

Persistent Neurological Deficit from Iodinated Contrast Encephalopathy Following Intracranial Aneurysm Coiling A Case Report and Review of the Literature

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Summary

Neurotoxicity from iodinated contrast agents is a known but rare complication of angiography and neurovascular intervention. Neurotoxicity results from contrast penetrating the blood-brain barrier with resultant cerebral oedema and altered neuronal excitability. Clinical effects include encephalopathy, seizures, cortical blindness and focal neurological deficits. Contrast induced encephalopathy is extensively reported as a transient and reversible phenomenon. We describe a patient with a persistent motor deficit due to an encephalopathy from iodinated contrast media administered during cerebral aneurysm coiling. This observation and a review of the literature highlights that contrast-induced encephalopathy may not always have a benign outcome and can cause permanent deficits. This potential harmful effect should be recognised by the angiographer and the interventionalist.

Introduction

Iodinated contrast induced encephalopathy is a rare complication of angiography. It was first reported in 1970 as a transient cortical blindness after coronary angiography¹. Clinical manifestations include encephalopathy, seizures, cortical blindness and focal neurological deficits. Imaging is important in confirming the diagnosis and in excluding thromboembolic and haemorrhagic complications of angiography². Typical CT findings include abnor-

mal cortical contrast enhancement and oedema, subarachnoid contrast enhancement, and striatal contrast enhancement. Since the first clinical description, there are 39 CT/MR confirmed cases of contrast-induced encephalopathy in the English language medical literature with documented clinical follow-up, summarized in Tables 1 and 2. Prognosis is generally reported as favourable with rapid recovery²⁻²⁵. There are two reports of persistent visual field deficits following contrast-induced encephalopathy^{26,27}. Here, we describe a patient with a persistent neurological deficit following a contrast-induced encephalopathy after endovascular aneurysm treatment. A literature review reveals eight cases of autopsy proven fatal cerebral oedema due to contrast neurotoxicity²⁸⁻³⁰. This report highlights the neurotoxic potential for iodinated contrast media to result in a permanent neurological deficit.

Case Report

A 50-year-old woman on screening CT angiogram was found to have three cerebral aneurysms: 7 mm paraophthalmic artery, 4 mm left middle cerebral artery, and 5 mm left carotid cave aneurysms. Risk factors for aneurysm formation included a family history of subarachnoid haemorrhage (sibling died following middle cerebral artery aneurysm rupture), hypertension and smoking. 120 mL of Iohexol (Omnipaque 300, GE Healthcare Ireland, Cork, Ireland), a low osmolar non-ionic contrast

agent, was used for the CT angiogram without complication.

She underwent successful coiling of the paraophthalmic artery aneurysm using a balloon remodeling technique. The patient had received a total of 220 mL of Iopramide (Ultravist 300, Bayer Healthcare Pharmaceuticals, Wayne, NJ, USA), a low osmolar non-ionic contrast agent. The final angiogram showed occlusion of the distal dome of this aneurysm with some filling of the proximal lobe. All arteries were shown to be patent. Immediately following the procedure the patient had a complete right hemiparesis (face, arm and leg, power 0/5), sensory loss and right-sided neglect. A non-contrast CT brain within one hour of the coiling showed oedema in the left cerebral hemisphere, involving the frontal, parietal and occipital lobes (Figure 1). There was no haemorrhage or infarct. She was commenced on dexamethasone and mannitol. By day 2, her motor deficit was unchanged but her right-sided neglect had resolved. CT brain studies on day 3 and day 7 showed a progressive decrease in the cortical oedema in most of the left hemisphere, but with residual oedema in the peri-rolandic region. MRI on day 11 showed persistent oedema in the precentral and postcentral gyri (Figure 1). There was no restricted diffusion or infarct. There was a slow progressive clinical improvement, and on discharge at day 20, the right arm and leg motor weakness had improved to power 3/5, but there was right-sided spasticity with hyperreflexia and clonus. Her sensory symptoms had resolved. Three-month follow-up MRI showed resolution of the perirolandic oedema but with high signal in keeping with gliosis in the motor cortex (Figure 1). Follow-up cerebral angiography at one year showed occlusion of the paraophthalmic aneurysm. On this occasion 100 mL of Iohexol (Omnipaque 300) was used without issue. At one year, the patient had no motor power deficit but had persistent spasticity in her right hand and leg. This deficit caused some lifestyle restriction but she was able to care for herself (modified Rankin Score 2).

