

Neurosarcoidosis-related intracranial haemorrhage: three new cases and a systematic review of the literature

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Background and purpose: Intracranial haemorrhage in neurosarcoidosis (NS-ICH) is rare, poorly understood and the diagnosis of NS may not be immediately apparent.

Methods: The clinical features of three new NS-ICH cases are described including new neuropathological findings and collated with cases from a systematic literature review.

Results: *Cases:* (i) A 41-year-old man with headaches, hypoandrogenism and encephalopathy developed a cerebellar haemorrhage. He had neuropathological confirmation of NS with biopsy-proven angiocentric granulomata and venous disruption. He responded to immunosuppressive therapy. (ii) A 41-year-old man with no history of hypertension was found unconscious. A subsequently fatal pontine haemorrhage was diagnosed. Liver biopsy revealed sarcoid granulomas. (iii) A 36-year-old man with raised intracranial pressure headaches presented with a seizure and a frontal haemorrhage. Hilar lymph node biopsy confirmed sarcoidosis, and he was treated successfully. *Systematic Review:* Twelve other published cases were identified and collated with our cases. Average age was 36 years and M:F = 2.3:1; 46% presented with neurological symptoms and 31% had CNS-isolated disease. Immediate symptoms of ICH were acute/worsening headache or seizures (60%). ICH was supratentorial (62%), infratentorial (31%) or subarachnoid (7%). 40% had definite NS, 53% probable NS and 7% possible NS (Zajicek criteria). Antigranulomatous/immunosuppressive therapy regimens varied and 31% died.

Conclusions: This series expands our knowledge of the pathology of NS-ICH, which may be of arterial or venous origin. One-third have isolated NS. Clinicians should consider NS in young-onset ICH because early aggressive antigranulomatous therapy may improve outcome.

Introduction

Sarcoidosis is a multisystem granulomatous disease typically presenting in early adulthood [1]. Over 90% of patients with sarcoidosis have pulmonary involvement, and although only 5% are reported to have clinically evident neurosarcoidosis (NS), 10% have neuroimaging changes and 14% have CNS

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involvement at autopsy [2–5]. Published pathological studies have identified CNS microvascular changes in the majority (86%) of patients with NS, including the involvement of small arteries, arterioles and small veins, but usually without vascular complications [6–9]. There are few published reports of intracranial haemorrhage (ICH) in sarcoidosis [10–13]. We aimed to describe three new cases of ICH in neurosarcoidosis (NS-ICH) and present a detailed systematic review of the literature to enhance knowledge regarding the clinical presentation and outcome in patients with NS-ICH.

Methods

The authors encountered three new cases of ICH in patients with sarcoidosis. We collated anonymized clinical details, laboratory, neuroimaging and histopathology results. A detailed systematic review of the literature was performed to look for published cases of ICH in NS. Google Scholar and PubMed (MEDLINE 1966–2010) were searched to identify relevant peer-reviewed manuscripts using MeSH terms: sarcoid (-osis), haemorrhage, stroke, intracerebral bleed, vasculitis and granuloma; and non-MeSH terms: neurosarcoid (-osis) and CNS sarcoid (-osis). Manuscripts in

all languages were reviewed/translated. Reference lists in relevant articles and textbooks were hand searched. Pre-specified data were extracted and tabulated. Written consent for the use of data was obtained from patients/relatives where possible. This work was conducted in accordance with good clinical practice, subject to privacy requirements and adhered to the principles of the Declaration of Helsinki.

Results

Case 1

A 41-year-old, right-handed, non-smoking Caucasian man presented with a 4-month history of headaches, hemisensory aura, fatigue, somnolence, decreased libido and reduced facial hair growth. He developed complex partial seizures and raised intracranial pressure-type headaches. Neurological examination demonstrated slow mental processing speed with impaired verbal recall, absent spontaneous venous pulsation on fundoscopy bilaterally, bilateral upper limb intention tremor, reduced deep tendon reflexes and gait ataxia, but was otherwise normal.

