Case Report

Long-term use of methylphenidate in a boy with hypothalamic tumor, drug-resistant epilepsy and ADHD

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1. Introduction

Both attention deficit/hyperactivity disorder (ADHD) as well as epilepsy are common in children and can strongly affect their learning capacities, cognitive and psychosocial functioning and behavior. ADHD is characterized by a persistent pattern of hyperactivity-impulsivity and/or inattention. The onset of key symptoms is mainly before the age of 7 (DSM-IV) [1], or up to age 16 (DSM-V) [2], with altered behavior observed in at least two settings. Clear evidence of interference of the ADHD symptoms with social and school functioning is required by the American Psychiatric Association [1]. The diagnosis of ADHD does not refer to the specific underlying pathology, and ADHD is common in children with epilepsy [3–5].

Gelastic seizures (GS) characterized by early-onset of uncontrollable laughter, typically occur in children with hypothalamic hamartoma (HH). These seizures are usually frequent and drug-resistant, often associated with cognitive decline and behavioral disorder. Other types of seizures and precocious puberty can also occur. Combination of all these features is not constant and, when present, their evaluation may be variable [6–11].

The aim of this case report is to highlight the association between hypothalamic tumor, drug-resistant seizures and ADHD symptoms. We report the effects of 12-month treatment with methylphenidate (MPH) co-administered with anti-seizure drugs (ASDs), on both ADHD symptoms and seizure control in a 7.5 year-old boy.

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2. Case report

A 7.5-year-old boy with epilepsy caused by hypothalamic tumor was referred to our Department of Child Psychiatry for behavioral disorder. He lives with his parents and 3 years older brother who is healthy. His birth and early psychomotor development was normal. He began with episodes of mild episodic laughing when he has 3.5 years of age. The epileptic origin of these stereotyped recurrent non-precipitated bouts of laughter (focal impaired awareness emotional seizures) was not initially recognized. Other seizure types, mainly focal aware seizures, versive or motor affecting the face, sometimes with laughing-like expression, lasting several seconds with or without retained awareness soon appeared and occurred twice monthly.

At age 5, because of increased seizure frequency, the boy was hospitalized at the Pediatric Department for epilepsy investigation. A neurological finding was normal. At that time, he presented with focal seizures lasting ≤2 min and occurring several times daily (28 weekly). Apart from gelastic and other seizures, sudden and brief episodes of unresponsiveness and forced deviation of the head appeared (focal aware motor seizures). Focal to bilateral tonic–clonic seizures rarely occurred. Initial EEG was done when he was 5 years old and without treatment for epilepsy. It showed focal epileptiform abnormalities over the right-sided temporal regions and diffuse slowing of the background activity. MRI of the brain revealed a small tumor in the right hypothalamus without mass effect or morphological signs of increased intracranial pressure. Hypothalamic hamartoma was suggested. A follow-up MRI of the brain, was performed 24 months after the initial examination, and disclosed the previously detected, non-progressive tumorous lesion (Fig. 1). Initial and follow-up neurosurgical and oncological examinations recommended a non-operative therapeutic approach. Our case report concerns the period of the pharmacological treatment although the surgical therapy was not definitely cancelled.

Initial treatment for epilepsy with carbamazepine (CBZ) was started when he was 5 years old. Despite the short-term initial improvement (CBZ serum level of 37 μmol/L; ref. 15–45 μmol/L), no favorable seizure control was achieved. Lamotrigine (LTG) was added to CBZ. Daily CBZ dose was tapered and it was withdrawn two months later because of its inefficacy. Seizures with sudden tonic posturing, unresponsiveness and clonic movements of arms (focal impaired awareness motor seizures), lasting 1–2 min, still occurred 1–2 times daily (averaging 11 weekly). Because of the aggressive behavior and insomnia, nitrazepam 2.5–5 mg

in a single evening dose was started and used for two months with no effect. Topiramate was added to LTG when he was 6.5 years old. The focal impaired awareness seizures, lasting 1–2 min disappeared. However, focal aware and focal impaired awareness seizures, lasting several second, appeared 25 times weekly, as is illustrated with the spike in the Fig. 1, illustrating seizure frequency and use of ASDs and methylpheniate (MPH). A better seizure control was achieved with combination of LTG (200 mg/day) and TPM (200 mg/day). Brief focal aware and focal impaired awareness seizures, lasting several seconds occurred with frequency of 5 to 15 seizures weekly. Neither focal to bilateral tonic–clonic seizures, nor seizures with fall and injury were observed for more than 12 months.

