Monogenic models of migraine : from clinical phenotypes to pathophysiological mechanisms

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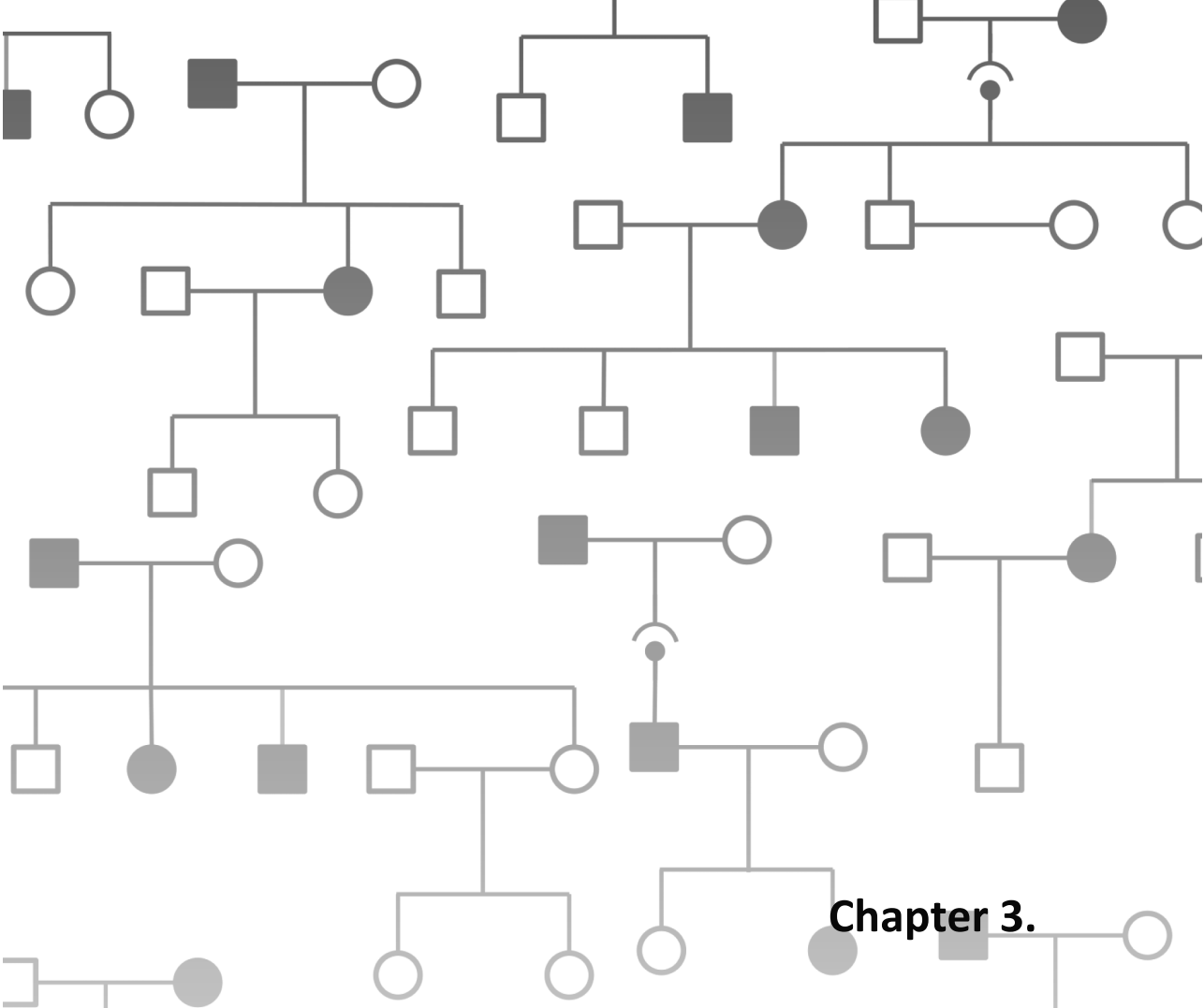

Chapter 3.

