of the symptoms, was treated. Since neurological presentation precedes cancer diagnosis in more than 70% of the cases[1,2], our case again illustrate the importance of considering the possibility of an occult malignancy in unexplained, atypical syndromes, even in younger patients.

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To the Editor

A Case of Phenytoin-Induced Encephalopathy in a Mathematician with Stage IV NSCLC

It is estimated that more than 1,000,000 prescriptions for phenytoin (dilantin sodium) are filled per year in Canada[1]. Phenytoin is a widely prescribed anti-epileptic agent and in the context of advanced cancer with brain metastasis, it is often used for seizure prophylaxis post-craniotomy and/or radiotherapy. However, toxicity due to phenytoin can be mistaken for signs of disease progression and can result in significant functional deterioration. We present the case of a 65-year-old mathematician with Stage IV NSCLC whose unidentified phenytoin-induced encephalopathy caused by an interaction with sulfamethoxazole and trimethoprim resulted in admission to palliative care. Withdrawl of phenytoin led to a remarkable return to functional baseline. This case serves as a cautionary tale for all clinicians whose patients are treated with this agent.

A 65-year-old mathematician with stage IV adenocarcinoma of the lung underwent successful surgical resections of two brain metastases in January 2009 after presenting with increasing confusion. The first 2.3 cm diameter lesion was located in the left occipital-parietal region at the cortico-subcortical junction and the second, 2.4 cm in diameter, was located in the right superior frontal gyrus. She was treated with dexamethasone and 300 mg phenytoin daily for seizure prophylaxis. In the immediate post-operative period, she experienced a single complex partial seizure involving her right arm, which resolved without intervention. It was then decided that she would remain on phenytoin prophylactically. She underwent a course of whole brain radiation (30 Gy in 10 fractions) and regained the ability to walk. Two months post-resection, the patient obtained a perfect score on the Mini-Mental Status Exam (MMSE). An magnetic resonance image (MRI) six months post-radiation revealed complete resolution of all brain disease.

In June 2009, the patient began treatment with gemcitabine for the primary lung tumour. At the time she was treated with 450 mg phenytoin daily and had a normal serum albumin. She remained seizure-free. However, after 11 courses of chemotherapy, the patient began to deteriorate neurologically. Chemotherapy was then terminated in November 2009.

Increasingly aphasic, the patient became incontinent and developed significant left-sided neglect with spasticity in her left foot that progressed proximally. An MRI brain and spine revealed no new metastasis. Electroencephalogram (EEG) revealed disturbance of cerebral background activity but no evidence of seizure activity. Other organic causes of the deterioration such as infectious or metastatic etiologies were ruled out. The patient then lost the ability to weight bear due to spasticity and significantly increased motor tone bilaterally with clonus in deep tendon reflexes. She exhibited delayed swallowing and was unable to follow commands. Disoriented and apraxic, she obtained 3/30 on the MMSE. Treatment at the time was supportive and an indwelling urinary catheter was installed to manage incontinence and recurrent UTI secondary to urinary retention. The installation of the catheter resulted in episodes of urinary infection with lethargy, nausea and vomiting. She responded well to repeated courses of Septra DS (180 mg trimethoprim and 800 mg sulfamethoxazole) and intravenous fluids. Her total phenytoin levels remained at the high end of normal (79-80 μmol/L) thoughout this period. Serum albumin was within normal range. In February 2010, the patient was admitted to palliative care for generalized deterioration thought to be due to urosepsis. In hospital, the delayed swallowing and lower limb spasticity resolved completely after a bolus of normal saline and the patient began conversing with hospital personnel. However, within one hour of the usual 200 mg phenytoin at bedtime, the patient was somnolent, with significantly increased spasticity. She was again unable to follow instructions. Given that the neurological deterioration appeared to be temporally related to the administration of phenytoin, a decision to stop the medication was made. The patient had been receiving phenytoin for one year at therapeutic levels.

Within two days of discontinuing phenytoin, the patient was again able to weight bear. She became increasingly conversant, identifying an obscure flower in a photograph. Spasticity in her lower limbs was resolved and swallowing function returned to normal. Within one week, the patient was able to walk 100 metres with a walker. She remained with a mild-moderate foot drop on the left with a positive Babinski reflex. The urinary catheter was discontinued and bladder retraining was begun. Within two weeks, her MMSE score was 27/30. The patient returned to previous activities including crosswords and Sudokus. With a proclivity for math, she began solving problems involving the binomial theorem and stated, when asked, the

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derivative of $d(x^3)/x = 3x^2$. The patient was discharged with a diagnosis of resolving phenytoin-induced encephalopathy.

