PRACTICE

Amphetamine abuse and intracranial haemorrhage

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SUMMARY

Amphetamines taken by any route can cause cerebral vasculitis and intracranial haemorrhage. 8 cases were seen in a neurosurgical unit over 3.5 years. The published work indicates that those who experience these complications, mainly young adults, have poor outcomes.

INTRODUCTION

The first reported death from amphetamine abuse was in 1939, in a 25-year-old man who had taken the drug repeatedly as a stimulant before a college examination[1]. Intracerebral haemorrhage (ICH) from amphetamine abuse was first described in 1945[2], since when a further 36 cases have been reported[3–32]. Similar cases have been described after use of amphetamine-like stimulants such as ephedrine, phenylpropanolamine and 3,4-methylenedioxy-amphetamine ('ecstasy')[33–36].

We report 8 cases of ICH associated with amphetamine, seen in our neurosurgical unit in the past 3.5 years—4 analysed retrospectively and 4 prospectively. All patients underwent computed tomography (CT) and cerebral digital subtraction angiography (DSA).

CASE SERIES

Table 1 lists presenting symptoms, CT scan appearances, angiographic findings, diagnosis, therapy and outcome for each patient (numbers 38–45). 7 had a parenchymal haematoma (Figures 1 and 2)—3 in the frontal lobe, 1 in the frontoparietal region, 1 in the parietal lobe, 1 in the temporal lobe and 1 in the brainstem. One patient had a subarachnoid haemorrhage (SAH). He also had 'beading' of small and medium-sized arteries that persisted on follow-up (Figure 3). DSAs in the remaining patients were unremarkable.

The time from exposure to onset of symptoms ranged from less than 10 minutes to about 2 months (median within 1 day). None of our patients had confirmatory toxicological tests since all admitted to having abused amphetamine.

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PREVIOUS REPORTS

The apparent increase in frequency of ICH associated with amphetamines and amphetamine-like agents presumably reflects an increase in use of these recreational drugs. Young people seem to be the main group at risk: only 4 reported cases were in people over 40 years (*see* Table 1). Taking our 8 cases in conjunction with the 37 previously reported, we find a mean age of 28 years (median 26, range 16–60). Most patients were repeat abusers (31) but nearly one-third claimed to be first-time or infrequent users. 57% had taken the drug orally, 34% intravenously (i.v.) and 5% by inhalation. One patient used the drug both i.v. and by inhalation, and in one the route was unknown. ICH is seen with all routes of intake.

Of the 25 patients who underwent CT examination, 21 (84%) had proven ICH (3 with additional SAH); 3 had SAH alone, and 1 had a brainstem haemorrhage. One patient, in whom CT was negative, had SAH confirmed by lumbar puncture. In the 35 patients who underwent angiography, twenty examinations were normal (or revealed only mass effect from a haematoma), 16 showed vasculitic beading, and 1 showed arteriovenous malformation.

The effects of amphetamine abuse are reported elsewhere[37]. Kaufman *et al.*[38] have suggested that there is a wide margin of safety between a therapeutic and a toxic dose, and in many patients with ICH the event has followed prolonged usage[8,15]. However, ICH has occurred in some individuals after a single low-dose exposure[3,6,9].

The close temporal relation between exposure and the onset of ICH suggests that the cause is systemic hypertension induced by the drug[8,11,23]. Most of our patients presented with ICH within 24 hours. However, one case is described in which ICH occurred 2 years after the last amphetamine exposure and was thought to be associated with vasculitis[15].