He had mild anaemia and lymphopenia, normal serum angiotensin-converting enzyme (ACE) levels, ele-

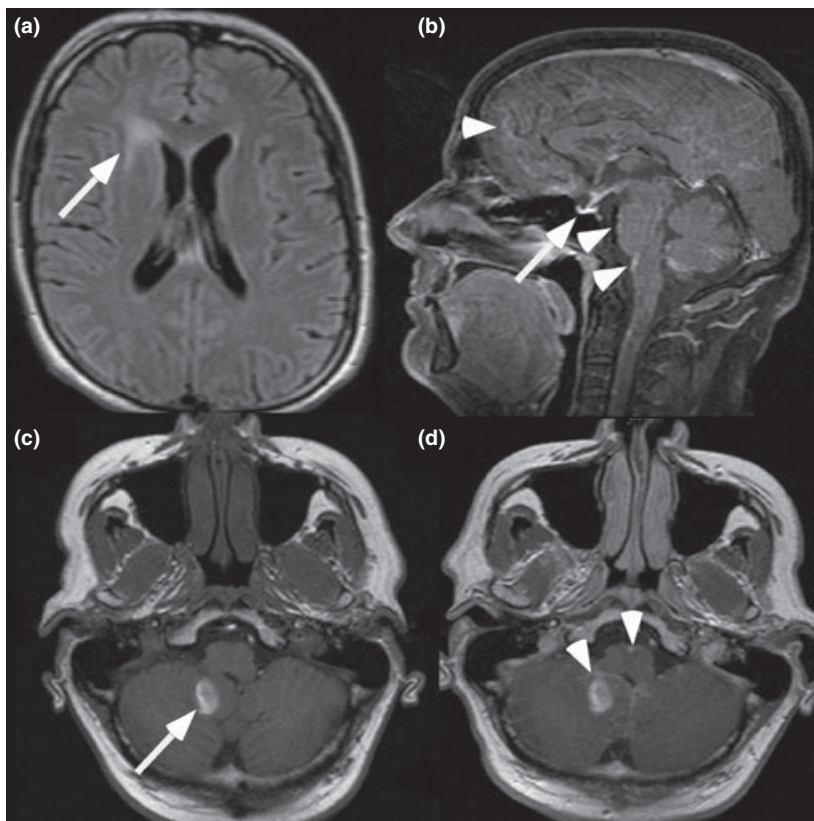


Figure 1 (a) Axial FLAIR MRI brain revealing confluent increased signal in the right frontal periventricular and deep white matter (arrow). (b) Sagittal T1-weighted MRI post-gadolinium showing enhancement of the infundibulum (arrow) and patchy meningeal enhancement (arrowheads). (c) Axial T1-weighted MRI of brain pre-gadolinium showing high signal intensity consistent with right cerebellar tonsil haemorrhage (arrow), and (d) T1-weighted MRI post-gadolinium showing medullary and cerebellar leptomeningeal enhancement (arrowheads).

vated prolactin and hypogonadotropic hypogonadism. MRI brain showed enhancement in the deep white matter, pituitary and meninges (Fig. 1). EEG revealed frontal intermittent rhythmic delta. CSF opening pressure was elevated, with lymphocytosis, elevated protein, low glucose, and negative oligoclonal bands, cytology, and microbiology. Clinical suspicion of sarcoidosis prompted a CT thorax, transbronchial biopsy and endoscopic ultrasound-guided fine needle aspirates from random lymph nodes; these tests were normal.

His encephalopathy worsened with increasing seizures, headache, vomiting, hiccoughs and ataxia. He developed mild neck stiffness, intermittent skew deviation, more vestibulo-cerebellar signs, right-sided pyramidal signs and stimulus-sensitive myoclonus. Repeat neuroimaging showed a right cerebellar tonsil haemorrhage, mild medullary compression and increased meningeal enhancement (Fig. 1), with normal intracranial CT angiography. The cerebellar haemorrhage was managed conservatively. Right frontal brain biopsy showed non-necrotizing granulomas involving dura, leptomeninges and cortex, surrounding and investing cortical arterioles and cortical veins, with vessel wall destruction, rupture of a vein and fibrin deposition, without hemosiderin deposition (Fig. 2). A diagnosis of definite NS with ICH was made.