Phenytoin is a voltage dependent Na+ channel blocker introduced in 1938, considered to be a first line treatment for partial and generalized tonic-clonic seizures[2,3]. Phenytoin has a narrow therapeutic index. and many adverse reactions including and not limited to: hirsuitism, gingival hyperplasia, lymphadenopathies, blood dyscrasias, arrhythmias and hypotension[2,3]. GI side effects are common with nausea and vomiting, constipation, dysphagia, loss of taste, anorexia and weight loss attributed to phenytoin use. Dizziness, diplopia, ataxia, confusion, drowsiness can occur at therapeutic levels[2,3]. Case reports of choreoathetosis, asterixis, dystonia, myoclonus have been reported[2]. Specific effects in overdose include decreased level of conscious progressing from confusion to coma at levels > 100 μmol/L and include nystagmus, hyperreflexia, clonus and lethargy[2].

Phenytoin is approximately 90% plasma protein bound. There is great individual variation in the degree of binding, which can be affected by uremia, chronic liver disease, pregnancy, advanced age, critical illness, interaction with other protein-binding agents and hypoalbuminemia[2,3]. In fact, when measuring total phenytoin levels, a correction formula is applied for patients with albumin < 32 g/L[2]. It is now recommended that free serum levels be measured, as the total does not correlate well with toxicity caused by high levels of freely circulating drug[4]. Unfortunately, due to technical difficulties, free levels are not routinely available[4]. As this case illustrates, competition with other highly protein-bound agents is one potential mechanism for the development of toxicity via competitive displacement of phenytoin from plasma proteins. Here, the repeated use of sulfamethoxazole and trimethoprim in the context of chronic phenytoin use is hypothesized to be the cause.

The mathematician's situation was further complicated by the mechanism by which phenytoin is metabolized. Metabolism occurs via para-hydroxylation and requires hepatic enzymes CYP2C9 (predominantly) and CYP2C19 to produce the inactive metabolite 5-(p-hydroxyphenyl)-5-phenylhydantoin (HPPH)[2,5], which is excreted in urine and accounts for 80% of drug elimination. At steady state, the Michaelis-Menten (MM) model of saturable enzyme kinetics explains the relationship between dosage and plasma concentrations[2]. Generally, at total phenytoin concentrations below 40 μmol/L, elimination is first order, and the half-life ranges from 6 to 24 hours (average 22 hours). At higher concentrations, zero-order elimination (or dose-dependent elimination) occurs due to saturation of the para-hydroxylation reaction at the CYP2C9 enzyme. The elimination half-life has been found to increase to as much as 20-60 hours[2,5].

In this case, the patient was undergoing repeated treatment with 800 mg sulfamethoxazole and 160 mg trimethoprim (Septra DS) BID for urinary tract infections with lactose positive coliforms. In fact, between December 2009 and February 2010 she received four 7-day courses. It is hypothesized that the introduction of sulfamethoxazole, which is 65% protein-bound[6], increased the concentration of free phenytoin via displacement from serum albumin. Sulfamethoxazole has been found to competitively displace phenytoin from albumin in both in vitro and in vivo studies[6]. At varying concentrations of the antibiotic, Dasgupta et al[6] reported a statistically significant increase in free phenytoin levels. With increasing levels of albumin (samples ranged from 25 g/L to 45 g/L), the effect was reduced. Thus, this mathematician, whose albumin remained at the low end of normal, was likely experiencing an antibiotic-induced displacement of bound phenytoin. Repeated courses of IV hydration effectively diluted the free concentration, thereby reducing the toxic effects. Side effects were dampened until the next oral dose of phenytoin was absorbed. Because only total levels of phenytoin were measured, the high concentration of free phenytoin went unnoticed until the hydration effect was observed.

Trimethoprim compounded the situation. Trimethoprim decreases phenytoin metabolism via the inhibition of CYP2C9[7]. As phenytoin undergoes zero-order elimination at higher concentrations, the elimination half-life was probably significantly greater than the usual 22 hour estimate. The presence of both antibiotics is likely to have an additive effect via CYP 2C9 inhibition[5]. The withdrawl of phenytoin and the use of IV hydration resulted in a decrease in free serum concentration with a concomitant return to baseline functioning from both a physical (and cognitive or mathematical) standpoint. This case is significant in that it underlines the importance of considering toxicity in all cases of patient deterioration where drugs with narrow therapeutic ranges are used. In this case, phenytoin had been used for over 12 months before nefarious effects were apparent. Since it was not a "new addition" to the pharmacological mix, its effect on the patient was not considered especially given therapeutic total levels. This case also underscores the importance of free serum monitoring rather than reliance on total serum levels. While measurement of free levels may be difficult, Dasgupta et al[6,8] have validated an equation with which the concentration of free phenytoin can be calculated given total concentration, serum albumin (> 32 g/L) and no phenytoin-displacing agents present.