Neuropsychological assessment at age of 7 showed delayed cognitive functioning for 2–3 years when compared with age-expected abilities. His parent reported that two years after the GS onset and before the ASD introduction, he presented with mild attention difficulties, hyperactivity and altered behavior which aggravated in time. He was diagnosed with ADHD (combined type) at the age of 7.5. A neurological finding was normal. According to the clinical protocol for the MPH administration, a 4-week initial titration regimen of MPH (immediate-release tablets which effects last about 3–4 h was applied with capsules containing different MPH doses or placebo, taken three times daily and the last dose was taken before 4 PM. Appropriate placebo capsules were prepared in a pharmacy. Fully informed consent for this treatment was obtained from the parents. Severity of ADHD symptoms before the treatment and after the therapy was compared. Four values of the ADHD rating Scale were obtained: a) baseline, b) after the low dose MPH, c) with placebo and d) with moderate MPH dose, each administered for one week. After the first week of observation with no therapy, in the 2nd week the boy received MPH in low-doses of 0.5 mg/kg, up to maximum of 15 mg daily. During the 3rd week he received placebo following the same schedule. Moderate dose (1 mg/kg up to a maximum of 30 mg daily) was given in the 4th week. The ADHD symptoms were quantified by the standardized ADHD rating scale-IV having 18 items [12]. Each item corresponds to a DSM-IV ADHD criterion rated on a scale from 0 (not present) to 3 (frequent). Reports based on the ADHD rating scales IV, Parent Version and Teacher Version, were obtained weekly and scored. In addition, adverse side effects of MPH were also registered on an objective inventory [13].

Treatment with MPH significantly reduced ADHD symptoms. According to the total scores for ADHD RS-IV, as well as to the inattention and hyperactive/impulsive subscale scores, MPH given in low or in moderate doses was superior to placebo (Table 1). Difference in total scores between MPH (low dose) and placebo was - 33 for parent's rating and - 27 for the teacher's rating. Difference in total score between MPH (moderate) and placebo was – 29 for parent's rating and - 25 for teacher's rating. No advantage of moderate MPH dose (1 mg/kg) over the low dose (0,5 mg/kg) was observed in terms of efficacy. Tolerability

Table 1
Summary of ADHD RS-IV-parent and-teacher scores.

Measure	Rating	Treatment	Baseline	End	Change from baseline
Total score	Parent	MPH (low)	52	16	− 36
		MPH (mod)	52	20	− 32
		Placebo	52	49	− 3
	Teacher	MPH (low)	48	17	− 31
		MPH (mod)	48	19	− 29
		Placebo	48	44	− 4
Inattention	Parent	MPH (low)	27	10	− 17
		MPH (mod)	27	12	− 15
		Placebo	27	26	− 1
	Teacher	MPH (low)	26	9	− 17
		MPH (mod)	26	10	− 16
		Placebo	26	24	− 2
Hyperactivity/impulsivity	Parent	MPH (low)	25	6	− 19
		MPH (mod)	25	8	− 17
		Placebo	25	23	− 2
	Teacher	MPH (low)	22	8	− 14
		MPH (mod)	22	9	− 13
		Placebo	22	20	− 2

ADHD RS-IV (Attention-Deficit/Hyperactivity Disorder Rating Scale-IV).
MPH (methylphenidate), PBO (placebo).

was better with low MPH dose while mild anorexia and somnolence were reported with moderate dose.

At baseline he had brief 5–15 focal seizures weekly (focal aware seizures, and/or focal impaired awareness seizures). Seizure frequency remained unchanged during the first month of treatment irrespective of the MPH doses. The patient continued with MPH (extended-release tablets) with a dose of 0.5 mg/kg once daily in the morning for 12 months. Seizure control remained stable with no significant change in either frequency or severity of seizures. No EEG worsening during the MPH therapy in comparison to both early and pre-MPH records. Follow-up awake EEG, recorded 3 months after the stable MPH dose regimen showed the right-sided frontal-temporal epileptiform abnormality and diffuse slow-wave background activity (Fig. 3). The EEG record during the follow up when he was 8.5 years old showed no epileptiform activity. Table 1 summarizes ADHD-RS total and scores on subscales for parent's and teacher's rating of behaviour with different MPH doses and placebo. Significant improvement of ADHD (reduced hyperactivity/impulsivity and inattention) was achieved.