Intravenous methylprednisolone 1 g/day for 5 days was given, followed by 60 mg of oral prednisolone/day and six cycles of IV cyclophosphamide (500 mg fortnightly). After cyclophosphamide, 1 g/day of oral mycophenolate was added with titration up to 2.5 g/day and the alternate day steroid dose was slowly tapered. Gradient-echo MRI confirmed the haemorrhage and identified a left superior temporal juxtacortical microhaemorrhage. Over the next year, his NS clinically fluctuated with headaches and visual blurring. Steroids were increased and he was changed from mycophenolate to methotrexate 15 mg/week. Radiological appearances improved. He remained clinically stable on methotrexate, reducing the doses of prednisolone (40 mg alternate days), levetiracetam 500 mg BD and testosterone 100 mg/day.

Case 2

A 41-year-old non-smoking Caucasian man, with a 2-day history of headache, was found unresponsive in bed. The primary care physician had previously prescribed diclofenac for gout. There was no history of hypertension. In the emergency department, blood pressure was 170/90 mm Hg, but general exam was normal otherwise. There was eye opening and extension to painful stimuli, with intermittent decerebrate posturing, but no verbalization. Spontaneous venous

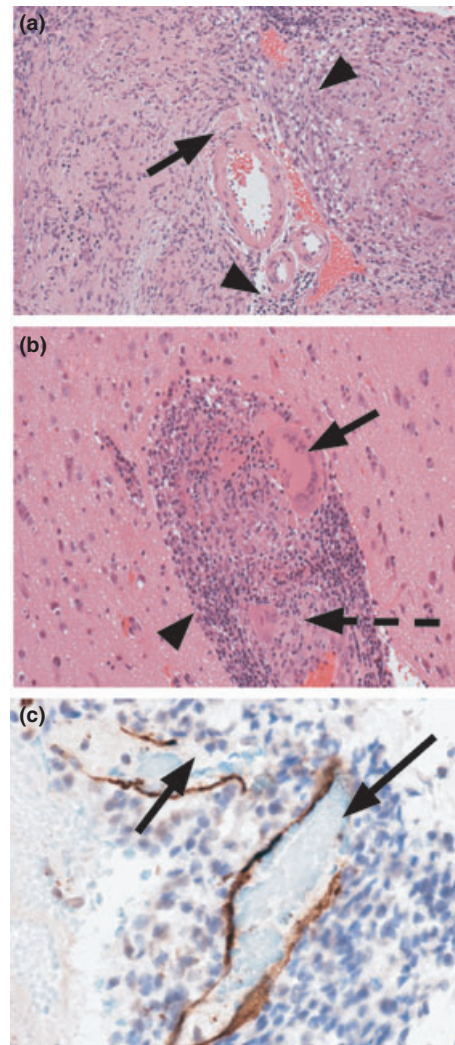


Figure 2 (a) Haematoxylin and Eosin stain of a section of right frontal cortex showing juxtameningeal venules with granulomatous thickening of the tunica media (arrow) and perivenular mononuclear cell aggregation (arrowhead). (b) Haematoxylin and Eosin stain showing a perivascular inflammatory infiltrate (arrowhead), a non-necrotizing granuloma (blunt arrow), and vessel wall invasion and destruction by inflammatory cells forming a granuloma (dashed arrow). (c) CD34 immunostain of right frontal cortex showing two veins, with rupture of the wall (arrows).

pulsation was absent with normal discs otherwise. Pupils were pinpoint, with absent vestibulo-ocular, corneal and gag/cough reflexes. He had a flaccid quadriplegia with brisk deep tendon reflexes and a left extensor plantar response. The patient was intubated and ventilated.

Laboratory investigations showed lymphopenia, mild hyponatremia, alkaline phosphatase 291 IU/l (normal < 120), gamma-glutamyl transferase 247 IU/l (normal < 60) and normal serum ACE. Urgent CT

