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Inadvertent Intrathecal Use of Ionic Contrast Media for Myelography

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PURPOSE: To describe instances of inadvertent intrathecal injection of ionic contrast media and to consider treatment approaches, and diagnostic and medicolegal issues. **METHODS:** Ten cases of inadvertent injection, of which nine were reported to the manufacturers/authors and one appeared in the literature, are related with emphasis on similarity of reactions. **RESULTS:** Six criteria are enumerated and used to coin the term "ascending tonic-clonic seizure syndrome." **CONCLUSIONS:** Therapeutic possibilities seem limited, but several methods for controlling seizures are suggested. The importance of identifying the contrast material is underscored. Awareness of the grave possibility of administering the wrong contrast material is the first step in avoiding this problem; awareness of the symptoms is the first step toward therapy.

Index terms: Contrast media, effects; Liquid chromatography; Iatrogenic disease or disorder

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Most of the water-soluble, iodinated contrast media (CM) of the nonionic, low osmolar class are generally safe for intrathecal use. Ionic contrast media, on the other hand, may cause severe and occasionally fatal reactions following intrathecal administration and, therefore, are explicitly contraindicated.

Cases of inadvertent intrathecal use of ionic CM have become known to the manufacturers during the last few years. A total of 10 well-documented cases are presented here; nine of these were reported to the manufacturers of iohexol (Nycomed AS, Oslo, Norway and Sanofi Winthrop Pharmaceuticals, New York, NY) and one has appeared in the scientific literature (1). Presently, seven well-documented additional cases are known to the originators of iopamidol (2) and another two cases are known to the originators of ioversol (Mallinckrodt Medical Inc, St. Louis, MO, personal communication). The number of cases reported to other suppliers is not known to the authors. It is not unlikely that additional cases may have occurred, but have never been reported to the manufacturers or published in the literature.

The seriousness of the problem is illustrated by the case descriptions that follow. We hope that the current article will contribute to a better awareness of this problem and thereby reduce the likelihood of such misadventures. It is also hoped that future recognition of the reaction syndrome may contribute to early intervention and optimal treatment.

Case Descriptions

Case 1

A 41-year-old woman underwent lumbar myelography for low back pain. The initial report stated that 15 mL of iohexol 180 mgI/mL had been used. Thirty minutes after completion of the procedure, she developed myoclonic jerks of the lower extremities. Meperidine and hydroxyzine hydrochloride were administered but her mental status deteriorated and she began to develop myoclonic jerks of all extremities, stupor, and apneic episodes. The apnea was thought to be a manifestation of convulsions because her jaw was clenched tight. She eventually became comatose and was then placed on a ventilator and partially paralyzed with pancuronium bromide. Phenytoin sodium and phenobarbital were given to control seizures. A computed tomography (CT) scan without CM on the next day showed an increased density in the cerebrospinal fluid (CSF) space consistent with CM or fluid. An electroencephalogram (EEG) exhibited generalized spike wave activity. A lumbar puncture showed pleocytosis, but was otherwise normal. The patient died of cardiac arrest 2 days after the myelogram. Neuropathologic examination of the brain showed no signs of disease. High performance liquid chromatog-

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raphy (HPLC) analysis of extracts from the preserved brain tissue performed several months later indicated the presence of diatrizoate in the samples. No trace of iohexol was seen.

Case 2

A 49-year-old man underwent lumbar myelography with what was reported to be 15 mL of iohexol 180 mgI/mL. Three hours after completion of the injection, the patient developed painful myoclonic jerks of both lower extremities. The spasms occurred spontaneously, but could also be elicited by touching the patient. By 7 hours after injection he developed myoclonic jerks of the upper extremities also, along with coma and hyperthermia (42°C/107.6°F). He was given a neuromuscular blocking agent and placed on a ventilator. A lumbar puncture the next day was normal, except for a mildly elevated CSF protein. A CT scan showed evidence of CM in the cerebral cisterns and ventricles with some paraventricular uptake. The patient died a week later after a progressively downhill course marked by rhabdomyolysis and multiorgan failure. Autopsy was not performed. HPLC analysis of serum and spinal fluid taken at the time of seizures indicated the presence of metrizoate; no evidence of iohexol was found.

Case 3 (1)

A 76-year-old man inadvertently received 10 mL of meglumine diatrizoate for a lumbar myelogram because of low back pain. Two hours after the injection the patient experienced myoclonic jerks of both lower extremities that subsequently became generalized. Interestingly, the reporting physician stated that the generalized seizures were not epileptic in nature and also noted that the patient was conscious. He was initially treated with diazepam, prednisolone, and pentazocine. Five hours after the injection he had less frequent seizures, although they could be induced by any kind of external stimulation such as neurologic examination. The paroxysms were painful and lasted for 15–25 seconds. Eight hours after injection, the patient was drowsy and had a metabolic acidosis that was refractory to bicarbonate. Nine hours after injection, the patient suffered aspiration and cardiac arrest and could not be resuscitated. A postmortem examination of the brain was essentially negative. HPLC analysis of body fluids confirmed the presence of diatrizoate.

