Alternating hemiplegia of childhood successfully treated with topiramate: 18 months of follow-up

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Alternating hemiplegia of childhood (AHC) is a rare neurologic syndrome with recurrent hemiplegic attacks shifting from one side to the other and lasting from minutes to several days. The attacks typically begin in infancy, are triggered by emotion or fatigue, and disappear during sleep. Additional features are pependular nystagmus, tonic/dystonic attacks, dyspneic episodes, mental retardation, and epilepsy. The etiology of AHC is unknown. Some consider it a variant of migraine and differentiation from familial hemiplegic migraine (FHM) may be difficult. The majority of AHC cases are sporadic, although a few familial cases have been reported, including one family with a mutation in the ATP1A2 FHM2 gene. There is no standard therapy for AHC. Flunarizine is the most frequently used drug. Topiramate (TPM) is a relatively new agent effective in the prophylactic treatment of both epilepsy and migraine. It inhibits carbonic anhydrase and displays modulatory effects on voltage-gated Na⁺ and Ca²⁺ ion channels, and glutamate non-NMDA and GABA-A receptors. Here we report 18 months of follow-up of a patient with AHC who dramatically improved following treatment with TPM.

Case report. The patient is a 12-year-old girl, with a family history of migraine. Pregnancy and delivery were uneventful. At 2 months she displayed tonic and dystonic spells associated with apnea and cyanosis; EEG was unremarkable. At 7 months she exhibited hemiplegic attacks shifting from one side to the other and associated with pendular nystagmus and autonomic changes. She averaged two to three attacks per week, which lasted for 24 to 36 hours and completely recovered with sleep. Consciousness was unaltered. Emotional stimuli or fever triggered the attacks. She had delayed psychomotor development; only two-word sentences were pronounced at 3 years and walking was achieved at age 4.5 years. At 5 months she had a more severe attack that lasted up to 6 days. Each attack was followed by further worsening of her motor and social skills, and she missed many days from school. Moderate mental retardation (IQ 48) was scored by Wechsler Intelligence test. Walking and language were severely impaired, despite treatment with valproate (30 mg/kg/day) and flunarizine (5 mg/day). At this time we added TPM, initially in a dose of 1 mg/kg/day, and later increasing over several weeks to 3 mg/kg/day. This resulted in a prompt reduction of both the severity and frequency of the attacks to one episode per 1 to 2 months. After 7 months the daily short-lasting attacks reappeared but their frequency dropped again to one mild attack of 5 to 10 minutes per week after adjustment of the TPM dose up to 4 mg/kg/day. Neurologic examination revealed improvement of ataxia and dystonia. Mild improvement of communicative and social skills was evident at clinical observation and recorded from parents' interview; she could also return to school. There were no serious adverse effects; a mild hyperoxaluria resolved with sodium citrate. The clinical improvement following TPM treatment continued for the whole 18-month follow-up period.

Discussion. This 12-year-old girl with severe AHC, resistant to traditional therapies, showed a dramatic and long-lasting improvement following treatment with TPM. The underlying pharmacotherapeutic mechanism is unknown but may be related to the inhibitory effects of TPM on carbon anhydrase activity. This may explain the extracellular pH increase in the brainstem nuclei. AHC shows clinical similarities with FHM. FHM1 is caused by missense mutations in the CACNA1A gene encoding a neuronal Ca²⁺ channel P/Q type calcium channel subunit. Episodic ataxia type 2 is caused by severe mutations in the same gene and responds clinically often extremely well to oral treatment with acetazolamide, a carbonic anhydrase inhibitor that stabilizes ion channels and raises extracellular pH. A similar mechanism was suggested in our patient by the presence of hyperoxaluria. Ion channels modulating activation and inhibition of non-NMDA mediated excitatory neurotransmission are possible other mechanisms that may have contributed to the beneficial effect of TPM in our patient. TPM might be effective in the treatment of AHC.

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References


Intrathecal chemokine levels in Alzheimer disease and frontotemporal lobar degeneration

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Amyloid beta (Ab) 1–42 deposition into the brain is considered a crucial pathogenetic step during Alzheimer disease (AD) development, as it generates a cascade of events leading to irreversible neuronal damage. Conversely, frontotemporal lobar degeneration (FTLD) is characterized by intracellular deposition of abnormally phosphorylated tau protein responsible for neuronal death. Immunoactivity for a number of chemokines and for their related receptors has been demonstrated in resident cells of the CNS. Some of them have been proposed as candidate genes for AD, and increased levels have been found in CSF from patients with AD, whereas no information on chemokines in FTLD is available at present.

