Familial hypokalemic periodic paralysis
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SUMMARY AND CONCLUSIONS

This thesis has been centered around one family with hypokalemic periodic paralysis. Five generations were studied retrospectively and/or prospectively during 8 years (1984-1992).

Hypokalemic periodic paralysis is one of a group of periodic paralyses, which have been described in Chapter 1. This Chapter also gives an outline of the studies which form the subject of this thesis.

After review of the literature about hypokalemic periodic paralysis (Chapter 2) several remarkable points emerged:

a) In this autosomal dominant disease the occurrence of paralytic attacks in the described families was less than 50%. Moreover, the disease could skip generations, without clinical features in these generations.
b) Permanent muscle weakness was thought to occur only after frequent and severe attacks. However, no clear definition of this entity was given and long-lasting abortive attacks were also considered as permanent muscle weakness.
c) No satisfactory non-invasive clinical test was available to confirm the diagnosis.
d) Pathophysiologically an increased conductance to sodium has been considered as the basic defect. Insulin may also be involved, but its role has never become clear.

These points were discussed successively in the following Chapters in relation to the investigated family.

Screening of 120 family members (Chapter 3) revealed 64 patients with hypokalemic periodic paralysis. Only 38 of them suffered from paralytic attacks (60% of the patients and 32% of the investigated family members). The diagnosis in the 26 patients without attacks was made on account of other criteria (see below).

In the 38 patients with paralytic attacks the attacks occurred more often in men than in women. In most patients the attacks stopped after the age of 50 years. Provocative factors for paralytic attacks were stress, exercise, carbohydrate rich meals and cold, all well-known. However several patients also mentioned chinese food, which had not been reported before.

In 5 of the 26 patients without attacks the diagnosis hypokalemic periodic paralysis was made by muscle biopsies, which showed PAS positive vacuoles.

Surface EMG measurement proved to be a valuable and easily applicable tool in making the diagnosis hypokalemic periodic paralysis (Chapters 3 and 4). It showed characteristic changes of mean fiber conduction velocity in 87% of the patients, which were investigated with this method, including 12 without attacks. In these 12 patients this
finding was the criterion on which the diagnosis hypokalemic periodic paralysis was made. The reduced muscle fiber conduction velocity may be considered as a manifestation of the supposed membrane disturbance that underlies this disease. As far as we know today only steroid myopathy and polymyositis show the same reduction in conduction velocity. Using surface EMG in familial screening of hypokalemic periodic paralysis this method is specific, when the above mentioned conditions have been excluded.

Permanent muscle weakness was defined in this study as complaints of difficulties with walking up and down the stairs, being weaker than age-like people, severe walking difficulties or being wheelchair bound. Using this definition permanent muscle weakness was present in all patients at older age, independent of the occurrence of paralytic attacks.

The term permanent muscle weakness in hypokalemic periodic paralysis should be used only when the muscle weakness can not be improved by medication, and is an indication of muscle damage.

Our studies demonstrated that permanent muscle weakness can be diagnosed by dynamometry. Moreover, hypodense lesions on CT scans were found to be indicative of muscle damage, that may be reflected in permanent muscle weakness. In 2 patients CT findings were compared with autopsy specimens. It was found that hypodense lesions on the CT scans correlated with replacement of muscle by fat.

The diagnosis hypokalemic periodic paralysis could be made, if permanent weakness was present in combination with first or second degree relatives (children or grandchildren) with hypokalemic periodic paralytic attacks. This was the case in 9 of the 26 patients without paralytic attacks.

In 2 patients with hypokalemic periodic paralysis autopsy showed no abnormalities in smooth muscle tissue and cardiac muscle (Chapters 3 and 4).

Serum creatine kinase and myoglobin concentrations were increased to a varying degree in all patients with hypokalemic periodic paralysis during routine examination. No difference was found between patients with and without attacks. These increased concentrations can be explained as a consequence of a permanently present muscle membrane disturbance which results in leakage of muscle proteins.

In summary the diagnosis hypokalemic periodic paralysis was made in 64 patients by using the following diagnostic criteria:

- hypokalemia during a paralytic attack (38 patients)
- reduced muscle fiber conduction velocity in surface EMG (12 patients without attacks)
- characteristic findings in muscle biopsy (5 patients without attacks)
- permanent muscle weakness in combination with children or grandchildren with paralytic attacks (9 patients without attacks).
Applying these criteria skipping of generations of hypokalemic periodic paralysis did not occur in our family.

Acetazolamide, known to be very effective in prevention of paralytic attacks was also found to decrease the frequency of paralytic attacks in this family. Its effects on muscle strength, serum creatine kinase and myoglobin were studied in a double-blind study in 7 patients, 4 with and 3 without attacks. A significant increase in muscle strength was found in patients with attacks as well as in those without attacks. No changes in serum muscle enzymes or muscle fiber conduction velocity were found. These findings suggest that acetazolamide does not exert its influence on the primary membrane disturbance (Chapter 4).

Chapter 4 also includes a clinical observation of a patient during a paralytic attack and in the early and late recovery phase. It was remarkable that the normalization of muscle force preceded complete recovery of the muscle membrane excitability, expressed in mean fiber conduction velocity and integrated EMG. This suggests that a partial recovery of the electrophysiological properties after an attack of paralysis is sufficient to generate a normal muscle strength.

The role of insulin in the pathogenesis of hypokalemic periodic paralysis was studied in patients and in normals (Chapter 5). In comparison to normals the patients showed an initial increase in insulin release after glucose loading. The significance of the ATP-sensitive potassium channels, known to be involved in insulin release, was evaluated. For this purpose patients were treated with glibenclamide or pinacidil which represent, respectively, a blocker and an opener of these ATP-sensitive potassium channels followed by intravenous glucose loading. These studies indicated a disturbance of these channels of the beta cell of the pancreas in patients with hypokalemic periodic paralysis, resulting in an increased insulin release.

In conclusion it seems likely that the membrane defect in patients with hypokalemic periodic paralysis is not restricted to the membranes of muscle cells and the ATP-sensitive potassium channels may be involved in the pathophysiological process.