Case 4

A 49-year-old man inadvertently received 12 mL of meglumine diatrizoate 60% for a lumbar myelogram. He complained of minor cramps in the legs immediately after the injection. Six hours after the injection he developed severe and painful spasms in the back and lower extremities. The spasms could be elicited by just touching his legs or even the bed. He was initially treated with lorazepam intravenously, then dexamethasone in addition to phenytoin sodium 1000 mg intravenously followed by another 600 mg 4 hours later. He was kept in the intensive care unit for 3 days under continued medication and gradually improved until he was discharged on the fourth hospitalization day.

Case 5

A 44-year-old woman inadvertently received meglumine metrizoate for a lumbar myelogram because of low back pain. She had an 8-year history of temporal lobe epilepsy but had been seizure free for the last 3 years. Immediately after the injection she had pain radiating down both lower extremities. Approximately 1 hour later she developed severe and painful tonic-clonic cramps in the left leg. She was without pain in the period between the cramps, which could be triggered by simply touching her leg. Sensation still seemed normal and she was able to move her toes and lift both legs voluntarily. The cramps gradually became more severe and spread to the other leg. She was given intravenous diazepam and phenytoin. The cramps disappeared for a while, but returned thereafter. Approximately 5 hours after the injection she was stuporous and had generalized seizures. It was decided to put her under general anaesthesia. Three hours later, an EEG examination indicated solitary, local sharp wave activity. However, she showed no signs of status epilepticus and was free from cramps, conscious, and extubated by the next day. She was later discharged, with some residual weakness of uncertain origin in the lower extremities.

Case 6

A 34-year-old woman underwent lumbar myelography for suspected disk disease. The CM injected was reported to be 10 mL of iohexol 180 mgI/mL. The films indicated a total stop at L4-L5 indicating the need for next-day surgery. Two-and-a-half hours after the injection she complained of radicular pain; 20 mg of piritamide was administered. Three hours after the injection leg spasms occurred with increased pain; during the next half hour she was given more piritamide. The patient then began to exhibit myoclonus in the legs, progressing also to the arms and back with opisthotonos. Diazepam was administered intravenously with only a short-lasting effect. The patient thereafter became stuporous with hyperpyrexia (42°C/107.6°F) and a severe metabolic acidosis. Two hours later, she was placed on a ventilator under general anaesthesia. A CT scan showed contrast in the cisterns and in the sulci over the cerebral convexities, but no signs of cerebral edema. The next day she exhibited disseminated intravascular coagulation and rhabdomyolysis with acute renal failure necessitating dialysis. In spite of intensive treatment, she died a few days later. HPLC analysis of plasma samples from the first 24 hours was performed: the results indicated the presence of ioxithalamate; no trace of iohexol was seen.

Case 7

A 71-year-old alcoholic man with spinal stenosis underwent a lumbar myelogram. The CM was initially reported to be iohexol 240 mgI/mL (the amount of drug administered was not reported). Fifteen minutes after the injection he started to develop back and leg spasms. He was given two injections of midazolam (2 mg × 2) and two injections of meperidine (25 mg × 2). After a while, he developed generalized myoclonic jerks of both upper and lower extremities. Touching the patient's legs would precipitate the attacks. He then developed hyperthermia (42°C/107.6°F), lost consciousness, and was given 1800 mg phenytoin sodium and dexamethasone. Thereafter he was intubated and given pentobarbital. The EEG was described as abnormal. The patient never regained consciousness. After EEG confirmation of brain death, he was disconnected from the respirator. Serum and urine samples from the patient were later analyzed by HPLC: the results indicated presence of diatrizoate in all samples; iohexol was not seen.

Case 8

A 41-year-old man with disk disease inadvertently received 10 mL of metrizoate 370 mgI/mL for a myelographic examination. Radiographic examination was completed without any complaints from the patient and he was returned to the ward. One hour after the injection, the hospital staff realized he had received the wrong CM and he was returned to the radiology department for drainage of the spinal canal. Initially, the patient had paresthesia of the lower extremities, but he soon developed myoclonic jerks in both. After a repeat lumbar puncture he was put under general anesthesia while the CSF was withdrawn 20 mL at a time and replaced with 20 mL of atmospheric air; all the time, the patient's head and trunk were kept elevated by 10–15°. In all, 180 mL of spinal fluid was withdrawn. Radiography disclosed no visible CM in the spinal canal. He was transferred to the intensive care unit where he was kept deeply sedated for several days. Following extubation on the third day, he complained of some residual headache, but had no remaining neurologic deficits.