Angiography has two main purposes in these patients—to identify any underlying structural abnormality[1] and to detect vasculitis. Use of amphetamine may provoke ICH in the presence of a structural abnormality such as an

Table 1 **Details of published cases including current series**

Case No.	Year	Ref.	Sex	Age	Drug abuser	Route	Presenting symptom	CT appearance	Angiogram	Therapy	Diagnosis	Outcome
1	1945	2	M	36	Y	Oral	R hemi	N/A	N/A	?	?	Died
2	1956	26	M	42	N	Oral	Headache; L hemi	N/A	N/A	Craniotomy	R parietal ICH	L hemi
3	1965	3	F	30	N	Oral	Headache	N/A	N/A	Supportive	L parietal ICH	Died
4	1967	7	M	16	?	Oral	'Coma'	N/A	N/A	Supportive	ICH	Died
5	1969	18	M	24	Y	i.v.	Headache; L hemi	N/A	N/A	Supportive	?	L hemi
6	1970	11	M	18	Y	Oral	Headache; LP blood	N/A	Normal	Supportive	SAH	Normal
7	1970	11	M	26	Y	i.v.	R headache; L hemi	N/A	R frontal mass	Craniotomy	R frontal ICH	L hemi
8	1970	31	M	25	Y	i.v.	Headache, seizure, L hemi	N/A	R frontal mass	Craniotomy	R frontal ICH	L hemi
9	1970	31	M	26	N	Oral	Headache; L hemi	N/A	R frontal mass	Craniotomy	R frontal ICH	L hemi
10	1971	27	F	38	Y	i.v.	Headache; R hemi, aphasia	N/A	Beading	Supportive	L ICH	R hemi
11	1971	27	F	32	Y	i.v.	?	N/A	Beading	?	?	Convalescence
12	1971	27	M	24	Y	?	R hemi	N/A	Beading	?	L ICH	Convalescence
13	1971	27	F	29	Y	i.v.	?	N/A	Beading	?	?	Normal
14	1971	27	M	37	Y	i.v.	Coma	N/A	Beading	?	?	Normal
15	1971	24	F	35	Y	i.v.	Headache, L hemi	N/A	Beading, R mass	Steroids	R ICH	L hemi
16	1973	14	M	26	Y	i.v.	Headache, R hemi	N/A	L frontal mass	Supportive	L frontal ICH	Died
17	1975	5	F	19	?	Oral	Headache, R hemi	N/A	Beading	Steroids	L ICH	R hemi
18	1977	25	M	25	Y	i.v.	Headache, coma	N/A	Beading	Supportive	?	Died
19	1978	19	M	22	Y	i.v.	Headache, R hemi	N/A	L frontal mass, beading	Craniotomy	L frontal ICH	Dysphasia, R hemi
20	1979	22	M	25	Y	i.v.	Headache, R hemi	L frontal ICH	L frontal mass	Supportive	L frontal ICH	Seizures
21	1979	8	F	24	Y	i.v., inhaled	Headache, R hemi, coma	L frontal ICH, SAH	N/A	Supportive	L frontal ICH	Died
22	1981	4	M	25	Y	Oral	Headache, seizure	Normal (LP blood)	Beading	Supportive	SAH	Normal
23	1982	9	M	17	?	Oral	Headache, L hemi	R parietal ICH	Normal	Supportive	R parietal ICH	?
24	1983	30	M	24	?	Oral	Headache, L hemi, coma	R parietal ICH	Normal	Craniotomy	R parietal ICH	L hemi
25	1983	15	M	60	?	Oral	L hemi, confused	R parietal ICH	Beading	Supportive	R parietal ICH	L hemi
26	1983	15	M	51	Y	Oral	R hemi	L thalamic ICH	?	Supportive	L ICH	R hemi

