, including IL-6, by monocytes.¹¹ It will be interesting to study MIF levels in MWS patients, once a suitable assay is available.

Since a specific treatment selectively reducing IL-6 *in vivo* is not yet available, short-term therapeutic trials including different types of antihistamines and NSAIDs, nifedipine, pentoxifylline, theophylline, colchicine, dapsone, disodium cromoglycate, urso- and chenodeoxycholic acid, prednisone and even thalidomide have been conducted. Dapsone and thalidomide delayed, urso- and chenodeoxycholic acid as well as small doses of prednisone weakened, but only high doses of prednisone (50 mg/day) suppressed the urticaria and associated symptoms.

In conclusion, we find elevated IL-6 levels with a striking circadian pattern in two patients with MWS. To our knowledge, this is the first report of such a prominent circadian expression of an isolated cytokine due to a hereditary disorder.

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