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Dopamine-deficiency-enhanced hyperthermia and rhabdomyolysis during a heat wave in a metachromatic leucodystrophy heterozygote with metabolic myopathy

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Abstract

Whether a dopamine-deficiency syndrome in a Parkinson-syndrome (PS) may occur more easily during a heat wave than during more temperate climate conditions is unknown. We report a case that may suggest this.

A 56 yo male with heterozygosity for metachromatic leucodystrophy and a history of metabolic myopathy, PS and diabetes experienced worsening of the PS during a heat wave. His condition further deteriorated upon reduction of ropinirol, resulting in hyperthermia, respiratory insufficiency, rhabdomyolysis, and severe thrombocytopenia. One month later he was alert but tetraplegic and required ventilatory support. Hyper-CK-emia returned to similar levels as before rhabdomyolysis.

Reduction of dopamine agonists during a heat wave may induce a dopamine deficiency syndrome with hyperthermia, rhabdomyolysis and thrombocytopenia.

Key words: Heat wave; hyperthermia; hyperpyrexia; dopamine-deficiency; metabolic myopathy; hyper-CK-emia; leucodystrophy; heterozygote.

Introduction

There are several reports indicating that patients with Parkinson syndrome (PS) are at risk to develop complications during heat waves (1, 2). Whether these patients are also prone to develop dopamine-deficiency syndrome easier during a heat wave than during more temperate climate conditions, as in the following case, is unknown.

Case report

The patient is a 56 yo Caucasian male, height 174 cm, weight 75 kg, with a history of strabismus surgery in childhood, chronic alcoholism between age 32y after his divorce and age 50 y, type 2 diabetes since age 50 y with HbA1c-values of up to 14.6, and PS since age 50 y with an Unified Parkinson Disease Rating Scale (UPDRS) score of 31. The beta-CIT SPECT at age 50 y revealed a blurred delineation of the basal ganglia bilaterally with a ratio basal ganglia/cerebellum of 2.8 3 h after tracer application. The family history was positive for diabetes (mother, brother of mother), adult metachromatic leucodystrophy (father), arterial hypertension (mother), and mild cognitive impairment (mother). He had no children but a half brother (same father) who was healthy. Initially, PS was only treated with pramipexole with a prompt effect. At age 52 y he developed micrographia, hypokinesia, mild gait stepping, and recurrent falls with an UPDRS of 18. He was thus switched to ropinirole and biperiden. At age 54 y he was in a Hoehn & Yahr stage 2. Cerebral MRI showed non-specific white matter lesions on T2-weighted images. From age 52 y on he developed paresthesias in the distal lower limbs and muscle pain and cramps in lower limb muscles. Since at least age 54 y recurrent blood samples showed hyper-CK-emia up to 308 U/l. Shortly before admission he was on a therapy with ropinirole (17 mg/d), L-dopa (4 × 100 mg/d), selegiline (5 mg/d) and biperiden (2 mg/d). He also received zolpidem (5 mg/d) at night.

During a heat wave in July 2010 (Fig. 1) PS worsened and he developed dyskinesias, general dystonia, dysarthria, more frequent falls than before, reduced verbal communication, and voiding urgency. Hence, ropinirole was reduced to 14 mg/d ten days before admission. Because of further deterioration, ropinirole was further decreased to 9 mg/d four days before admission. One day before admission the patient was advised to increase L-dopa to 100 mg every two hours. On the day of admission the patient became unable to walk, moved only by crawling, and developed shivering of the lower limbs, elevation of body temperature, and vomiting one hour before admission. On arrival at the emergency department

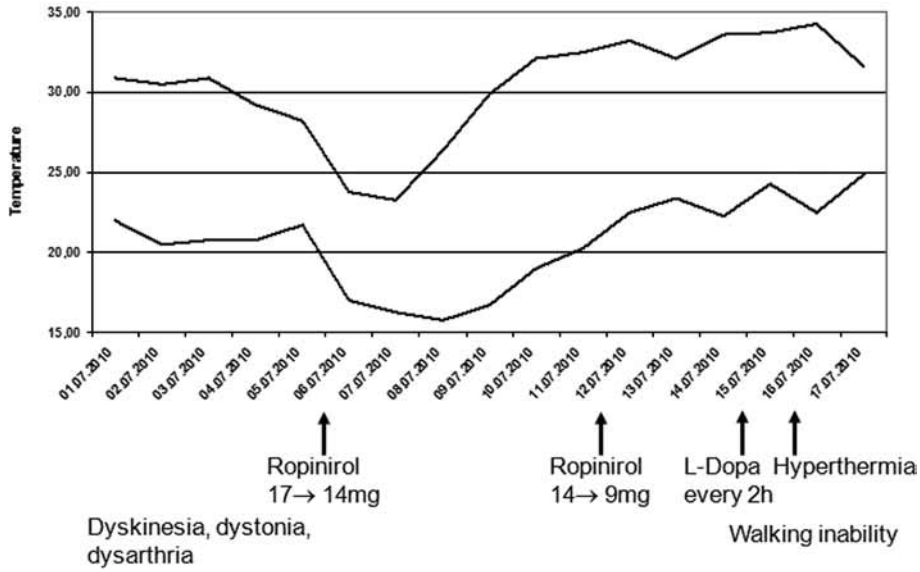

FIG. 1. — Highest and lowest day temperatures two weeks before admission

he became respiratory insufficient and required intubation and mechanical ventilation.