Discussion

Iodinated contrast media are reported to disrupt the blood-brain barrier temporarily causing an encephalopathy that is usually self-limiting. We describe a case that was not self-limiting. Contrast encephalopathy has been report-

ed following angiography of most vascular territories^{2,5,15,16,24,31,32}, and also following endovascular aneurysm treatment^{19,26,27,33}. Transient cortical blindness is the most frequent reported clinical presentation. The reported incidence is 0.06% of patients undergoing coronary angiography³², 0.3%-1% of patients undergoing vertebral angiography^{31,34} and 2.9% (4/139) with endovascular coil treatment of posterior circulation aneurysms²⁷.

Clinical effects of neurotoxicity from iodinated contrast agents include encephalopathy, seizures, cortical blindness and focal neurological deficits. Contrast encephalopathy is extensively reported to have a benign clinical course^{2-25,35}. Table 1 summarises the published cases in the English language literature of CT proven contrast encephalopathy with clinical follow-up. From these studies, neurological recovery occurs at a median time of 2.5 days [range, 0.2-30 days].

We have shown that contrast encephalopathy may result in a persistent neurological deficit. Table 2 summarises the available data on published cases of proven contrast encephalopathy with persistent deficits or death. These include reports of persistent visual field defects²⁶⁻²⁷, retrograde amnesia^{36,37} and fatal cerebral oedema following iodinated contrast administration^{28-30,38}. Junck and Marshall reported a clear case of contrast overdose²⁸, where 15.5 mL/kg of body weight of diatrizoate meglumine was given, similar to the median lethal dose (LD50) of 10-20 mg/kg in most species³⁹. All these fatal cerebral oedema cases involved the use of high osmolar contrast agents. While high osmolar contrast agents are no longer used in routine practice, contrast encephalopathy is reported with all types of contrast agents, and these cases highlight the potential for iodinated contrast agents to cause fatal cerebral oedema.

Diagnosis of contrast encephalopathy is important as it may have a similar presentation to embolic, haemodynamic, and haemorrhagic complications following angiography or endovascular intervention. It is essential to have a post treatment angiogram that shows no arterial branch occlusions and a CT or MRI study that shows no acute infarct. Cases of contrast encephalopathy usually show characteristic CT brain findings – abnormal cortical contrast enhancement and oedema, subarachnoid contrast enhancement, striatal contrast enhancement – if the CT is performed soon after presentation²⁷. However, recent reports have also highlighted