continued

Table 1 continued

Case No.	Year	Ref.	Sex	Age	Drug abuser	Route	Presenting symptom	CT appearance	Angiogram	Therapy	Diagnosis	Outcome
27	1983	15	M	19	Y	Oral	Bifrontal headache	L frontal ICH	Beading	Supportive	L frontal ICH	Normal
28	1983	15	M	19	Y	Inhaled	R hemi	L parietal ICH	Normal	Supportive	L parietal ICH	R hemi
29	1983	23	M	28	Y	i.v.	Blurred vision, headache	R temporal ICH, AVM	R sylvian AVM	Craniotomy	AVM	Hemianopia
30	1983	32	M	16	Y	Oral	Seizures	L parietal ICH	Beading	Supportive	L parietal ICH	Normal
31	1984	28	M	18	Y	Oral	L frontal headache, R hemi	L parietal ICH	Beading	Supportive	L parietal ICH	R hemi
32	1988	6	M	18	Y	i.v.	Headache, vomiting	L parietal ICH, SAH	Spasm, beading	Supportive	L parietal ICH	Normal
33	1989	21	M	24	?	Oral	Dysphasia, R hemi	L frontal ICH	Normal	Supportive	L frontal ICH	Normal
34	1990	17	M	31	Y	i.v.	Seizure	SAH	Normal	Supportive	SAH	Mental impairment
35	1993	16	F	21	?	Oral	R hemi, aphasia	L frontal ICH	N/A	Craniotomy	Angioma	R hemi
36	1995	29	F	19	Y	Oral	L hemi	R parietal ICH, SAH	N/A	Craniotomy	AVM	Normal
37	1996	10	F	23	Y	Oral	L hemi	R Frontal ICH	Normal	Supportive	R frontal ICH	Mild L hemi
38	This series		M	27	N	Inhaled	Headache, vomiting	R temporal ICH	Normal	Supportive	R temporal ICH	Normal
39	This series		M	26	Y	Oral	Headache	Brain stem bleed	Normal	Supportive	Brainstem bleed	Normal
40	This series		M	32	N	Oral	Headache	SAH	Beading	Supportive	SAH	Normal
41	This series		M	30	N	Oral	Headache, L hemi	R frontal ICH	Normal	Supportive	R frontal ICH	Normal
42	This series		M	47	Y	Oral	Headache	SAH, hydrocephalus	N/A	EVD	SAH	Died
43	This series		M	30	Y	Oral	Headache, vomiting	R frontal ICH	Normal	Supportive	R frontal ICH	L hemi
44	This series		M	24	N	Oral	R hemi	L frontoparietal ICH	Normal	Supportive	L frontal ICH	R hemi
45	This series		M	28	Y	Oral	Headache, coma	L parietal ICH	Normal	Craniotomy	L parietal ICH	R hemi, dysphasia

Hemi=Hemiplegia; LP=lumbar puncture; ICH=intracranial haemorrhage; SAH=subarachnoid haemorrhage; i.v.=intravenous; CT=computed tomography; L=left, R=right; EVD=external ventricular drain; AVM=arteriovenous malformation