Case 9

A 37-year-old woman with disk disease inadvertently received meglumine metrizoate 200 mgI/mL for a myelogram. An hour and a half after this injection, she complained of paresthesia in both lower extremities and soon developed pains and muscle spasms. The patient was treated with hydrocortisone intravenously and diazepam intramuscularly, with only transient improvement. The pain and myoclonus spread in a cephalad direction involving the arms. She was treated with injections of diazepam at regular intervals. Nine hours later she still had bouts of severe spasms lasting 15–30 seconds. Throughout this experience, the patient was somewhat distant, but still conscious. After 14 hours, the spasms began to taper off and then disappear. She still had some signs of meningeal irritation, headache, and nausea and was heavily sedated due to the diazepam. The following day she was quite well with total amnesia for the incident. She was discharged without any sequelae.

Case 10

A 52-year-old woman was admitted for myelography due to sciatica. She received 11 mL of meglumine metrizoate 280 mgI/mL into the lumbar subarachnoid space. Following an uneventful radiographic examination she was returned to the ward. Approximately 4 hours after the injection she was noted to have generalized intermittent myoclonic spasms, pyrexia (38°C/100.4°F), tachypnea, and tachycardia (140 bpm). Her blood pressure was 200/90 mm Hg. She was transferred to the intensive care unit and was given intravenous fluids, oral baclophen, and diazepam, as well as hydrocortisone. The myoclonic spasms tapered off over the ensuing 24 hours. She was discharged 48 hours later, complaining only of a minor residual headache and her original presenting leg symptoms.

Discussion

These 10 cases appear similar to the four described by Wollin et al (3) in 1967, in which diatrizoate and iodopyracet had inadvertently entered the spinal canal following diskography. Interestingly, the clinical presentation in some of these past cases differed somewhat from those presently described, particularly in the pattern of spasm spread. This difference may possibly be ascribed to the difference between positioning of patients undergoing diskography and those undergoing lumbar myelography, allowing a more rapid cephalad migration of the CM within the subarachnoid space. The present cases also resemble published reports of severe adverse reactions following intrathecal use of the ionic CM meglumine iothalamate (4, 5). Similar tonic-clonic spasms have also been seen in test animals following intrathecal injection of meglumine iothalamate or metrizoate (6), likewise with diatrizoate and also with a number of ionic, water-soluble CM that are no longer in use (3, 7).

In the present series, following lumbar injection, the onset of the reaction was typically heralded by paresthesiae and, between ½ hour to 6 hours later, painful spasms of the lower extremities. The spasms have been described as myotonic (increased tonus) initially, later developing into clonic (jerking) spasms. When fully developed, the spasms seem to occur in intensely painful paroxysms lasting for 15–30 seconds separated by pain-free intervals. An interesting and

frequently described feature is that the paroxysms are readily elicited by external stimuli and may be precipitated by merely touching the affected extremities, or in some instances, the patient's bed. The patients were all fully conscious at the onset. After several hours, the myoclonic activity seems to ascend to involve the muscles of the back and trunk and then the upper extremities. The stronger muscle groups seem to dominate to give plantar flexion at the ankles and, in one case, opisthotonos was seen. Finally the spasms become generalized, resulting in generalized seizures, and may also affect the muscles of respiration. By this time, most of the patients had lost consciousness.

Just as in a true status epilepticus, the uncontrolled muscular activity may result in a refractory metabolic acidosis. This probably happened in cases 3 and 6. It may also lead to a hyperpyrexia as in cases 2, 6, 7, and 10. In cases 2, 3, and 6, there was evidence of muscular destruction (rhabdomyolysis) or injury (elevated creatinine kinase). This was followed by multiorgan failure in cases 2 and 6, in addition to disseminated intravascular coagulation in the latter. From this series, it may be concluded that of the five fatalities, most died from complications that may be ascribed to uncontrolled seizures with muscular hyperactivity.