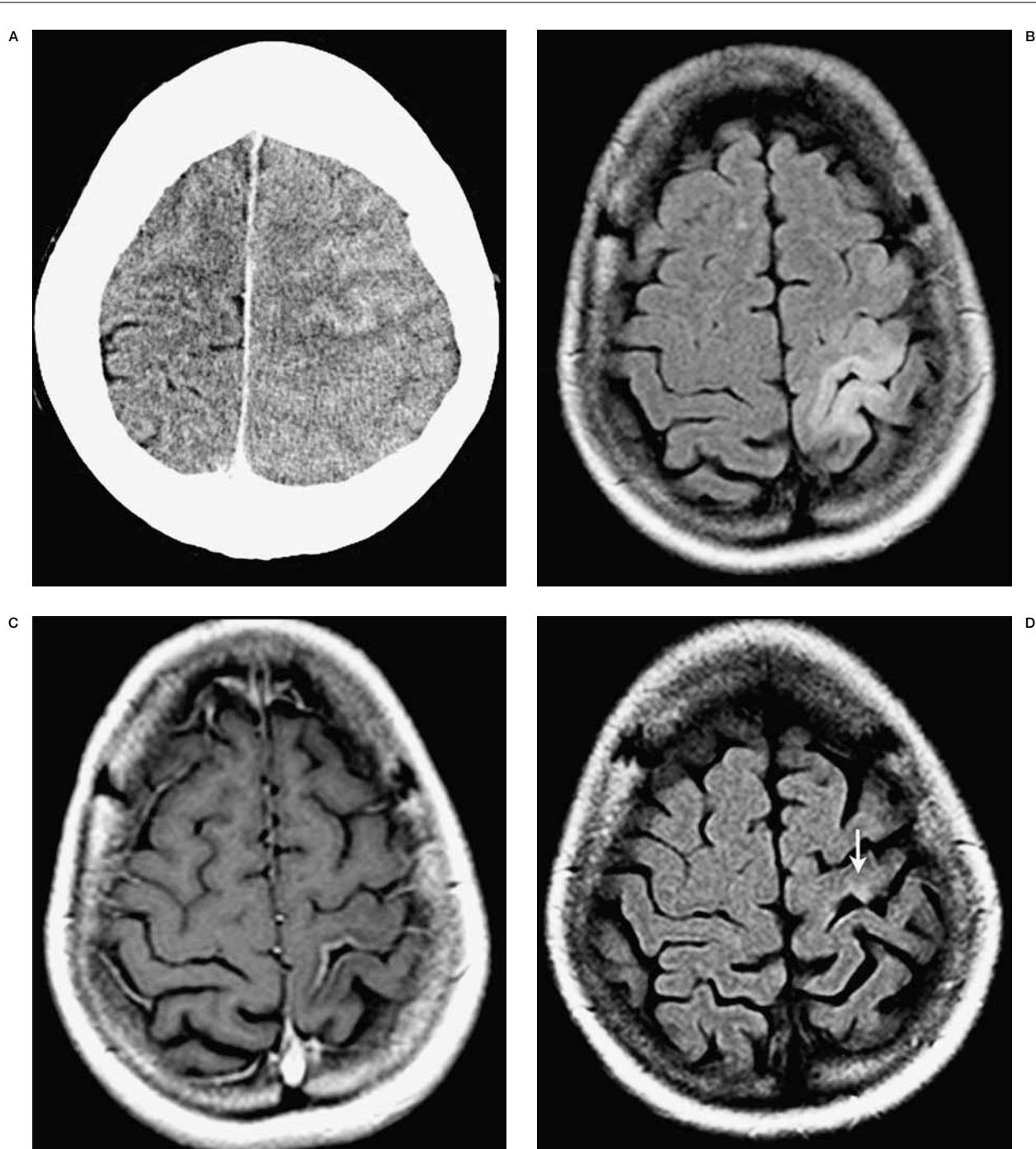


Figure 1 A) Non contrast CT brain immediately following coiling shows abnormal cortical contrast enhancement and edema in the left hemisphere and subarachnoid contrast enhancement. B) Axial FLAIR image on day 11 post coiling shows residual signal change particularly in the precentral and postcentral gyri. C) Contrast T1-weighted image on day 11 shows enhancement in the precentral gyrus, indicating persistent breakdown in the blood-brain barrier. D) Axial FLAIR image three months post coiling shows persistent signal change in the precentral gyrus, consistent with gliosis (arrow).

ed that asymptomatic contrast enhancement and oedema of the cortex is a fairly common finding and reported in 23-54% of CTs performed within two hours of uneventful emboli-

zation of cerebral aneurysms⁴⁰⁻⁴². The enhancement resolves by 25 hours in most cases. Diagnosis of contrast encephalopathy is therefore made by finding typical CT findings in a symp-

Table 1 CT/MRI confirmed blood brain barrier disruption following arteriography with favourable clinical outcomes: demographics, contrast agents, presentation, CT findings and outcome.