Familial hemiplegic migraine treated by sodium valproate and lamotrigine

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Abstract

Background: Familial hemiplegic migraine (FHM) is a rare monogenic subtype of migraine with aura that includes motor auras. Prophylactic treatment of FHM often has marginal effects and involves a trial-and-error strategy based on therapeutic guidelines for non-hemiplegic migraine and on case reports in FHM.

Methods: We assessed the response to prophylactic medication in an FHM family and sequenced the FHM2 *ATP1A2* gene in all available relatives.

Results: A novel p.Met731Val *ATP1A2* mutation was identified. Attack frequency was reduced significantly with sodium valproate monotherapy (n=1) and attacks ceased completely with a combination of sodium valproate and lamotrigine (n=2).

Conclusions: We report dramatic prophylactic effects of sodium valproate and lamotrigine in an FHM2 family, making these drugs worth considering in the treatment of other FHM patients.

Introduction

Familial hemiplegic migraine (FHM) is a rare and severe subtype of migraine with aura. FHM patients experience at least one of the common aura symptoms, such as visual, sensory and dysphasic auras. In addition, attacks include reversible motor auras, varying from a mild paresis to hemiplegia. At least one first- or second degree relative must also suffer from hemiplegic migraine. FHM is genetically heterogeneous, with genetic subtypes FHM1, FHM2 and FHM3. The *CACNA1A* gene associated with FHM1 encodes the pore-forming a1 -subunit of CaV2.1 (P/Q-type) voltage-gated Ca^{2+}-channels.[1] The FHM2 *ATP1A2* gene encodes the a2-subunit of an Na^+/K^+-ATPase, which exchanges Na^+ ions for K^+ ions, creating a Na^+ gradient that facilitates removal of K^+ and glutamate from the synaptic cleft into glial cells.[1] The FHM3 gene *SCN1A* encodes the a-subunit of voltage-gated Na^+-channels.[1] Mutations in the FHM1-3 genes cause an increase in glutamate and K^+ levels in the synaptic cleft, which facilitates cortical spreading depression, the phenomenon that underlies aura symptoms.

Controlled clinical drug trials in FHM have not been performed because of the low prevalence of the disease. Prophylactic treatment of FHM is often difficult, with only marginal effects. A trial-and-error strategy is applied, based on treatment options for non-hemiplegic migraine and on case reports in FHM.[2] Here we report an FHM2 family with a novel *ATP1A2* mutation and a remarkable response to prophylactic treatment with sodium valproate alone and in combination with lamotrigine.

Report of cases

The index patient (Figure 1, I-1) is a 44-year-old male with migraine attacks since age 11 that started with a cold feeling in the face, followed by dysarthria, seeing wave-shaped lights and paresthesia spreading from the fingers to the arm. Subsequently, the arm felt numb and often became paretic or even plegic, followed by headache with photophobia, nausea and vomiting. On average attacks lasted eight hours and all symptoms resolved after a night's sleep. Attack frequency used to vary from weekly to every two months, but at age 38 increased to three times a week. Prophylactic treatment with sodium valproate (500mg b.i.d.) subsequently led to a maximum frequency of one attack per year for eight and a half years so far.

His 15-year-old son (Figure 1, II-4) experienced attacks similar to his father's since age 8. His attacks often started with visual disturbances for about 30 minutes, after which paresthesia and a paresis developed in one hand. His legs were unaffected, as was his speech. Aura symptoms were always followed by a migraine headache, accompanied by phonophobia, severe nausea and vomiting. After three to four hours of sleep all symptoms had usually disappeared. At age 13, attack frequency

increased from four per year to once per week. Sodium valproate (up to 1000mg b.i.d.) reduced attack frequency, but attacks persisted and higher dosages caused intolerable side effects. Add-on treatment with topiramate (30mg b.i.d.) reduced attack frequency by another 50%, but was associated with unacceptable adverse events (weight loss, cognitive dysfunction, fatigue) and was therefore stopped. Subsequently, a combination of lamotrigine 100mg per day and sodium valproate 1000 mg per day ceased attacks completely without any reported side effects. After one year of being attack free, the patient decided independently to acutely stop taking both lamotrigine and sodium valproate. However, he experienced a hemiplegic migraine attack after one week, followed by another attack the day after (after playing sports), and a third attack after another week. He then restarted the medication and remained attack free during the follow-up period of another year.

