Hepatitis C Infection and Thyrotoxic Periodic Paralysis—A Novel Use of an Old Drug

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ABSTRACT: Hypokalaemic thyrotoxic periodic paralysis is an enigmatic and uncommon condition which occurs exclusively in males of Asian descent. The underlying causes of thyrotoxicosis may be any of the well-recognized etiologies including a toxic multinodular goiter, Graves' disease or iodine excess. Beside thyrotoxicosis, a number of other hormonal factors have been hypothesized to contribute to hypokalaemic thyrotoxic periodic paralysis, particularly postprandial hyperinsulinaemia and testosterone. We hereby present a case of a 48-year-old hepatitis C positive gender-assigned man in whom all of these factors are proposed to interact, lending further support to these hypotheses. The patient presented with interferon-induced thyroiditis causing acute generalized weakness whilst undergoing combination interferon-α-2β and ribavirin therapy. As part of his hepatitis C infection, marked insulin resistance with hyperinsulinaemia was also present, exacerbating the paresis. Initial treatment with beta-blocker failed to normalize his serum potassium concentration, requiring the novel use of spironolactone, despite euthyroidism. This continued to be required until his testosterone supplement dissipated. **KEY INDEXING TERMS:** Hepatitis C infection; Hypokalemia; Thyrotoxic periodic paralysis; Spironolactone. **[Am J Med Sci 2008;336(6):515–518.]**

Clinical Course

A 48-year-old Filipino gender-assigned man presented with acute onset of quadraparesis after breakfast one morning. He had been generally well until the event. There were no respiratory symptoms or sphincter disturbances. System review showed recent weight loss of about 6 kg over 3 months with general lethargy and tiredness. No cardiovascular or gastrointestinal symptoms were forthcoming. His medical history included hepatitis C infection, chronic alcoholism (ceased 5 years prior), ex-smoker of 10 years, and gender reassignment since 19 years of age from female to male. His hepatitis C was of genotype 2, contracted from intravenous drug use in his early 20s. He was in the 18th week of his combination pegylated interferon-α-2β and ribavirin treatment for his hepatitis C infection. His major reactions to this therapy included emotional lability, listlessness, and mild anemia which required no intervention. Other medications include testosterone implants at 800 mg every 6 months, last given 4 weeks prior. The patient denied any use of alternative or over-the-counter medicines. There was no family or prior personal history of thyroid disease. Clinical examination showed a well-masculinized patient, weight of 65 kg, height of 1.64 m (body mass index of ~24 kg/m^2). Blood pressure was 140/70 mm Hg with no postural drop and resting regular pulse rate of 100 beats per minute. Peripheral stigmata of thyrotoxicosis were present. His Achilles tendon reflexes were absent, despite the Jendrassik manoeuvre. No goiter or ophthalmopathy was detected. Respiratory examination was unremarkable. The bedside peak expiratory flow rate was ~350 L/min. Electrocardiogram showed sinus rhythm with a rate of 104 beats per minute.

Laboratory test results are shown in Tables 1 and 2. Note that his serum potassium level was 1.8 mmol/L. A 3-hour oral glucose tolerance test with insulin levels was performed 7 days after presentation. The thyroid pertechnetate uptake was absent at 0% uptake at 6 hours, consistent with the diagnosis of biphasic interferon-induced thyroiditis.

The patient was treated with 240 mg of oral propanolol (at 3 mg/kg) followed by 80 mg thrice daily. At 1 hour, his hypokalemia remained unchanged at 1.9 mmol/L and only slightly improved to 2.3 mmol/L at 4 hours. At 8 hours, it remained static at 2.4 mmol/L. The patient had a slight improvement in symptoms although he felt weak and could only walk with 1 person assisting. His tendon reflexes remained absent, and his peak expiratory flow rate had decreased to 300 L/min. At 24 hours, his serum potassium level remained low at 2.5 mmol/L with no further improvement of symptoms. His propanolol

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Table 1. Summary of the Patient's Laboratory Test Results