Reference	Sex/ Age	Arteriography	Indication for study	Possible Risk Factors	Previous angiography class	Contrast agent	Volume (mL)	Presentation	CT brain region involved	Clinical resolution	CT Brain resolution
Studdard et al. (1981) ²²	F/59	Aortic arch	Post carotid surgery check	Renal impairment; hypertension	Yes	Ionic monomer high osmolar	Diatrizoate meglumine	150	Cortical blindness (Anton); headache, myoclonus or seizure	Bilateral parieto-occipital	3 d
Numaguchi et al. (1984) ¹⁶	F/53	Carotid artery & Carotid arteries	Meningioma investigation	None reported	No	Ionic monomer high osmolar	Diatrizoate meglumine	60	Partial motor seizure	Right Temporo-parietal	1 d
Uitz et al. (1988) ²⁴	F/72	Aorta, Coronary & Carotid arteries	Carotid artery stenosis	Renal impairment	No	Ionic monomer high osmolar	Diatrizoate meglumine; Iothalamate meglumine	120	Partial motor seizure	Bilateral fronto-parietal	1 d
Henzlova et al. (1988) ¹⁰	F/57	Abdominal aorta	Renal artery angioplasty	Renal artery angioplasty	No	Ionic monomer high osmolar	Diatrizoate meglumine	250	Cortical blindness; right facial palsy; left hemiparesis	Bilateral occipital, basal ganglia	4-5 d
Lantos (1989) ²	F/49	Aortocoronary bypass graft disease	Coronary artery disease	Peripheral vascular disease	Yes	Ionic dimer low osmolar	Ioxaglate (Hexabrix)	200	Blindness and severe headache	Bilateral occipital	N/A
M/64	Carotid artery Aorta	Subclavian artery Aorta	Smoker, Hypertension	Carotid artery stenosis	No	Ionic monomer high osmolar	Diatrizoate meglumine	30	Cortical blindness (Anton); seizure; nystagmus	Right occipital, thalamus, brainstem	N/A
M/71	Carotid artery Vertebral artery	Carotid artery PCOMY aneurysm	None reported	Carotid artery stenosis	No	Non-ionic monomer low osmolar	Iohexol (Omnipaque)	38	Cortical blindness; ophthalmoplegia	Left (temporo-parieto) occipital aphasia	3 d
F/68	Carotid artery Vertebral artery	Arch, Carotid & Vertebral arteries	None reported	Carotid artery stenosis	No	Non-ionic monomer low osmolar	Iohexol	24	Cortical blindness (Anton); confusion; amnesia	Bilateral occipital	6 d
Shyn & Bell (1989) ²⁰			None reported	Carotid artery stenosis	No	Ionic monomer high osmolar	Diatrizoate meglumine; Iothalamate meglumine	50	Cortical blindness	Bilateral occipital	2 d
Kinn & Breisblatt (1991) ¹²	M/55	Aortic arch Coronary artery disease	None reported	Coronary artery disease	Yes	Ionic monomer high osmolar	Diatrizoate meglumine	228	Cortical blindness	Bilateral occipital	1 d
Parry et al. (1993) ¹⁷	M/62	Aortic arch Coronary artery	None reported	Coronary artery disease	No	Non-ionic monomer low osmolar	Iopamidol (Niopam)	270	Cortical blindness; clumsy right upper limb	Bilateral occipital	3 d
Kamata et al. (1995) ¹¹	M/62	Coronary artery	None reported	Coronary artery disease	Yes	Non-ionic monomer low osmolar	Iopamidol 370	170	Severe headache; bilateral blindness; amnesia	Bilateral cerebellum, occipital and thalamus	2 d
Sticherling et al. (1998) ²¹	M/55	Aortic arch Coronary artery stenting	None reported	Coronary artery	No	Non-ionic monomer low osmolar	Iomeprol (Iomeiron)	280	Cortical blindness; confusion; amnesia	Bilateral occipital	5 d
Eckel et al. (1998) ⁵	F/71	Spinal angiogram	None reported	Spinal angiography	No	Ionic dimer low osmolar	Ioxaglate	360	Right-sided visual neglect; Wernicke's aphasia	Bilateral occipital and left parietal lobes	4 d

