



Theophylline, a drug efficient to increase intracranial pressure. Case report and review of literature

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ABSTRACT

Introduction: Limited information is available regarding the direct effect of drugs prescribed to elevate intracranial pressure (ICP) in contrast to the abundance of evidence in support of medication utilized to lower ICP. Theophylline is a methylxanthine derivate used in the treatment of respiratory diseases with only a few randomized control trials or case reports describing pain improvement in low CSF pressure states or spontaneous intracranial hypotension (SIH). We present the case of a recorded increase in intracranial pressure under theophylline.

Case report: A 23-year-old female with a complex history of hydrocephalus and syringomyelia was experiencing debilitating symptoms due to refractory intracranial hypotension. Medical management with oral theophylline was attempted for a period of three months. Intracranial pressure measurements were obtained via the telemetric pressure sensor reservoir (Miethke®, M.scio®) incorporated in the patient's ventriculoperitoneal shunt system.

Results: A significant increase in intracranial pressure was recorded at therapeutic drug levels.

Conclusion: This is the first report of an increase in intracranial pressure under oral theophylline medication.

1. Introduction

While an abundance of evidence in support of medication utilized to lower intracranial pressure (ICP) such as mannitol and hypertonic saline exists, the direct impact of drugs prescribed to elevate ICP is not well documented.

Theophylline is a methylxanthine derivate with a narrow therapeutic index (Jilani et al., 2023). Typically, it is used in the management of respiratory diseases like asthma and chronic obstructive pulmonary disease due to its bronchodilatory effects (Jilani et al., 2023). Theophylline can also be employed to manage low CSF pressure states and spontaneous intracranial hypotension with the aim to increase intracranial pressure (ICP). The exact mechanism of action remains elusive, nevertheless it is thought to work by decreasing intracranial blood flow and venous dilation and increasing CSF production similar to its analogues aminophylline (Skinhøj and Paulson, 1970) and caffeine (Yildirim et al., 2020).

Evidence regarding theophylline's effectiveness in elevating ICP is scant, with only a few case reports (Kasner et al., 1995; Williams et al., 2014) and randomized control trials (Yildirim et al., 2020) describing

pain improvement in low CSF pressure states or spontaneous intracranial hypotension (SIH). Although these publications indicate theophylline's potential in alleviating headaches, there is no concrete evidence providing an objective measurement of its effect on intracranial pressure thus far.

In the following report, we describe the first case of a measured increase in intracranial pressure under theophylline treatment over a three-month span in a patient with complex hydrocephalus and extensive syringomyelia.

2. Case presentation

We here present a case report of a 23-year-old female experiencing deterioration of the pre-existing bilateral lower extremities paraparesis, nausea and worsening headaches over a period of two months. No further neurological deficits were documented. The vital signs were within normal range.

The patient's past medical history is complex and marked by hydrocephalus and syringomyelia. Clinically she was known to be affected by spasticity and paraparesis. The patient was dependent on a