Free phenytoin (μmol/L) = 5.47 x [total phenytoin (μmol/L)/ albumin (g/L)] – 0.45

The case of the mathematician underscores the need to be cautious in the administration of phenytoin with other protein-binding agents including salicylic acid, ibuprofen, valproic acid, ceftriaxone, nafcillin and sulfamethoxaole that can displace phenytoin from binding sites[3,6]. It also underlines the need for astute observation of patients and their reactions to pharmacological agents even when these are not new. Removal of phenytoin allowed this patient to experience remarkable functional improvement. And thus, the authors thank her for her editorial comments on previous drafts of this manuscript and her calculus lessons.

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To the Editor

Spinal Cord Injury after Prolonged Neck Flexion, is it an Underestimated Risk?

Prolonged extreme neck flexion is a reported risk factor for cervical spinal cord injury.[1-4] This is usually precipitated by altered level of consciousness as in intoxicated patients or patients under general anesthesia. We present a case of cervical spinal cord injury secondary to prolonged neck flexion after opioid abuse and discuss the postulated mechanisms of this rare injury and provide a review of the available literature on this topic in order to increase awareness of this complication.

History and Examination

This is a 20-year-old male with a past history significant only for intravenous abuse of opioids. He was brought to the hospital after he was found in the morning with inability to move arms and legs following a six-hour period of loss of awareness. The patient admitted having used a total of 160 mg of long acting oxycodone intravenously, and subsequently fallen asleep for approximately six hours with his neck-flexed forwards against the wall under a confined space. The patient's partner verified the history. On examination, the patient was awake and alert. His vital signs were normal. There were no obvious signs of external trauma. There was no neck stiffness. Cranial nerves were intact. Motor exam of the upper extremity revealed biceps and deltoids power to be 3/5 bilaterally, triceps and wrist extension were 2/5 bilaterally and hand intrinsic muscles were 1/5 bilaterally. Motor exam in the lower extremities was 0/5 with absent reflexes and decreased tone. Anal tone was absent.

Investigation

Relevant laboratory tests revealed absolute white blood count (WBC) count of 10.8 bil/L and erythrocyte sedimentation rate (ESR) of 4 mm/h. Blood and urine cultures were negative. Creatinine was 121 μmol/L. Myoglobin was not tested. Creatine kinase (CK) was 7189 U/L. Magnetic resonance imaging (MRI) of the spine showed marked cord expansion with high signal within the cord from C2 to C7 on T2WI (Figure 1). There was no significant cord enhancement. At the cranial end of the spinal cord signal changes, the signal abnormality assumes an H-shaped configuration indicating selective involvement of the grey matter suggestive of vascular injury (Figure 2). There were extensive signal changes in the paraspinal muscles with some

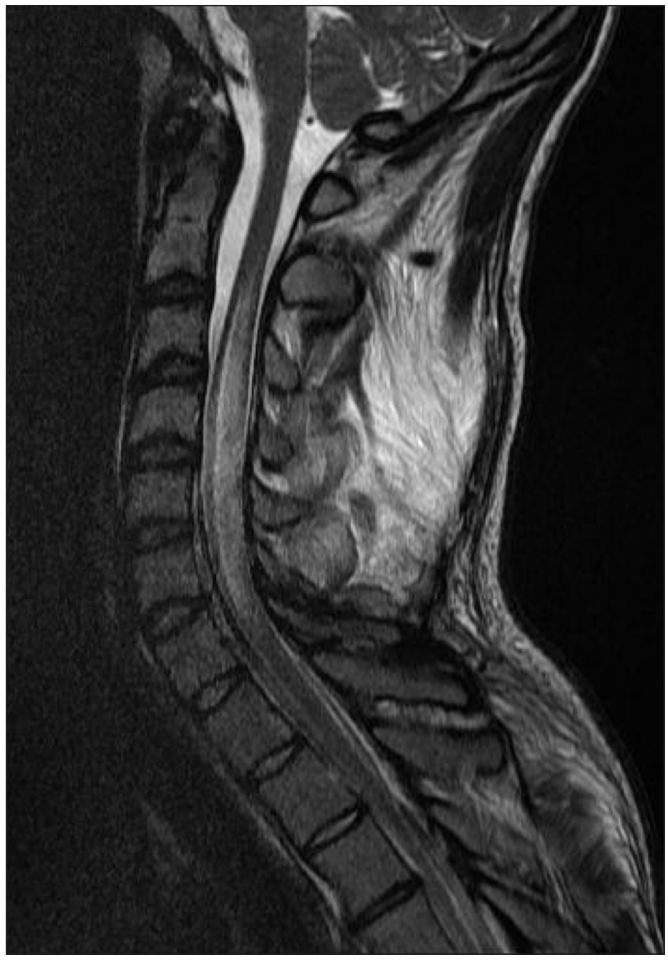

Figure 1: *Sagital T2 MRI image of the cervical spine showing spinal cord signal changes and paraspinal muscle edema .*

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