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Dangas et al. (2001) ⁴	M/82	Carotid artery	Carotid artery stenting	Hypertension	Yes	Ionic dimer low osmolar	Ioxaglate	50	Confusion; left hemiparesis and left neglect	Right fronto-parietal	2 d	2 d (MRI)
Lim & Radford (2002) ¹⁴	F/63	Coronary artery	Coronary artery disease	Hypertension; diabetes	No	Non-ionic monomer low osmolar	Iopromide (Ultravist)	160	Headache; loss of vision (light or objects); Occipital lobe impaired alertness	Bilateral parieto-occipital	5 d	1 d
Merchut & Richie (2002) ¹⁵	F/74	Abdominal aorta	Renal artery angioplasty	Renal impairment; hypertension	No	Non-ionic monomer low osmolar	Iopamidol	415	Visuospatial disorder	Bilateral parieto-occipital	4 d	4 d
Zwicker & Sila (2002) ¹⁵	F/52	Renal artery	Coronary artery stenting	None reported	Yes	Non-ionic monomer low osmolar	Ioversol (Optiray)	280	Visual loss; headache; confusion; right pronator drift; aphasia	Bilateral fronto-and parieto-occipital	1.5 d	4 d
Gellen et al. (2003) ⁸	..52	Coronary artery	Coronary artery disease	Renal impairment; hypertension	No	Non-ionic monomer low osmolar	Iopamidol	400	Bilateral complete blindness	Cerebellum, bilateral occipital, thalamus	3 d	N/A
Saigal et al. (2004) ¹⁹	F/74	Carotid artery	Coiling basilar apex aneurysm	Hypertension	No	Non-ionic monomer low osmolar	Iohexol 300	N/A	Complete bilateral blindness; confusion	Left fronto-occipital	1 d	N/A
Uchiyama et al. (2004) ³³	M/72	Carotid artery	Coiling anterior aneurysm	None reported	No	Non-ionic monomer low osmolar	Iopamidol	260	Right hemiparesis and motor aphasia.	Left cerebral cortex and left basal ganglia	7 d	N/A
Yazici et al. (2007) ⁴²	F/70	Coronary artery	Coronary artery disease	Hypertension; diabetes	No	Non-ionic monomer low osmolar	Iobitidol 350 (Xenetix)	75	Bilateral cortical blindness; headache; confusion; amnesia and disorientation	Bilateral occipital	3 d	1.5 d
Tatli et al. (2007) ²³	F/52	Coronary artery	Coronary artery disease	None reported	No	Non-ionic monomer low osmolar	Iomeprol	150	Bilateral blindness; nausea and vomiting	Bilateral occipital	5 hours	N/A
Garcia de Lara et al. (2008) ⁷	..61	Coronary artery	Coronary artery disease	None reported	No	Non-ionic monomer low osmolar	Iohexol 350	300	Decreased consciousness and bilateral blindness	Bilateral occipital, deep gray regions	3 d	N/A
..78	Coronary artery	Coronary artery disease	Renal impairment; hypertension	Yes	No	Non-ionic monomer low osmolar	Iohexol 350	624	Bilateral blindness	Bilateral occipital, deep gray regions	10 d	N/A
González et al. (2008) ⁶³	F/70	Coronary artery	Coronary artery disease	None reported	No	Non-ionic monomer low osmolar	Not reported	1500	Seizure	Right frontal	1 d	1 d
Niimi et al. (2008) ²⁷	F/54	Vertebral artery	Coiling basilar apex aneurysm	Hypertension	No	Non-ionic monomer low osmolar	Not reported	62	Vision loss to light perception	Occipital lobe (MRI)	30 d	N/A
Fang et al. (2009) ⁶	M/80	Carotid artery	Coronary and carotid stenting	Hyper tension	No	Non-ionic monomer low osmolar	Iohexol	250	Right hemiparesis	Left fronto-parietal-occipital	2 d	4 d
Guimaraens et al. (2009) ⁹	M/51	Carotid artery	Right ICA aneurysm coiling	Hyper tension	No	Non-ionic monomer low osmolar	Iopromide	300	Gerstmann's left visual field deficit & hemiparesis; right gaze deviation	Right fronto-parietal-occipital	2 d	5 d (MRI)
Alp et al. (2009) ³	M/56	Coronary artery	Coronary artery disease	None reported	Yes	Non-ionic monomer low osmolar	Iohexol 350	220	Bilateral cortical blindness	Bilateral occipital and frontal lobes	4 d	4 d
Kocabay & Karabay (2011) ¹³	M/47	Coronary artery	Coronary artery stenting	None reported	No	Non-ionic monomer low osmolar	Iopromide 300	150	Confusion; agitation; nausea; headache	Right occipital lobe	8 hours	2 d
M/70	Coronary artery	Diabetes	Coronary artery stenting	None reported	No	Non-ionic monomer low osmolar	Iopromide	120	Confusion; nausea	Occipital lobe	12 hours	1.5 d