3. Discussion

Children with HH and GS often present with high rates of psychiatric comorbidity, associated with cognitive decline [14–18]. Weissenberger et al. [19] studied aggression and psychiatric comorbidity in a sample of 12 children with HH and GS and included siblings of study subjects
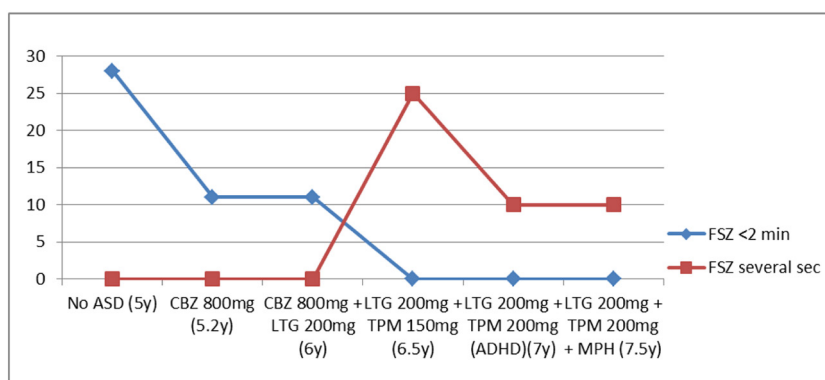

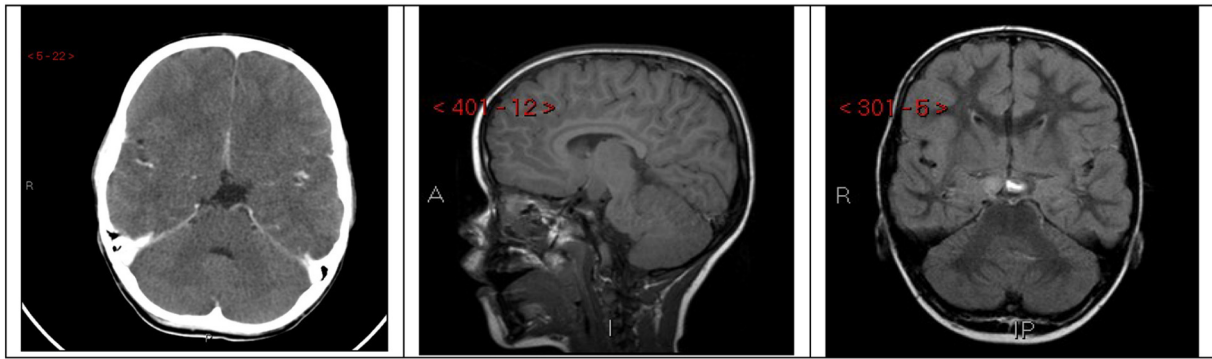**Fig. 1.** Seizure frequency and use of ASDs and MPH.

Fig. 2. ABC: Right-sided hypothalamic tumor. A- Contrast enhanced CT, showed impression on the suprasellar cistern, consistent with an isodense mass in the right hypothalamus. B. Brain MRI: Space occupying mass is isointense with gray matter on a sagittal T1 weighted image. C. Transversal FLAIR image shows the lesion which is slightly hyperintense with respect to the gray matter.

in psychiatric assessment. Compared to the healthy siblings, children with HH and GS displayed a statistically significant increase in comorbid psychiatric conditions, including oppositional defiant disorder, ADHD, conduct, and anxiety and mood disorder. The parents reported that healthy siblings had very low rates of psychiatric pathology and aggression [19]. Neither pharmacological treatment of these comorbid conditions, nor other treatments options were discussed.

Interictal conventional EEG recording in HH is mainly nonspecific or with focal, irregular spike–wave or rhythmic low voltage delta activity. Both initial and late EEG records (including ictal) can be normal or show desynchronization of the background activity [7,15,20]. The described EEG abnormalities were also seen in our material.