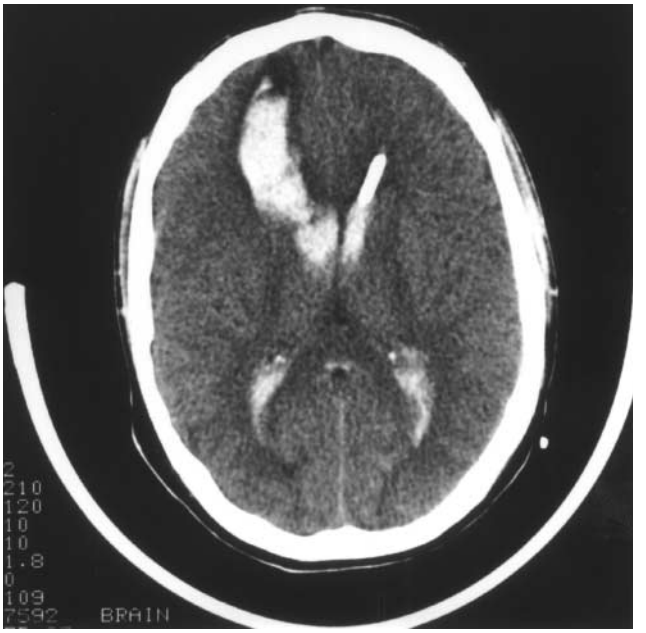

Figure 1 **Large frontal haemorrhage extending into the lateral ventricle**

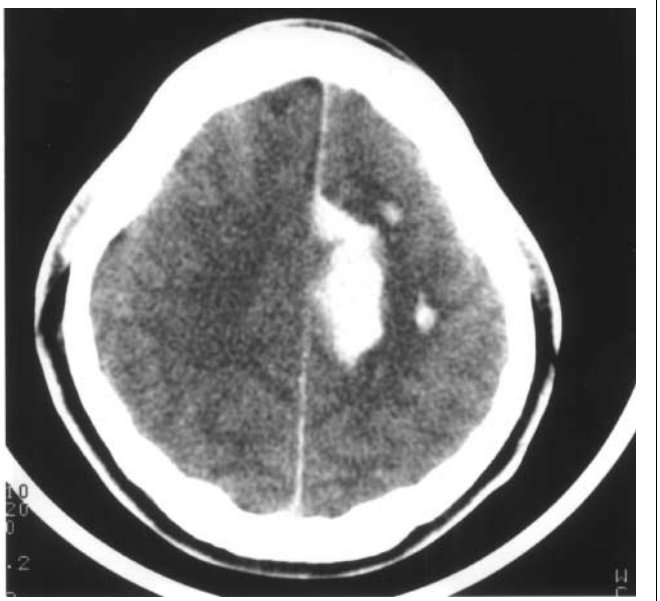

Figure 2 **Left cerebral haematoma involving cingulate gyrus and frontoparietal white matter**