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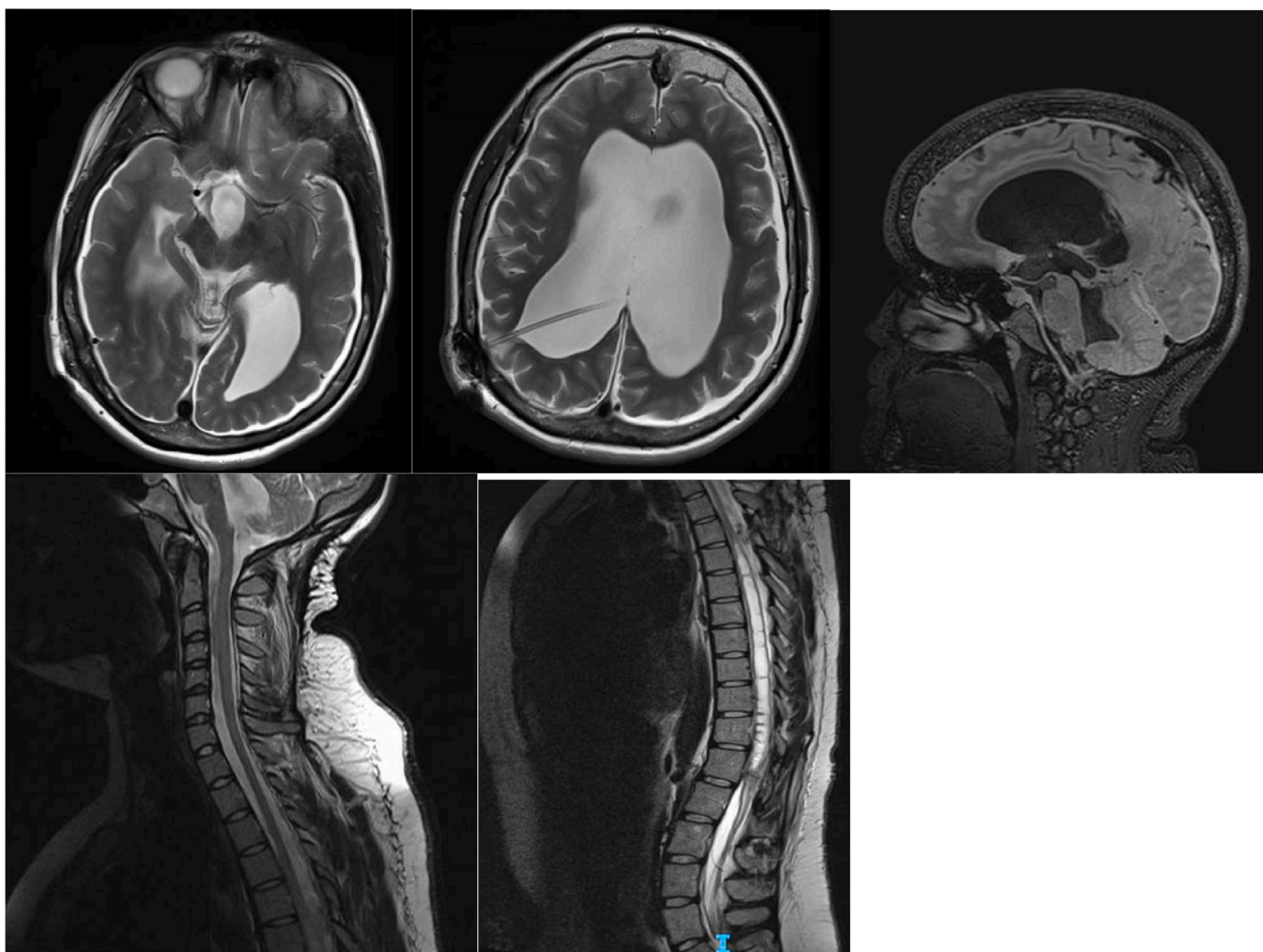


Fig. 1. T2 and FLAIR MRI images of the brain and spinal cord prior to theophylline.

wheelchair for ambulation. The surgical past medical history includes a ventriculoperitoneal shunt (VPS) and a foramen magnum decompression for Chiari malformation associated syringomyelia at age of 8 and 14 years respectively, followed by a syngo-plural shunt insertion. The latter has proven to be blocked for several years before the patient's care was transferred to our department. For an interval of five years the patient's condition had stabilized and she was able to be independent. However, in due course, she developed symptoms consistent with intracranial hypotension and underwent ligation of the existing VPS after which she remained asymptomatic for a period of several months until the current presentation. Subsequent MRI imaging demonstrated progression of the known syringomyelia with enlarged third and fourth ventricles.

On the basis of CSF flow interruption between the cranial and spinal CSF compartments due to underlying crowding and adhesions at the level of foramen magnum as cause for worsening of syringomyelia the decision was made to insert a right sided ventriculo-theal shunt in the attempt to equilibrate these two compartments following ligation of the original VPS. The previous sprung reservoir (Miethke) was exchanged for a telemetric intracranial sensor reservoir (M.scio, Miethke). The shunt has not been revised since insertion nor were there concerns regarding functionality.

In the two weeks following the procedure the patient developed symptoms suggestive of intracranial hypotension. An acquired MRI brain scan demonstrated bilateral hygromas in the axial T2 sequences (Fig. 1). Measurement of ICP via the telemetric sensor reservoir recorded

Table 1
intracranial pressure values (in mmHg) measured via the telemetric sensor reservoir (M.scio, Miethke) from July to end of September.

Date/ Position	06/07	14/07	20/07	26/07	27/ 07	21/ 09
Supine	-5.65 mmHg	-7.88	-9.16	-1.18	0.98	62.68
Sitting	-18.44 mmHg	-16.78	-20.80	-14.78	-9.91	-0.08
Standing	Not measurable due to severe paraparesis					

pressures of -7.88 mmHg in supine position and -16.78 mmHg sitting (Table 1.). Following a multi-disciplinary meeting involving neurology, neurosurgery, and autonomic medicine a trial of oral theophylline 200mg BD for a period of three months was commenced with the aim to increase ICP.