Arzimanoglou et al. [6] pointed out that seizures associated with HH may start early in life and evolve either towards a catastrophic encephalopathy or may be transiently severe and will progressively settle down. Intermediate conditions also exist as well as the cases presenting with mild epilepsy. In most cases of HH and GS the use of ASDs and non-pharmacological treatment remains ineffective and epilepsy became

drug resistant. There is evidence that surgical treatment or stereotactic radiosurgery can be successful, with removal, destruction, or disconnection of HH leading to remarkable control of seizures, as well as to the improvement of behavior and probably slowing/cessation of cognitive decline [20–22]. However, such improvement was not observed in patients with seizures and interictal EEG discharges that persisted after the radiosurgery [23]. Epilepsy in many patients is drug resistant, and has a high association with progressive cognitive, learning and behavioral difficulty [18]. No treatment guidelines have so far been proposed for drug resistant epilepsy associated with behavioral and psychiatric sequelae in HH. Patients with frequent seizures may be most likely to demonstrate uncontrolled seizures or have no change in seizures frequency. On the other hand, the use of MPH in patients with epilepsy (unrelated to HH) and ADHD has been reported in some publications [24–27].

Our patient with epilepsy caused by hypothalamic tumor, has ADHD syndrome of the combined type according to the DSM IV criteria. His seizure control was incomplete at the start of the ADHD treatment,
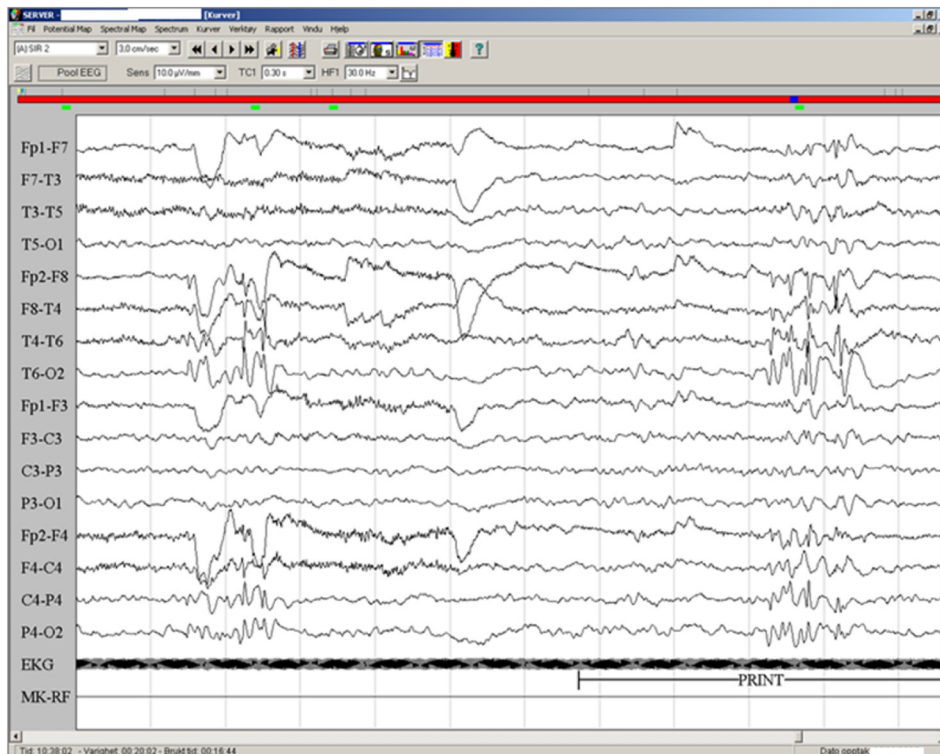

Fig. 3. Follow-up awake EEG, recorded 3 months after a stable MPH dose regimen: right-sided frontal-temporal epileptiform abnormality and diffuse slow-wave background activity.

but significantly improved long-term seizure control was achieved by a combination of LTG and TPM in stable doses. There was no change in treatment for epilepsy before, during the 4 weeks MPH/placebo initial therapy and during the 12 months clinical follow-up. Improvement of the ADHD symptoms was achieved with MPH without seizure aggravation. Such therapeutic effect of MPH could prevent the possible worsening of behavioral disorder and enables other treatment options and approaches to lesional epilepsy (Fig. 2).

The association between GS and ADHD has been described before, but this case report appears to be the first report of the successful long-term MPH therapy (follow-up for 12 months) of ADHD in one child with GS, hypothalamic tumor and drug-resistant epilepsy. Prospective studies are needed to evaluate, not only the outcome in terms of controlling seizures, but also to assess the cognitive and behavioral profile of children with drug-resistant epilepsy and ADHD.

4. Conclusions

This case report describes a relationship between hypothalamic tumor and psychiatric comorbidity, ADHD, behavioral problems and cognitive delay. Although it is a single case report which needs to be confirmed in other studies, our results support the usefulness and safety of MPH treatment of behavioral disorder in children with both symptomatic, drug-resistant epilepsy and ADHD.

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