On admission at the intensive care unit he had a sinus rhythm of 149/min and a body temperature of 42.7°C. Laboratory parameters were unremarkable except for slightly increased CRP and creatine-kinase (Table 1). Imaging studies of the cerebrum showed only the previous non-specific white matter lesions and a hyperintensity in the right lenticular nucleus. CSF investigations revealed 7 cells/mm^3 (n: < 12), lactate at 2.22 mmol/l (n: < 2.1 mmol/l), and a protein level of 48 mg/dl (n: 18-43 mg/dl). Since infection and other causes of hyperthermia were excluded, cooling with cool bags and the Cool-Garth system was started resulting in normalization of the body temperature within 6 hours. On hospital day (hd) 2 he developed transient but severe thrombocytopenia with a minimal value of 18 (Table 1). Creatine-kinase further increased, reaching the highest value of 11747 U/L on hd7 (Table 1). All anti-Parkinson agents were discontinued since admission but after three days amantadine and L-dopa were restarted. After discontinuation of all sedating medication the patient was alert but presented with severe weakness and still required noradrenaline and mechanical ventilation. Nerve conduction studies revealed severe axonal polyneuropathy and needle-EMG signs of acute denervation. CSF-investigations at hd17 revealed 2 cells/mm^3, lactate at 1.94 nmol/l and protein at 244 mg/dl. Guillain-Barre-syndrome (GBS) was suspected and IVIGs were started without effect. Subsequently, plasmapheresis was also ineffective. The aryl-sulfatase serum level was slightly decreased, which was interpreted as reflecting heterozygosity for metachromatic leucodystrophy. Though muscle/nerve biopsy was not carried out. a systemic metabolic defect was suspected, based on the family history, the personal history (PS, diabetes, myalgias, muscle cramps), and the laboratory findings (hyper-CK-emia, thrombocytopenia, elevated CSF protein, elevated CSF-lactate, steatosis hepatis).

Discussion

The cause of hyperthermia (hyperpyrexia) in the presented patient is most likely multifactorial. First, autonomic dysfunction (3, 4) either affecting the central or peripheral sympathetic projections may have contributed to hyperthermia due to denervation of the precapillary sphincters or sweating glands (5). Severe multifactorial polyneuropathy (alcoholism, diabetes, metabolic myopathy) or small fiber neuropathy (6) may have affected vegetative fibers and thus contributed to heat retention due to impaired sweating (7). Second, dopamine-deficiency may have increased endogenous heat production, as has been previously described (8). Third, exogenous increase of the surrounding temperature has contributed to impairment of the heat release and convection from the body.

Development of functional tetraplegia with absent tendon reflexes after admission could be compatible with a rapidly developing critical illness polyneuropathy or myopathy, with Guillain-Barre syndrome, or with worsening of the underlying metabolic

Table 1

Blood chemical investigations during one month since admission

Parameter	RL	hd1	hd2	hd3	hd4	hd5	hd6	hd7	hd8	hd10	hd12	hd14	hd16	hd18	hd23	hd25	hd27
GOT	-34U/l	43	nd	215	364	369	410	nd	404	196	78	nd	nd	38	nd	30	25
GPT	-44U/l	30	nd	243	356	461	458	nd	324	256	171	nd	nd	59	nd	20	18
GGT	-54U/l	85	nd	81	61	76	76	nd	77	83	115	nd	nd	114	nd	16	12
CK	-170U/l	313	1048	753	2061	nd	11117	11749	7762	2810	270	287	166	283	530	nd	129
CRP	-0.6mg/dl	2.9	nd	2.6	4.7	8.8	20.0	nd	14.6	11.6	6.9	4.3	3.6	2.4	1.0	2.2	2.5
Leuko	4.0-9.0/nl	8.8	10.7	14.7	12.5	15.6	13.1	nd	6.7	7.9	8.3	9.0	6.5	7.0	7.0	6.9	5.2
Thrombo	150-450/nl	130	19	18	23	53	89	nd	231	435	480	562	357	257	122	138	149

RL: reference limits, hd: hospital day, GOT: glutamate-oxalate transaminase, GPT: glutamate-pyruvate transaminase, GGT: gamma-glutamyl transpeptidase, CRP: C-reactive protein, Leuko: leukocyte count, Thrombo: thrombocyte count.

myopathy. An argument against critical illness polyneuropathy is that tetraplegia developed shortly after admission and that risk factors such as steroids or antibiotics were not given at that time. Arguments against GBS are that he had no previous infection and that immunoglobulins and plasmapheresis were ineffective. Most likely metabolic myopathy worsened due to hyperthermia or the drugs administered during hospitalisation, as has been reported previously (9). Heterozygosity for metachromatic leucodystrophy is unlikely the cause since these patients are usually asymptomatic, but the metabolic myopathy possibly had an aggravating effect.

That the patient was a symptomatic heterozygote of an adult metachromatic leucodystrophy was excluded because of the only slightly reduced arylsulfatase levels and the autosomal recessive transmission of the disease, allowing only homozygotes to develop the full picture of the disease. According to the literature, heterozygotes do not manifest phenotypically except for slightly decreased arylsulfatase (10). Severe thrombocytopenia could be explained by the hyperthermia but lack of previous reports describing such a relation argues against this assumption. A second explanation could be worsening of a preexisting thrombocytopenia from a metabolic defect due to the hyperthermia or an adverse reaction to a drug. Most likely, PS worsened due to the heat wave and reduction of dopamine-agonists resulting in a dopamine-deficiency syndrome, possibly enhanced by the heat wave, the metabolic myopathy, polyneuropathy, or the heterozygous state for metachromatic leucodystrophy.

The case suggests that reduction of dopamine-agonists during a heat wave should be avoided, to prevent the development of a dopamine-deficiency syndrome with hyperthermia, rhabdomyolysis and thrombocytopenia. To which degree metabolic myopathy and heterozygosity for metachromatic leucodystrophy contributed to the poor outcome remains speculative.

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