ICP measurements were taken after the introduction of theophylline which demonstrated a gradual increase in pressure over a period of several weeks (Table 1). The delay of a few days between the first theophylline dose and ICP increase is probably explained by the time necessary for the drug to achieve its effect. Two months after the treatment had begun, a further increase in ICP was documented to a supine ICP of $+62.68$ mmHg and -0.08 mmHg in sitting (Table 1.). The measured ICP wave over the telemetric sensor reservoir had a good curve. These values were recorded during continuous measurements as

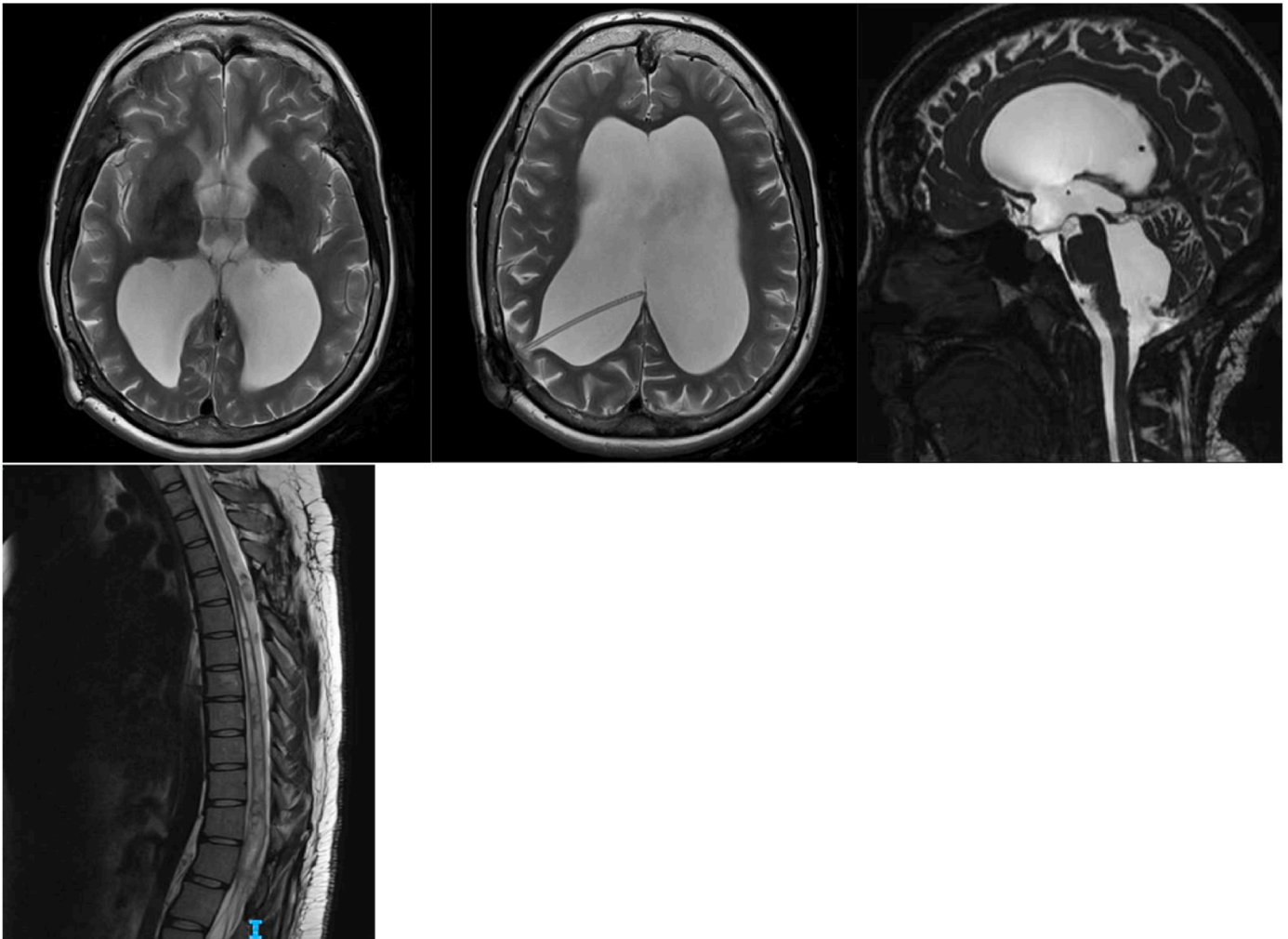


Fig. 2. CISS and T2 MRI slices of the brain and spinal cord after the theophylline treatment was commenced.

well, where the ICP curve was observed over a period of several minutes. There was no other concurrent pathology or explanation for the ICP values and the patient's medication had remained unchanged. With regards to the technique of interrogating the M.scio device, the reader is initially switched in "fast measurements" with the purpose of evaluating the ICP curve and amplitude. Once this is satisfactory, the reader is switched either in "single" or "continuous measurement" mode to obtain ICP values.

