Responses to Brief

Re: Adam Strain

Prepared on behalf of:

Northern Ireland Inquiry into Hyponatraemia Related Deaths

By:

Dr Waney Squier Consultant and Clinical Lecturer

Department of Neuropathology

Level 1, West Wing

John Radcliffe Hospital

Headley Way, Oxford

OX3 9DU

Response to report of Professor Rating.

My comments are below. I have appended a Power Point presentation of case examples to illustrate my responses.

In his second report, Professor Rating seeks your views on the following points:

1. Page 6 (document reference 240-004-006): "A fulminant SVT leading to death in such a short time would have produced some cortical bleedings."

Although this is what is written in the textbooks, I don't think it is necessarily always the case. The first effect of venous thrombosis is to obstruct venous outflow which leads to oedema in the tissue drained by the obstructed vein. The subcortical white matter is the first area to be affected when the superficial system is involved. Venous outflow obstruction in neonates and infants is most commonly hamorrhagic but not always so; a quarter of babies may have ischaemic infarction only (Ramenghi, Govaert et al. 2009; Yang, Chan et al. 2010). In older patients the proportion of ischaemic infarction may be higher; Ruiz cites 53% (Ruiz, Yilmaz et al. 2009) Wasay (Wasay and Azeemuddin 2005) lists non haemorrhagic infarction as an indirect sign of cerebral venous thrombosis. In some cases bleeding may be related to associated clotting disorders rather than the venous obstruction per se.

As examples pictures are appended of cases where swelling and ischaemic infarction were the first or sole manifestation of venous thrombosis. A premature baby 7 weeks old (corrected age 1 week) developed brain swelling and only three days later developed bleeding. Figure 1 (left) shows the CT scan on day 1 with brain swelling. By day 3 MRI scan showed development of subcortical and subarachnoid bleeding (arrows).

In another case (Figure 2) a baby of 3 months had sinus thrombosis after trauma and developed severe brain swelling without haemorrhage (Figure 2 left). This case was complicated by hypoxia occurring subsequent to the trauma. Haemorrhage was not seen on scan or at autopsy, but sinus thrombosis was confirmed.

A third baby, Figure 3, who was 3 months old, developed CVT. The clotted surface veins were identified on brain scans (left image, white arrows) but the brain parenchyma showed only swelling without bleeding (left image black arrows). The extent and severity of the parenchymal damage was clear on the follow up scan 5 months later (right image) when only a thin rim of meninges remained following death of the affected brain tissue.

These cases confirm that, while parenchymal haemorrhage is common in fatal venous thrombosis it is not inevitable.

2. Page 6 (document reference 240-004-006): "how likely is it that a peracute, severe SVT leading to death within the space of 1-2 hours was not seen during brain section?"

Venous and sinus thrombosis may be missed if the dural sinuses are not all examined carefully at autopsy. Some of the dural sinuses are very small and deeply placed at the base of the skull. The dural sinuses were not described in the autopsy report nor were they sampled for histology. It is not possible to be sure that there was not thrombosis. There may be no associated thrombosis in the cerebral veins, so even histological examination of the brain may not identify the presence of acute thrombus in the sinuses. I saw widespread and very obvious intravascular clot in case 1 but not in case 2 above.

3. Page 24 (document reference 240-004-024): "Whether the neuropathology in Adam's case
   - is in line with an increased intracranial pressure and furthermore
   - whether [she] *you* can exclude with certainty that Adam died as a result of increased intracranial pressure"

The neuropathology is absolutely consistent with raised intracranial pressure and brain swelling (particularly hindbrain swelling). I cannot exclude that Adam died as the result of increased intracranial pressure.

4. Document reference 240-004-028: Whether the "quite substantial neuropathololgical changes" are more in favour or against the diagnosis of PRES.

There is little known about the neuropathology in PRES, so this question is difficult to answer. If it is a disorder of regulation of cerebral blood flow there may be little to see apart from oedema.

5. Document reference 240-004-028: The influence of "time schedule...on the neuropathological findings in a case
   a. When oedema developed so quickly that death occurred in 2-3 hours time
   b. When a child after 8-10 hours came to death."
   What time is needed to see the characteristics of myelinolysis?

The answer is probably 4 or 5 days or more, but there are few studies to assist with timing the onset of the histological changes of myelinolysis. MRI studies show brainstem changes within 2 days (Chua, Sitoh et al. 2002), but this may reflect oedema and not true myelin

breakdown as recognised by pathology. Animal models suggest that pathological changes can occur at 2 days, but demyelination was described only at 5 days in a rat model (Iwama, Sugimura et al. 2011).