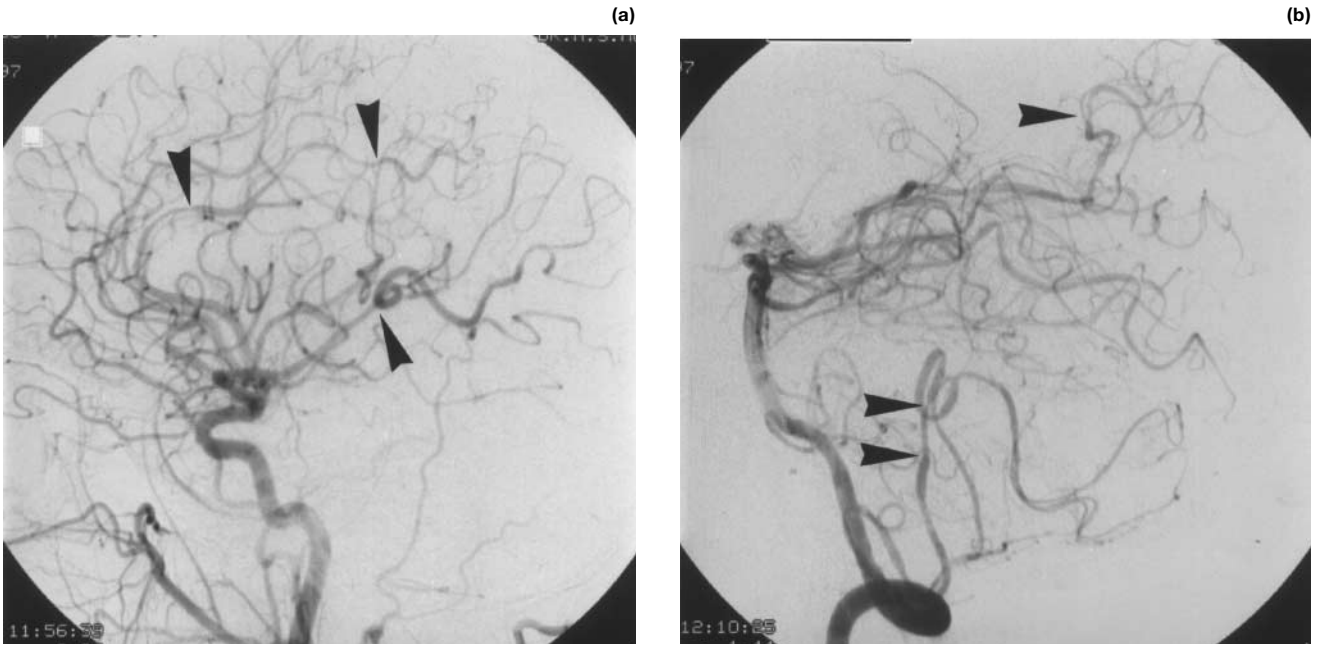

Figure 3 **Digital subtraction angiograms.** (*a*) Lateral view of right common carotid artery: note peripheral segmented narrowing and dilatation (beading) in middle and anterior cerebral artery branches (arrowheads); (*b*) beading of the posterior inferior cerebellar artery and posterior cerebral artery branches (arrowheads)

aneurysm or arteriovenous malformation[11,17,23,29]. Alternatively the fact that it has been used may be irrelevant, in a patient with spontaneous subarachnoid haemorrhage[39,40]. Particularly in this young population, there should be a low threshold for repeat angiography for SAH because of the risks of missing an underlying abnormality in the presence of vascular spasm[39].

The angiographic feature that is characteristic of vasculitis is extensive irregular segmental narrowing or beading of small arteries[41,42]. This pattern of narrowing and dilatation is in contrast to the more usual involvement of the trunks of major cerebral arteries seen in subarachnoid haemorrhage, in which there is relative sparing of the distal branches. This angiographic pattern is not specific to amphetamine abuse and can be seen in abusers of other drugs[43]. Although vasculitis may follow only a single exposure[6], repeated exposure to amphetamines is the usual history[14,38,44]. Conci *et al.*[6] believe that the vasculitis

resolves spontaneously[6]; Landi and Spickler[41] regard the changes in small and medium sized arteries as permanent (which might explain the occurrence of late bleeds).

The causal mechanism of vasculitis is not known. If it is related to catecholamine release[44], this might account for the similar angiographic pattern of medium and small vessel spasm sometimes seen with subarachnoid haemorrhage. An alternative explanation is that the vasculitis is due to contamination from microparticles in the injected solutes[8,27,45,46] This could explain the similarities found between intravenous abusers of different substances but it does not account for the vessel changes seen in those using amphetamine by mouth or inhalation. Deranged cerebral blood flow has been observed in users of amphetamine and other drugs[43] but the severity is not related to the dose or the duration of exposure, nor are the blood vessel changes confined to the cerebral circulation[47].

Work in animals has revealed immediate angiographic changes after exposure to amphetamine[48]. Affected vessels display fibrinoid angiitis, necrosis of the media and intima, leukocytic infiltration and intimal proliferation[15]. Amphetamine may produce direct vessel damage causing platelet aggregations and/or serotonin release, with increased vascular permeability[41].

Treatment must be decided case by case but is mainly supportive. Of the 45 cases reported (including our own series), 27 had purely supportive therapy; 9 had craniotomy for evacuation of haematoma. Full nursing care, reduction of blood pressure to normal and management of associated (possibly drug-related) disease are the key elements. Neurosurgical referral for possible intervention is appropriate; and, when fit enough, patients should undergo cerebral angiography.

Whilst the reported cases are almost certainly biased towards the severely affected, the outcomes have been notably poor: 7 patients died and only 14 (32%) achieved a good recovery. Can the results be improved? Salanova and Tauber[28] favour urgent treatment of the vasculitis with cyclophosphamide (2 mg/kg per day), intravenous dexamethasone (24 mg/day i.v.) and prednisolone (50 mg/day). The adverse factors probably go well beyond the obvious vascular lesions: this patient group is likely to have concurrent illnesses; there is the possibility of systemic as well as cerebral vascular damage[1,11,38,47]; and some patients will continue their drug habit on discharge. We should also not forget the possibility that some of these patients with ICH are victims of trauma[27]. The patient outcomes in the 45 published cases were described as normal in just 13.

CONCLUSION

ICH associated with amphetamine abuse causes a substantial number of deaths and considerable morbidity. In a young patient the finding of a frontal or parietal lobar haematoma should raise suspicion that an amphetamine is responsible.

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