The initial seizures seemed not to be epileptic (central) in nature and were more likely the result of abnormal activity at the level of the reflex arch or spinal cord. EEG monitoring, which was done on cases 1, 5, and 7, demonstrated abnormal sharp wave activity, but no sure signs of epilepsy were seen. This finding may help to differentiate the syndrome from those patients who suffer from epilepsy-like (central) seizures following myelography. Interestingly, in cases 1 and 3, no signs of localized, cellular reaction were found at autopsy and histopathologic examination of the brain and spinal cord. Slight edema of the brain was described in the latter and, in the former, the findings were entirely normal. It is tempting to take this as an indication that the syndrome may not be a result of inflammatory changes such as radiculitis, myelitis, or encephalitis resulting from chemical irritation or involvement of the immune system. A possible key to the etiology may be the ionic nature of the CM molecule itself, which may change or destabilize the membrane potential of affected neurons, resulting in abnormal function without visible changes at autopsy. Apart from the ionicity, other chemotoxic (neurotoxic) properties are probably equally important, suggested by the fact that the ionic CM meglumine iothalamate has been used routinely for myelography with only rare occurrences of tonic-clonic seizures, whereas the use of diatrizoate or metrizoate probably leads to seizures in the majority of cases.

In one of the cases described by Wollin et al (3), the patient was lying on her left side when she inadvertently received diatrizoate intrathecally. It is noteworthy that her initial symptoms such as numbness, pain, and weakness were localized to the left side of the body, whereas she later developed seizures localized to the right side. It is proposed that her lying on the left side with her head relatively low would allow CM to migrate rapidly to her head and reach the motor cortex of her left cerebral hemisphere, thereby giving right-sided seizures. This explanation suggests that the CM also has a toxic effect on the cerebral hemisphere, not only at the spinal level. However, with the head and trunk elevated for myelography, the symptoms will exhibit an ascending pattern in which cerebral toxicity comes into play at a later stage than spinal toxicity. It is not unlikely that it is the cerebral effect that is responsible for the loss of consciousness and generalized seizures seen later in the clinical course.

Based on the described series we suggest that the term "ascending tonic-clonic seizure (ATCS) syndrome" may be applied to cases fulfilling the criteria listed in Table 1.

Therapeutic possibilities after inadvertent intrathecal application of a CM seem limited. General measures are required to ensure monitoring and supporting vital functions. An anesthesiologist should be called at an early stage. Specific treatment should be aimed at controlling the seizures to avoid pain, fractures, hyperthermia,

TABLE 1: The ATCS syndrome

1) The patient has undergone a myelographic examination during the preceding 6 hours.
2) Painful tonic-clonic muscular spasms are present.
3) The spasms occur in paroxysms lasting approximately 15–30 seconds.
4) The spasms may be precipitated by touching or handling the affected limbs.
5) Following a lumbar myelogram, the spasms spread from the lower limbs in an ascending pattern to involve also the trunk and upper limbs.
6) The patient is at first fully conscious, but becomes stuporous or comatose as the symptoms ascend in a cephalad direction.

acidosis, and muscular injury. Intravenous diazepam, which was given to several patients in our series, had only a transient effect and seemed unable to prevent the seizures from recurring. Instead, persistent seizures may effectively be stopped by subjecting the patient to general anesthesia together with a neuromuscular blocking agent (eg, pancuronium bromide) and artificial ventilation as suggested by Wollin et al (3). They proposed that this treatment should be maintained for 48 hours before withholding the blocking agent to see if muscular twitchings recommence. Because this procedure will mask external signs of seizures, an EEG may be of help to distinguish the ATCS syndrome from postmyelographic seizures of epileptic origin. Steroids might have a role in reducing or preventing cerebral edema. When the accident is discovered early (within 2 to 3 hours) after intrathecal injection, it is quite reasonable to suggest that the patient be placed in "head and trunk up" position to confine the (heavier than CSF) CM solution to a low level. If there is evidence of a large dose of CM having been administered, a careful CSF exchange-washout may be seriously considered. General anesthesia could be required to prevent convulsions during this procedure.

The identification of the CM possibly causing ATCS is vitally important from both a medical and legal point of view. Therefore, efforts must be undertaken to identify the CM used in each case. This step is obviously equally important to any medical review procedure that the responsible institutional and medical authorities may want to perform following an event. HPLC was used in some of the cases in the present series. Presently, it is the most suitable method for exactly identifying a particular CM from among several alternatives.

The inadvertent injection of the wrong CM might not be immediately apparent for several reasons. In such cases we recommend obtaining a 10-mL serum or a 2-mL CSF sample from the patient at any time up to 12 hours after the intrathecal CM injection for the purpose of submitting it to HPLC analysis and CM identification. Analysis may also be performed on pieces of brain cortex obtained at autopsy. If the samples are sent to the CM manufacturer for analysis, it is advisable to retain one half of the samples at the hospital if for any reason reanalysis and/or confirmation by an independent body should later be required.

The authors, who are employed in the pharmaceutical industry, hope for a close and open cooperation with the medical profession to minimize the risk of injury to our patients. It is hoped that the present article will contribute to better awareness, and that all possible efforts will be made to avoid giving the wrong CM by close supervision and review of the routines in radiology departments.

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