	Results	Reference Intervals
Random glucose level	5.7	5.5–7.8 mmol/L
pH	7.39	7.35–7.45
Po_2	109	>75 mmHg
Pco_2	32	35–45 mmHg
Bicarbonate	38	35–45 mmol/L
Base excess	−1	±2
Anion gap	14	7–15 mmol/L
Sodium	142	136–146 mmol/L
Potassium	2.1	3.5–5.5 mmol/L
Urea	9.1	3.0–7.0 mmol/L
Creatinine	90	40–90 μmol/L
Bilirubin	18	6–10 μmol/L
Alanine aminotransferase	55	<50 IU/L
Alkaline phosphatase	136	<110 IU/L
Gamma glutamyl transpeptidase	25	<60 IU/L
Albumin	38	35–45 g/L
Hemoglobin	158	115–165 g/L
Neutrophil count	11.7	$4.0–7.0 \times 10^6$ per mL
Platelet	289	$150–450 \times 10^6$ per mL
Thyrotropin	<0.03	0.4–4.0 U/L
Free tetra-iodothyronine	72.8	10.5–24.5 pmol/L
Free tri-iodothyronine	21.94	3.3–6.2 pmol/L
Antithyroglobulin titre	<1	$<4 \times 10^2$
Antimicrosomal titre	64	$<4 \times 10^2$
Serum testosterone	15.4	<2.1 nmol/L; for adult females 10.5–21.5 nmol/L; for adult males
Serum sex hormone binding globulin	12	10–50 μg/L

Note that testosterone reference ranges for both adult males and females have been included.

was increased to 120 mg thrice daily and as a result his heart rate decreased to 54 beats per minute. Given that his gender reassignment history with testosterone supplementation may have played in exacerbating his hypokalemia, spironolactone was empirically given at 400 mg daily. At 48 hours his potassium level was 3.2 mmol/L, and at 60 hours 3.8 mmol/L. The patient felt that his leg strength had improved and was able to mobilize short distances unaided. At 72 hours his potassium level was 4.0 mmol/L. No potassium supplement was given at any stage and spironolactone was continued unchanged.

Table 2. The Patient's 3-hour Oral Glucose Tolerance Test Which Demonstrated Impaired Fasting Glycemia, Insulin Resistance (the Homeostasis Model of Assessment Index is 8.8, Which is Moderately High)

Relative Times	Serum Glucose (mmol/L)	Serum Insulin (mIU/L)	Potassium (mmol/L)
0	5.8	34	3.8
60	10.9	108	3.5
120	7.8	119	3.3
180	6.0	112	3.2

The test was aborted at 180 minutes due to progressive decline in potassium level and the risk of redeveloping generalized weakness.

His thyroiditis was treated expectantly according to the natural progression of the disease. Four weeks later, his potassium level remained stable at 4.3 mmol/L despite ongoing spironolactone use. Thyroid function tests showed a free T4 level of 24.5 and a free T3 level of 5.8 pmol/L, with suppressed thyroid stimulating hormone. He continued to require spironolactone despite the attainment of euthyroidism, as his potassium level dropped to 3.0 and 3.2 mmol/L on 2 occasions when this medication was temporarily withheld. His potassium level became progressively elevated to 5.8 and 6.2 mmol/L when his testosterone levels began to wear off, necessitating a reduction and subsequent removal of the spironolactone. Figure 1 summarizes the relationship between his serum potassium concentration, free T4 level and testosterone level. It is noteworthy that the potassium level increase was only possible after the testosterone effect had worn off. His interferon therapy was discontinued at the development of thyroid disease. When last reviewed, he remained euthyroid and was not on any medication.

Discussion

Hypokalaemic thyrotoxic periodic paralysis (HTPP) is an uncommon condition that is spreading beyond its traditional geographic Asian areas due to increased migration and ease of transport.[1] Adding this to the prevalence of hepatitis C, especially in developing countries, the development of this particular case scenario is not unexpected. HTPP in the setting of hepatitis C infection has been described previously but in association with Graves' disease.[2,3] Thyroid disease is the most common endocrine-related problem associated with hepatitis C and interferon-γ treatment. As part of this spectrum, Graves' like thyrotoxicosis has been described, but thyroiditis of a biphasic nature is more common.[4] In the absence of any other discernable causes, and through unknown mechanisms, the thyrotoxicosis leads to hypokalemia with subsequent paralysis in genetically predisposed patients.[5] Whilst many thyrotoxic conditions have been previously described to be associated with HTPP, this is the first case report to describe it in associated with interferon-γ induced thyroiditis in patient with hepatitis C infection. The course of thyroiditis, in this situation, unfortunately cannot be modified by any therapy. Prednisolone has little place in the treatment of thyroiditis[6] and may indeed exacerbate the hypokalemia, further aggravating the clinical state.[7] Potassium supplements are effective in alleviating the hypokalemic symptoms but rebound hyperkalemia is often a problem once the patient is rendered euthyroid.[8] Beta-blockers such as labetolol or atenolol have been employed effectively in the acute hypokalemic phase