The monozygotic twin brother of II-4 (Figure 1, II-5) experienced attacks since age 9. Attacks started with paresthesia in one hand, arm and foot for about 15 minutes, followed by a paresis in the hand. He has not had any visual symptoms or speech disturbances. After the aura symptoms a migraine headache developed, accompanied by a mild photophobia, nausea and vomiting. He lost consciousness for hours after a minor head trauma at age 5. At age 13, attacks started to occur weekly and were often triggered by heading soccer balls. Sodium valproate (1000 mg per day) decreased attack frequency to once a month. After addition of lamotrigine 100 mg, attacks ceased without reported side effects. So far, the therapeutic effect has persisted for 18 months.

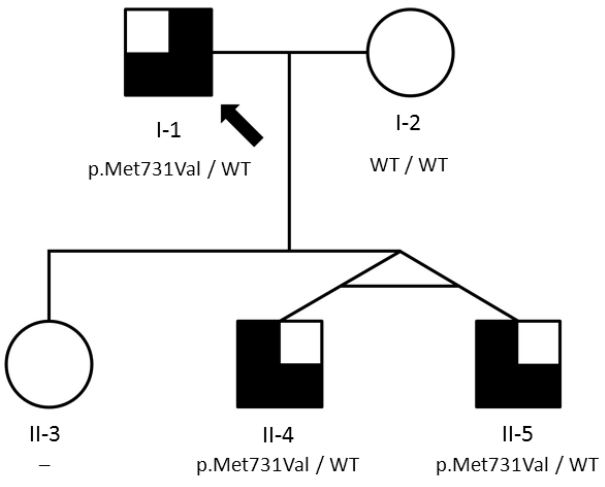

Figure 1. Pedigree of the FHM2 family. *Arrow*: proband; *black lower half*: familial hemiplegic migraine (FHM); *black right upper square*: migraine with aura; *black left upper square*: migraine without aura. p.Met731Val/WT indicates heterozygosity for the p.Met731Val *ATP1A2* mutation, WT/WT indicates homozygosity for the wild-type allele. Subject II-3 did not participate, hence no information is available, indicated by the '–' symbol.

Patient I-1 also experienced migraine with aura attacks (without motor auras), and his sons also experienced attacks of migraine without aura (Figure 1). With excellent treatment effects and no reported side effects, measuring serum levels of the migraine prophylactics was not required. There is no history of epilepsy or infantile convulsions in the family.

Genetic analysis

We identified a novel heterozygous 2191A>G substitution in exon 16 of the *ATP1A2* gene in this family, resulting in a change from methionine to valine at position 731 (p.Met731Val) in the large intracellular loop between transmembrane domains M4 and M5, containing the ATP-binding and hydrolase domains. The affected methionine residue is located in the highly conserved ''hinge'' sequence in the junction region, which is thought to be essential for the interactions between the catalytic and the membranous cation binding sites during cation translocation.[3]

Discussion

In our family with typical FHM symptoms, attack frequency was reduced significantly with sodium valproate monotherapy, and attacks ceased completely with a combination of sodium valproate and lamotrigine. In the twin brothers, polytherapy (adding lamotrigine to sodium valproate) was chosen because the first drug decreased attack frequency, but not sufficiently. Except for the short period during which patient II-4 stopped his medications, both young adults refused drug tapering after achieving complete remission from attacks on polytherapy, and lamotrigine monotherapy was not tried.

The p.Met731Val *ATP1A2* mutation in this family has not been reported before. At the same location, however, the p.Met731Thr mutation has been reported and functional analyses of this mutation revealed reduced activity of the mutant Na^+, K^+-ATPase pump.[3,4] This implies that methionine731 is important for normal functioning of the Na^+, K^+-ATPase pump and that the p.Met731Val mutation is pathogenic.