Theophylline levels were regularly monitored during this period, with values ranging between 6 and 10 mg/l, which are considered to be low effective plasma-theophylline concentration levels (Barnes, 2010).

Ventriculo-thecal shunts are valveless shunts that only incorporate a reservoir. The patient's ventriculo-peritoneal shunt was ligated with the use of a plug. Therefore, we are in a position to confirm lack of CSF flow over the past VPS since ligation. Further, an MRI brain scan performed at the same time the ICP values were above +60 mmHg demonstrated resolution of the subdural effusion and a mild increase in ventricular dimensions (Fig. 2). Clinically the increase in ICP was associated with the disappearance of the headaches and nausea. There is no explanation for the deterioration of the bilateral lower limb weakness continuing despite investigations.

The insertion of the telemetric sensor reservoir facilitated contemporaneous, non-invasive measurements of ICP with the introduction of oral theophylline. The findings explicitly showed a consistent rise in ICP, a trend that persisted with the continuation of treatment.

Review of literature

A systematic review of the literature was performed using PubMed and Google Scholar platforms to identify cases describing the use of theophylline in the treatment of intracranial hypotension (ICH). The search terms 'theophylline', 'intracranial pressure', 'intracranial hypotension', 'low CSF pressure states' and 'hydrocephalus' were employed to identify relevant publications.

Although several studies validate the effectiveness of theophylline in alleviating symptoms of intracranial hypotension, there appears to be no published evidence of an objectively quantified increase in ICP following theophylline administration.

Case reports and randomised control trials have described the efficacy of theophylline in post dural puncture headache (PDPH) (Amini et al., 2022; Basurto Ona et al., 2015), in Chiari Type 1 malformation (Kasner et al., 1995) and in spontaneous intracranial hypotension (SIH) with prolonged headache (Williams et al., 2014; Lin et al., 2017). A recent retrospective clinical study by Yildirim et al. (Yildirim et al., 2020), on 65 patients with PDPH who were given intravenous theophylline indicated that theophylline proved to be a potent and safe therapeutic approach for PDPH.

In an effort to explain the mechanism of action of theophylline in intracranial hypotension Ibayashi et al. (1988) studied the effects of theophylline on rat pial vessel diameter and demonstrated drug induced vasoconstriction of these vessels, possibly through its action as an adenosine receptor blocker.

4. Discussion

This case report presents the first documented report of a quantifiable rise in ICP following the twice daily administration of oral theophylline (200mg BD), for a period of three months, in a patient diagnosed with hydrocephalus and syringomyelia.

Telemetric sensor reservoirs have found their utility in particular in patients with complex CSF dynamic disturbances, allowing a contemporaneous and non-invasive method of measuring ICP. The reservoir can be easily incorporated within the shunt system. The goal is to either guide setting adjustments in patients with programmable valves or to determine whether the clinical complaints align with malfunctioning of the shunt.

The sensor reservoir allowed in this case serial ICP measurements which demonstrate a gradual increase in pressure values. Additionally, continuous measurements were performed, with the ICP graph displaying sequentially over a period of minutes, on which the same results were shown in the curve.

Based on the department's experience with false readings due to sensor reservoir malfunction, we believe that these values were not the result of an error reading. We base this statement on the fact that the ICP curve had an optimal wave form and the values obtained were both in negative and positive range, corresponding to the ICP in different postures. To the best of our knowledge proximal shunt blockages manifest with abnormal ICP curves and abnormal negative values.

Both clinical and radiological improvement come to support further the validity of the recordings, with near to complete symptom resolution and disappearance of the subdural collections on subsequent MRI scans. Ventriculothecal shunts are valveless systems with no options of valve settings changes and malfunction could be excluded by both by the normal measured ICP curve over the telemetric sensor reservoir as well as radiological lack of syrinx progression on MRI scans.

Utilized by neurologist with the intention to treat intracranial hypotension, theophylline's efficacy is supported by the literature. Nevertheless, with the disadvantage that the evidence up to date is based on clinical observations of symptom improvement only. This case report comes as an objective support of this drug's effectiveness in treating CSF hypovolemic states.

Conclusion

While theophylline has shown promise in subjectively alleviating symptoms of low ICP, particularly in the context of PDPH, the specific impact of theophylline on measured intracranial pressure remains largely unexplored. The findings emphasize the pertinent role of theophylline in raising ICP in intracranial hypotension and underscores the significance of considering it as an agent in patients experiencing low intracranial pressure.

Declaration of interests

The authors declare that they have no known competing financial

interests or personal relationships that could have appeared to influence the work reported in this paper.

Compliance with ethical standards

Written consent was obtained from the patient for the publication of this case report.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bas.2023.102709>.

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