It is very uncommon to examine the brains of children with osmotic myelinolysis. I can recall only one case in my experience, (Figure 4) a girl of 2 years ten months who died 20 days after metabolic disruption leading to myelinolysis. She had focal and well established myelin loss with intense macrophage infiltration, mostly in the immediate subcortical white matter of the cerebellar and cerebral hemispheres. I have not found a relevant series of pathological case studies in children. In a pathological study of adult cases, the earliest cases were examined 11 days after the onset of symptoms of central pontine myelinolysis (DeLuca 2002).

There is little to assist us in Adam's case. As he was essentially brain dead from the end of surgery, it is unlikely that he would have developed significant pathology and myelinolysis during the period of ventilation.

Waney Squier

December 4th 2012

Reference List

Chua, G. C., Y. Y. Sitoh, et al. (2002). "MRI findings in osmotic myelinolysis." Clinical radiology **57**(9): 800-806.

Iwama, S., Y. Sugimura, et al. (2011). "Time-dependent changes in proinflammatory and neurotrophic responses of microglia and astrocytes in a rat model of osmotic demyelination syndrome." Glia **59**(3): 452-462.

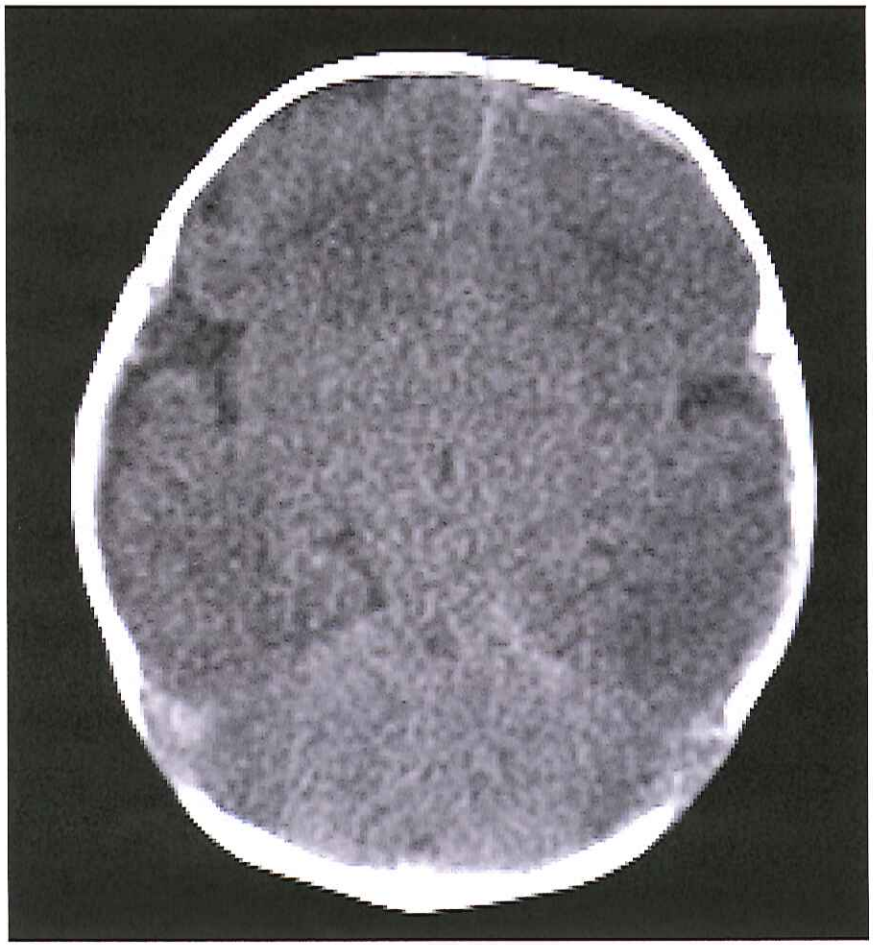
Ramenghi, L. A., P. Govaert, et al. (2009). "Neonatal cerebral sinovenous thrombosis." Semin.Fetal Neonatal Med. **14**(5): 278-283.

Ruiz, D. S., H. Yilmaz, et al. (2009). "Cerebral developmental venous anomalies: current concepts." Ann.Neurol. **66**(3): 271-283.

Wasay, M. and M. Azeemuddin (2005). "Neuroimaging of cerebral venous thrombosis." Journal of neuroimaging : official journal of the American Society of Neuroimaging **15**(2): 118-128.

Yang, J. Y., A. K. Chan, et al. (2010). "Neonatal cerebral sinovenous thrombosis: sifting the evidence for a diagnostic plan and treatment strategy." Pediatrics **126**(3): e693-e700.