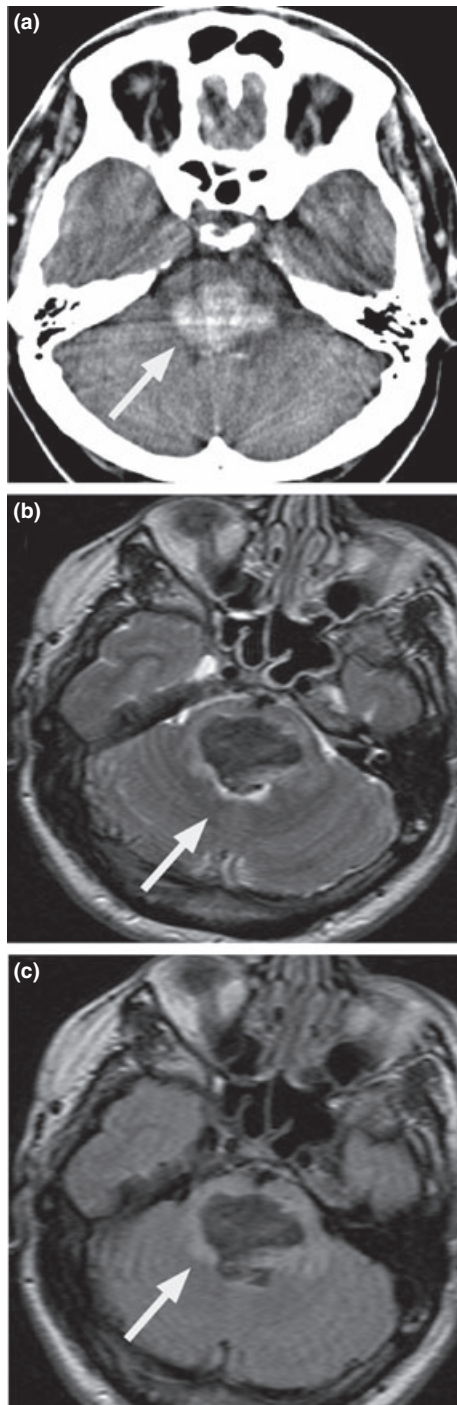


Figure 3 (a) Non-contrast CT brain showing pontomesencephalic acute haemorrhage (arrow). (b) Mid-pontine axial T2-weighted and (c) FLAIR MRI demonstrating low signal from subacute blood with the compression of the fourth ventricle (arrow).

brain showed a large dorsocentral pontomesencephalic haemorrhage, extending into the fourth ventricle without hydrocephalus (Fig. 3). Chest radiography was normal. MRI brain 1 day later confirmed subacute

pontomesencephalic haemorrhage (Fig. 3), and asymmetrical periventricular white matter changes and an intracallosal lesion consistent with CNS inflammatory changes; intracranial MR angiography was normal. He was given prednisolone 20 mg daily for acute gout. Pneumonia developed requiring IV piperacillin/tazobactam. His liver function tests worsened and a subsequent CT abdomen showed diffuse hepatosplenic hypodensities. Percutaneous ultrasound-guided liver biopsy revealed fibrosis, non-necrotizing granulomata, numerous multinucleated giant cells and asteroid bodies consistent with sarcoidosis, but no hepatic vasculitic changes. A diagnosis of 'probable neurosarcoid' with systemic sarcoidosis was made. The biopsy was complicated by an acute abdomen and cardiac arrest. He subsequently developed progressive right facial weakness and ipsilateral facial twitching. Despite antimicrobial therapy, and 3 days of IV methylprednisolone 1 g/day, there was no meaningful neurological recovery. The patient died from pneumonia and pulmonary oedema 54 days after admission. Permission for post-mortem examination was not secured.

Case 3

This 36-year-old Caucasian man had a 2-month history of worsening diurnal, headaches and facial pain, exacerbated by coughing, with photophobia and phonophobia. He also had intermittent bilateral earache, flu-like symptoms and mild pyrexias. He presented to the neurology service following an episode of transient expressive aphasia followed by a generalized tonic-clonic seizure. General and vascular examination was normal. There was postictal drowsiness and disorientation. Cranial nerve examination was unremarkable with no papilloedema; limb examination was entirely normal with a normal gait.

Laboratory tests revealed a mild lymphopenia; serum ACE was 77 U/l (normal < 52). Chest radiograph showed bulky hila, and CT brain confirmed a left frontal intracerebral haemorrhage (Fig. 4). First CSF examination was acellular, with elevated protein, normal glucose and matched oligoclonal bands; subsequent CSF examinations showed lymphocytosis. CT body showed enlarged paratracheal, hilar, subcarinal and aortopulmonary lymph nodes. MRI showed T2-weighted hyperintensities around the optic chiasm, subcortical white matter and right cerebellar hemisphere. Contrast-enhanced T1-weighted MRI showed widespread nodular enhancement of the meninges (Fig. 4). Digitally subtracted catheter cerebral angiogram was normal. A mediastinal lymph node biopsy revealed extensive non-necrotizing epithelioid granulomata with giant cells, consistent with sarcoidosis.