Materials and Methods. Interferon-γ-inducible protein-10 (IP-10), monocyte chemoattractant protein-1 (MCP-1), and interleukin-8 (IL-8) levels were evaluated in CSF from 32 patients with probable AD (11 men and 21 women; mean age at onset: 62 ± 8.0 years), 24 with FTLD (frontotemporal dementia [FTD] = 17; progressive aphasia [PA] = 5; semantic dementia [SD] = 2; 9 men and 15 women;
mean age at onset: 61.5 ± 1.6 years). All patients underwent a standard battery of examinations, including medical history, physical and neurologic examination, screening laboratory tests, neurocognitive evaluation (to assess memory, language, and constructional praxis), brain MRI or CT, and, if indicated, PET. The presence of significant vascular brain damage was excluded (Hachinski ischemic score <4). Dementia severity was assessed by the Clinical Dementia Rating and the Mini-Mental State Examination (MMSE) score. Patients with AD were diagnosed by exclusion according to National Institute of Neurological and Communication Disorders and Stroke/Alzheimer’s Disease and Related Disorders Association criteria. FTLD diagnosis met the criteria of Neary et al. The control group consisted of 40 subjects matched for ethnic background and age (15 men and 25 women; mean age: 62.8 ± 5.5 years), without memory complaints, with other noninflammatory neurologic affections: acute headache (10), vertigo (9), nonimmune peripheral neuropathies (8), compressive radiculopathies (6), cerebral edema (6), and neurofibromatosis type 1 (1). All these control subjects did not further develop dementia over a 6 to 12 months’ follow-up. Informed consent was given by all individuals or their caregivers. Chemokines were measured with human specific ELISA kits.

Nonparametric Wilcoxon rank sum test incorporating the Bonferroni correction for multiple testing was used for comparisons. Spearman test was used for correlations.

Results. IP-10 levels were significantly increased in CSF from 16 of 32 patients with AD. Median IP-10 levels were increased in patients with AD with a mild cognitive decline (MMSE >14 at time of sampling) as compared with severe AD patients (p = 0.007; figure, A). Conversely, IP-10 levels were similar to controls in all FTLD patients, independently of the severity of the disease (p > 0.05; see figure, A). Higher median CSF MCP-1 levels were found in all AD as well as FTLD patients compared with healthy subjects (991.0 and 972.5 vs 877.0 pg/mL; p < 0.02). IL-8 levels were increased in all AD and mostly in FTLD patients as compared with control subjects (p < 0.001; see figure, B). Chemokine CSF levels were not likely to be influenced by gender or age at onset. No significant differences in chemokine levels were observed among FTD, PA, and SD subtypes.

IP-10 and MCP-1 serum levels were lower than CSF concentrations, although no differences were observed among groups, whereas IL-8 was undetectable in all samples analyzed. These findings demonstrate that the blood–brain barrier was intact.

Discussion. It is conceivable that the increased IP-10 levels observed in patients with AD, compared with FTLD, could be linked to Aβ deposition, through the activation of microglia to produce proinflammatory cytokines. The highest peaks of IP-10 have been detected in patients with AD with a mild cognitive decline, suggesting that IP-10 increase can be restricted to an earlier stage of the disease, with implications for early differential diagnosis. Inflammatory events are thought to be more relevant in these stages, possibly related to an attempt of glial cell to remove Aβ deposits. Whereas IP-10 looks likely to be involved in AD pathogenesis only, MCP-1 and IL-8 are up-regulated also in FTLD, suggesting a possible involvement in a common step associated with neurodegeneration. A beneficial effect of these chemokines has been hypothesized, as MCP-1 seems to be involved in the regeneration of neural tissue via the induction of differentiation and neurotrophic factors by astrocytes and microglia, whereas IL-8 promotes neuronal survival.

Our findings point to the relevance of chemokine expression in pathogenesis and progression of the most important degenerative dementias. As confirmation of AD and FTLD diagnoses is possible only by postmortem analysis, the availability of neuropathologic findings is needed to confirm these results.

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