Table 2 Contrast encephalopathy following arteriography with adverse clinical outcomes: demographics, contrast agents, presentation, CT findings and clinical outcome.

Reference	Sex/Age	Arteriography	Indication for study	Possible Risk Factors	Previous angiography	Contrast agent class	Contrast agent	Volume (mL)	Presentation	CT brain region involved	Clinical outcome
Shrivastava et al. (1985) ²⁹	M/10	Cardiac chambers, aorta and pulmonary trunk	Tetralogy of Fallot with left Blalock-Taussig shunt	Hypoxaemia	Not stated	Ionic monomer high osmolar	Urografin 76	76	Sudden apnoea and cardiac arrest	No CT brain. Autopsy showed brain oedema, prominent gyri and tonsillar herniation	Death at 15 hours
Junck & Marshall (1986) ²⁸	F/7	Aortic arch	Aortic coarctation	Hypertension	No	Ionic monomer high osmolar	Renografin 76	340	Generalised seizures. Then developed supraventricular tachycardia progressive hypertension	Cortex, basal ganglia and thalamus	Death at 33 hours
Vranckx et al. (1999) ³⁷	F/68	Aortocoronary bypass graft	Coronary artery disease	Hypertension; diabetes	Yes	Non-ionic monomer low osmolar	Iohexol	180	Confusion; amnesia; aphasia; and cortical blindness	Bilateral occipital and thalami	Retrograde amnesia. Other symptoms resolved >6 d.
Sharp et al. (1999) ³⁶	F/73	Coronary artery stenting	Coronary artery	Hypertension	No	Non-ionic monomer Ionic monomer	Diatrizoate meglumine 350 Iohexol	800	Seizures; dysphasia; gait instability; bilateral postural tremor	Bilateral frontal and occipital	Retrograde amnesia. Other symptoms resolved <7 d.
Shinoda et al. (2004) ²⁶	F/62	Vertebral artery	Posterior inferior cerebellar aneurysm coiling	None reported	No	Non-ionic	Not specified	297	Cortical blindness; confusion	Bilateral occipital, basal ganglia, frontal	Persistent visual field deficit documented at 3 weeks
Niumi et al. (2008) ²⁷	M/41	Vertebral artery	Superior cerebellar aneurysm coiling	None reported	Yes	Non-ionic	Not specified	225	Bilateral visual loss; agitation	Right parietal	Persistent visual field deficit documented at 4 years

tomatic patient after exclusion of thromboembolic and haemorrhagic complications.