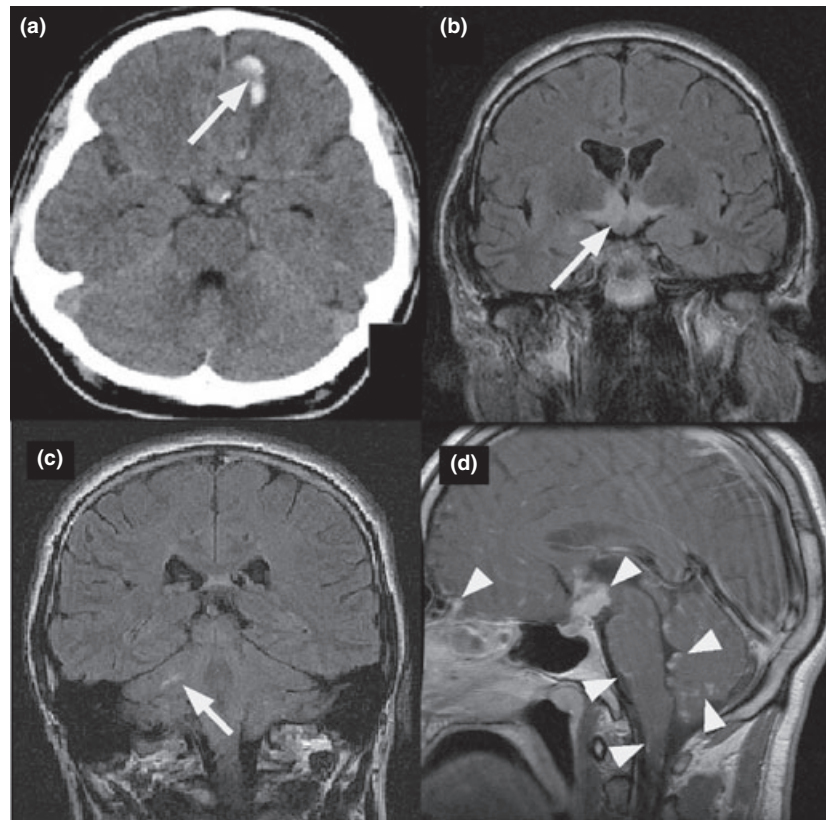


Figure 4 (a) Non-contrast CT brain demonstrating left frontal subcortical haemorrhage (arrow). (b) Coronal FLAIR MRI showing high signal around the optic chiasm (arrow), (c) right cerebellar subcortical white matter (arrow) and (d) diffuse nodular meningeal enhancement on post-contrast sagittal T1-weighted MRI (small arrowheads).

He was commenced on oral prednisolone 60 mg/day and 2 mg/kg per day of azathioprine. The prednisolone dose was reduced to 40 mg/day after 4 weeks, with further stepwise reductions every 2 weeks down to 20 mg/day, which he remained on for 3 months. Azathioprine was increased to 2.5 mg/kg per day after 3 months. Seizures were controlled on 1000 mg of sodium valproate daily. The patient stabilized on this treatment regimen, and at 3 months, the white matter changes on MRI had improved, but there was persistent posterior fossa meningeal and suprasellar region enhancement. Six months after presentation, he developed erectile dysfunction with hypogonadotropic hypogonadism requiring testosterone.

Systematic literature review

Twelve other cases of NS-ICH were identified in the literature with sufficient clinical details in ten cases [6, 8–12, 14–18]. Combined data from all 15 cases (including the three new cases) were collated (Table 1).

First symptoms of sarcoidosis were neurological in 46%. Five had no prodromal symptoms before ICH. Ten patients had one or a combination of prodromal symptoms for days to months: seven experienced new or worsening headaches, two had

ataxia, two had cognitive difficulties, one developed daytime somnolence and one had seizures. At presentation, six patients had worsening or acute severe headache, six had seizures, three had an acute posterior fossa syndrome and two coma. The exact ICH location was not specified in two cases, but the majority of haemorrhages (8/13 cases with sufficient details available) were supratentorial and varied in size; only one patient had extracerebral subarachnoid bleeding.