Although a few reports describe some efficacy of flunarizine, sodium valproate, lamotrigine, verapamil and acetazolamide in FHM, treatment of FHM still proves to be difficult and complete cessation of attacks with prophylactic medication is rare.[2] Sodium valproate is a well-established prophylactic treatment for migraine with and without aura, but its efficacy in FHM has been reported only in FHM with co-occurring epilepsy.[5] Prophylaxis with lamotrigine did not show a benefit over placebo in a double-blind randomised trial in migraine with and without aura.[6]

However, in a pilot study including three patients with motor auras, beneficial effects on aura frequency and duration were observed.[7] A large cohort of 59 migraine with aura patients treated with lamotrigine showed reduced frequency and intensity of all aura types in 75% of patients, including eight patients with motor auras.[8] Two hemiplegic migraine patients in a cohort of 47 migraine patients with severe auras showed reduced attack frequency after three to six months of 100–150mg lamotrigine daily.[9] Thus, treatment with lamotrigine has been reported in a few patients with motor auras, with moderate effects. The mechanism of action of sodium valproate and lamotrigine in FHM2 remains speculative. Sodium valproate inhibits gamma-aminobutyric acid (GABA) transaminase, activates glutamic acid decarboxylase and blocks Na^+-channels and low-voltage-activated T-type Ca^{2+}-channels, thereby enhancing neuronal inhibition.[10] Lamotrigine inhibits glutamate release by blocking voltage-gated Na^+-channels and N- and P/Q-type voltage-gated Ca^{2+}-channels.[11] FHM2-associated *ATP1A2* mutations cause decreased ATPase activity, possibly leading to an increase of glutamate in the synaptic cleft.[1] The mechanisms of action of sodium valproate and lamotrigine could well counteract the effect of such mutations.

Although our results in one family cannot prove efficacy of treatments, such case reports are valuable given the rarity of FHM. Treatment with sodium valproate led to reduced attack frequency in all three patients, which is a finding that has not been reported before. As explained, lamotrigine monotherapy was not tried because of our patients' resistance to withdraw from sodium valproate, but may prove to be as effective as the combination with sodium valproate. Previous reports of beneficial effects of lamotrigine treatment, however, all concern isolated cases without detailed description of motor auras and without genetic confirmation of hemiplegic migraine. Larger studies in FHM patients are needed to evaluate specific effects of lamotrigine.

In epilepsy treatment, polytherapy with sodium valproate and lamotrigine has been advocated as particularly effective and possibly synergistic.[12] This postulated synergistic effect may be responsible for the additional treatment effect. However, it must be kept in mind that side effects of lamotrigine, especially severe and sometimes irreversible cutaneous side effects, are more common when a patient also takes sodium valproate. When adding lamotrigine to sodium valproate treatment, the dosage should be built up cautiously with frequent monitoring of potential side effects. Furthermore, sodium valproate monotherapy and polytherapy with sodium valproate and lamotrigine are contraindicated during pregnancy because of risk of teratogenicity.[2]

Treatment with sodium valproate monotherapy or a combination of sodium valproate and lamotrigine had dramatic and sustained prophylactic effects in this FHM2 family with a novel *ATP1A2* mutation, making these drugs worth considering in other FHM patients.

Clinical implications

• Prophylactic treatment with sodium valproate, lamotrigine, or a combination of sodium valproate and lamotrigine should be considered in the treatment of familial hemiplegic migraine (FHM) patients.

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Conflict of interest: Dr. Pelzer reports support for conference visits from Menarini and Allergan UK. Dr. Ferrari reports grants and consultancy or industry support from Almirall, Coherex, Colucid, Eisai, GlaxoSmithKline, Linde, MAP, Medtronic, Menarini, Merck, Minster, Pfizer, and St Jude and independent support from NWO, National Institutes of Health (NIH), European Community FP6, Biomed EC, and the Dutch Heart Foundation. Dr. Terwindt reports grants and consultancy/industry support from Merck and Menarini, and independent support from NWO. Drs. Stam, Carpay, De Vries, Van den Maagdenberg and Haan have nothing to declare.

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