Reported demographic risk factors for clinically overt contrast encephalopathy include hypertension and renal failure. Of the imaging/autopsy proven cases with clinical follow-up (Tables 1 and 2), 43% had hypertension and 15% renal failure; 45% of cases had no reported underlying risk factor. Some studies have suggested a correlation between contrast load and CT findings in asymptomatic patients^{41,42}; however, in symptomatic patients no such correlation was found²⁷. Also there was no specific contrast load that reliably led to contrast gyral enhancement⁴¹ and indeed contrast encephalopathy has been reported in four patients with contrast (ionic and non-ionic media) volumes less than 40 mL². Most studies, including this case, suggest that prior and subsequent angiograms and procedures did not appear to result in the same complication^{3,4,10-12,22,25,27,35,37}. Based on current knowledge, this complication appears to be an idiosyncratic reaction to contrast. This fact makes avoidance of contrast encephalopathy difficult. Why some patients experienced contrast gyral enhancement whereas others do not and why only a minority are symptomatic remains unknown and requires further investigation.

The mechanism and causes of neurotoxicity is controversial. The blood-brain barrier is impermeable to radiographic contrast material under normal conditions. Transfer of contrast material increases if the blood-brain barrier is disrupted or if contrast material is overdosed or applied intra-arterially^{16,43-46}. In neurointerventional procedures, the contrast is injected repeatedly into a single vessel. As such, even if the total amount of contrast media is not excessive, the cumulative injections may contribute to blood-brain barrier breakdown³³. The neurotoxic effects of iodinated contrast media are usually attributed to a temporary blood brain barrier disruption⁴⁷. Uchiyama et al.³³ found elevated concentration of CSF iodine in their index case and not in 4 control cases, supporting evidence of a temporary breakdown of the blood-brain barrier. The cause of the blood brain barrier disruption is variably attributed to the hyperosmolality and chemotoxicity of contrast media^{2,16,21,28,43-56}. Studies suggest that contrast media penetrates the blood-brain barrier as a function of dosage, contact time, concentration of anions in the material, and lipophilic

characteristics²⁷. Hyperosmolality, especially with older high osmolar contrast agents, is hypothesized to cause shrinkage of endothelial cells and open tight junctions⁵⁴. However, hyperosmolality per se is not a requirement to induce blood-brain barrier disruption. Transient cortical blindness and global amnesia has been reported with iodixanol, a non-ionic dimer with osmolality equivalent to plasma⁵⁷. In addition, animal studies showed that blood-brain barrier damage caused by carotid angiography with non-ionic monomeric and dimeric contrast media was not attributable to their osmolalities, but due to some other physical and/or chemical effects of these media on the blood-brain barrier⁵⁸. One such factor may be the endothelin family of peptides. Endothelin release can be induced by radiocontrast media, have been shown to increase human brain endothelial cell permeability and is implicated in the pathophysiology of disorders associated with blood-brain barrier injury, including posterior reversible leukoencephalopathy syndrome⁵⁹⁻⁶¹.

Because of the transient and rare nature of this complication, no definitive evidence base exists for specific treatments. Some authors have described the use of intravenous dexamethasone and/or mannitol^{2,9,26,27}, whilst others appear to have settled for close observation of the patient in the immediate post procedure period⁶.

Conclusion

Neurotoxicity from iodinated contrast agents is a rare complication of angiography and neurovascular intervention. The infrequency with which it is encountered makes it a diagnostic challenge. Diagnosis of contrast encephalopathy is made by demonstrating typical CT findings in a symptomatic patient after exclusion of thromboembolic and haemorrhagic complications. Our report and literature review show that contrast-induced encephalopathy has the potential to cause permanent neurological dysfunction. This potential harmful effect should be recognised by doctors performing cardiovascular angiography and interventions. The challenge of future experimental studies will be to define the risk factors and neurotoxic mechanism of iodinated contrast agents, knowledge that may help us avoid this complication.

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