Thirty-one per cent had disease that remained confined to the CNS. According to Zajicek criteria, six (40%) were definite (three confirmed before death), eight (53%) probable and one (7%) possible NS [19]. Of the six definite NS cases, four showed pathologic vessel wall involvement with arterial wall granulomata of the media and/or intima [6, 8, 9, Case 1] and breach of the lumen in one case [6]. Two had fibrinoid necrosis of the media [6, 9] associated with granulomatous changes in one [6]. Venous wall involvement was described in one case [8], and our case showed clear biopsy-proven venous rupture (Fig. 2). Two other cases from the literature showed venous involvement with associated microhaemorrhages [6]. Serum ACE was elevated in 3/8 tested cases (38%), and CSF ACE was elevated in one of two tested.

Table 1 Demographic, clinical features, location of haemorrhage and outcome in published cases and three new cases of intracranial haemorrhage in neurosarcoidosis described in this report

Author	Year	Age (years)	Sex	Seizures	Cerebellar signs	Location of hemorrhage	CNS deficit	Relapsed	Progressive	Death
Herring and Ulrich [6]	1969	20	M	–	+	Basal ganglia	+	+	+	+
Caplan <i>et al.</i> [8]	1983	21	M	–	+	Cerebellum	+	–	–	+
Oksanen [16]	1986	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Oksanen [16]	1986	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Lavrnjic <i>et al.</i> [15]	1992	20	F	–	–	Occipital	+	–	–	–
Berek <i>et al.</i> [10]	1993	35	M	–	–	Subarachnoid	–	–	–	–
Libman <i>et al.</i> [9]	1997	48	F	–	–	Frontal	+	+	+	+
Eid <i>et al.</i> [18]	1998	31	F	+	–	Frontal	–	+	+	–
Cipri <i>et al.</i> [14]	2000	31	M	+	–	Occipital	–	–	–	–
Dakdouki <i>et al.</i> [11]	2005	25	M	–	+	Pontomesencephalic	–	+	–	–
Yamaguchi <i>et al.</i> [17]	2006	57	M	+	–	Parietal	–	–	–	–
Ferroir <i>et al.</i> [12]	2009	49	F	+	–	Basal ganglia	–	+	+	–
Case 1	–	41	M	+	+	Cerebellum	+	+	–	–
Case 2	–	41	M	+	–	Pontomesencephalic	+	–	+	+
Case 3	–	36	M	+	–	Frontal	+	–	–	–

N/A, information not available.

Information on initial medical treatment was available in eight cases with NS-ICH:

- 1 40–60 mg or 1 mg/kg of prednisolone daily in four patients, in whom two had a good initial therapeutic response.
- 2 0.75 mg/kg of prednisolone and 150 mg of azathioprine daily in two cases, of whom one had a therapeutic response.
- 3 One patient received 1 g/day of IV methylprednisolone only for 3 days, but did not respond to treatment.
- 4 One patient partially responded to 1 g of IV methylprednisolone daily for 5 days and pulsed 500 mg IV cyclophosphamide, with slowly tapering prednisolone from 60 mg/day.

Medical treatment was successful with the initial regimen in 3/8 patients. In three patients, higher doses of steroids and addition/change of a steroid-sparing agent led to clinical stabilization. Two patients did not respond to medical treatment and died.

Three patients had surgical treatment with good results: one underwent removal of a dural granulomatous mass and two had intraparenchymal haematoma evacuation. One of the latter also received 20 mg of prednisolone/day.

Discussion

The clinical course, laboratory, neuroimaging and histopathological data in three new patients with NS-ICH have been described and collated with available data in 12 further published cases with NS-ICH [6, 8–12, 14–18]. Historically, catastrophic 'neurovascular events' in three potential cases are alluded to in

a seminal publication [20], as well as fatal pulmonary and gastrointestinal haemorrhage [4, 21–23].

Intracranial haemorrhage in NS is possibly as common as ischaemic stroke in NS, occurring in 0.6% of unselected sarcoidosis and NS series (Table S1). Patients with NS-ICH are predominantly men (69%) in the fourth to fifth decade. Forty-six per cent of patients with NS-ICH present with neurological involvement without a prior diagnosis of sarcoidosis, and the disease remains isolated to the CNS in 31% of patients with NS-ICH compared with 11% of all NS cases.

