Thyrotoxic Periodic Paralysis

Dear Sir;

The report by Akar et al. [1] regarding hypokalaemic thyrotoxic periodic paralysis (HTPP) in a Turkish male is a timely reminder for the practising physicians about this interesting condition. This condition is both frightening to the patients and perplexing to the doctors.

Due to its similar clinical resemblance to the autosomal dominant Familial Hypokalaemic Periodic Paralysis (FHPP), mutation analyses have been performed to see if a similar situation exists at the molecular level. The mutations for FHPP have been linked to three mutations in the calcium channel alpha-1 subunit (CACN1AS) [2 – 4], one in the sodium channel alpha subunit (SCN4A) [5] and one in the human skeletal muscle voltage-gated potassium channel (KCNE3) [6], none of which has been detected in HTPP patients. A solitary HTPP case in a patient of Portuguese descent in whom KCNE3 mutation has been described [7] but it is still probable that this particular patient has coexisting HTPP and FHPP, as previously reported in the same group of patients [8]. Kung et al. [4] also failed to detect any association with the microsatellite markers that mapped to chromosome 1 where the genes for the α-1, α-2 and β-1 subunits for the Na-K-ATPase pump are located. Hence the exact genetic mutation and inheritance are yet to be determined but the disease can be almost viewed as an X-linked recessive condition with such a male preponderance because all the genes investigated so far are located on the non-X chromosomes.

The case is interesting in that the paralytic crisis can remit rapidly and spontaneously suggesting that there must be factors, other than the excessive thyroid hormone levels, influencing the Na⁺-K⁺-ATPase pumps and thus dictate a rapid shift of K⁺ across the cellular membrane. This process is clearly much shorter than the 7–10 day half-life of tetra-iodothyronine (T4) [9]. A possibility is the association of three novel single nucleotide polymorphisms (SNPs) in CACN1AS recently detected in HTPP [4]. These SNPs lie at or near the thyroid hormone response element and can modulate the binding of thyroid hormone on the calcium channel and thus account for the discrepancy between the rapid remission of the paralysis and the physiological long half-life of T4. The complete pathogenesis remains poorly understood however.

Consideration should also be given to a higher dose of propanolol as up to 4 mg/kg [10] may be required to prevent the K⁺ transmembrane flux and hence clinical symptoms. The effect of non-selective β-blockade on K⁺ kinetic (β₁ receptor dependent) is expected to parallel heart rate (β₂ receptor dependent), which can be used to monitor the adequacy of therapy.

It is critical that the patient is rendered euthyroid prior to radioactive iodine-131 (¹³¹I), particularly in this setting, to reduce/prevent paralytic crises. It is probable that 1 month is inadequate to achieve euthyroidism due the latent effect of carbimazole therapy. This latent effect of thionamide is influenced by a number of factors including the quantity of intra-thyroid hormone storage, the rate of release and the patient’s iodine status. The latency is much longer in an iodine replete patient, a situation unknown in this patient. Thus, it is likely that the paralytic crisis reflects the failure to adequately control the thyrotoxicosis prior to ¹³¹I therapy rather than the radiation thyroiditis effect. Nevertheless, should the latter be true, it is common practice to resume carbimazole 5–7 days after ¹³¹I therapy to prevent any exacerbation of the condition while awaiting the irradiation therapeutic effect.

In the post treatment phase of ¹³¹I therapy, it is worth noting that the underlying genetic abnormality remains and thus when challenged or exposed to exogenous thyroid hormones, the same symptomatology may return. This is particularly important in the replacement therapy of this patient who has developed hypothyroidism and recurrent flaccid paralysis may return if he is over-treated with thyroxine. Hypothetically, the situation may apply also to euthyroid family member(s) who harbor the unknown genetic abnormality but is yet to express the clinical state. However, the place of the T4/T3 challenge test in appropriate family members remains purely speculative at this stage.

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References