Compared with patients with NS without ICH, patients with NS-ICH more frequently had seizures (54% vs. 13%), headache (48% vs. 28%) [24], vestibulocerebellar dysfunction (31% vs. 13%) and aseptic meningitis (38% vs. 23%). Sixty-two per cent of patients with NS-ICH in whom adequate information was available had supratentorial haemorrhages, similar to primary ICH in young adults [25], with infratentorial haemorrhage in 31% and subarachnoid haemorrhage in 7%. Thirty-eight per cent had progressive disease, some because of ICH and one-third died. In contrast, mortality in NS without ICH is 5–10% [26]. Only 31% of the patients with NS-ICH recovered completely with no neurological deficit.

In the CNS, sarcoid granulomata follow perivascular spaces and penetrate brain parenchyma [6]. In autopsy series of patients with NS, basal leptomeninges (100%) are more commonly involved than the dura (28%) and the brain parenchyma is often involved [3, 6]. Cerebrovascular lesions in NS involve small- to medium-sized arteries, with three types of arterial pathology: granulomatous angiopathy,

granulomatous arteritis and fibrinoid necrosis of the wall [6]. Phlebitis and microhaemorrhages have been associated with neuropathological series [6] without the confirmation of a causal link between the two. Cerebral venous involvement causing phlebitis may be clearly seen [6, 8], but our detailed biopsy data confirm that destruction of venous structures may occur independent of any clinical or radiological evidence of venous thrombosis (Case 1). Biopsy correlation with MRI findings suggests that vascular involvement is more common in patients with leptomeningeal disease [27]. Haemorrhages occurred in various locations in this series, with 'mixed' vascular (venous and arterial) involvement on histological studies that could not necessarily be differentiated with traditional radiological investigations. Atypical locations of intracranial haemorrhage, smaller haemorrhages, microhaemorrhages on T2-weighted MRI and leptomeningeal enhancement in basal areas may be helpful markers for NS-ICH. Future MR imaging studies, including T2-weighted MRI, are warranted to study the extent and anatomical distribution of microbleeds in NS.

No evidence-based guidelines or randomized controlled trial data exist to guide treatment for NS-ICH. In addition to managing ICH, early high-dose steroids and other antigranulomatous therapy should be initiated [26]. Patients need to be monitored closely because antigranulomatous treatment may need to be altered if patients relapse during follow-up. In NS without ICH, oral corticosteroids alone have been reported to lead to initial improvement in 62–69%, stabilization in 15–25%, but 13–15% deteriorate [28, 29]. Of patients who start oral corticosteroids, 24% relapse/accrue disability. Methotrexate 7.5–15 mg/week, azathioprine 150–200 mg/day or cyclophosphamide 600–800 mg/m² per month IV have been empirically proposed. Additional immunosuppressive regimens induce improvement in 35%, stabilization in 55%, but 10% deteriorate [28].

Seizures occurred at presentation in 40% of NS-ICH cases (vs. 7–14% with primary ICH, Fishers' exact test $P \leq 0.01$) [30, 31] and are associated with a worse prognosis in NS [3, 32]. When the diagnosis is made and appropriate treatment administered, seizure control is usually good (Cases 1 and 3) [32]. The prognosis of NS-ICH remains guarded. One-third died; 33% had some deficit related to NS and ICH and 22% of survivors had progressive disease.

Conclusions

NS-ICH is possibly under-recognized, but importantly, is amenable to early aggressive antigranulomatous therapy. The pathogenesis of NS-ICH is poorly

understood, but an aggressive venous and/or arterial vasculopathy with granulomatous invasion is likely. Many patients present with an acute neurological syndrome, and one-third have CNS-isolated disease. The apparent heterogeneity of haemorrhage location may be due to mixed venous and arterial bleeding. Detailed neuroimaging studies with contrast enhancement and gradient-echo images, followed by appropriate biopsies facilitate diagnosis. Anti-granulomatous therapy with corticosteroids and immunomodulatory therapy is beneficial in individual cases and should be considered early to prevent deterioration and promote recovery.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Neurosarcoidosis series.

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