Figure 1



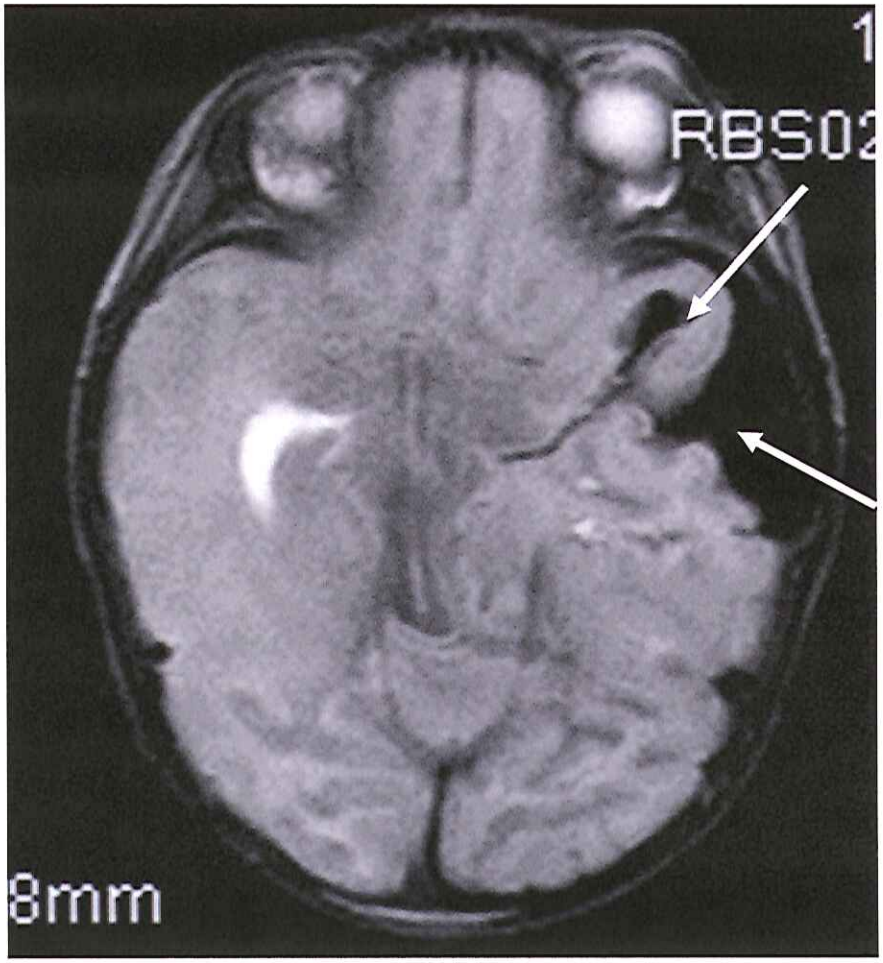
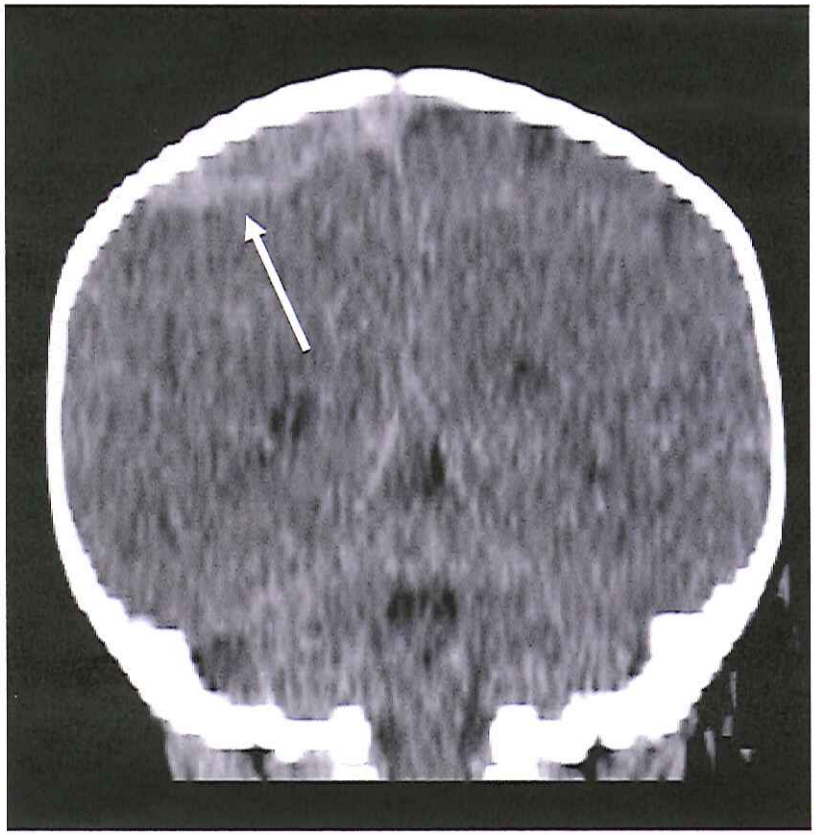


Figure 2



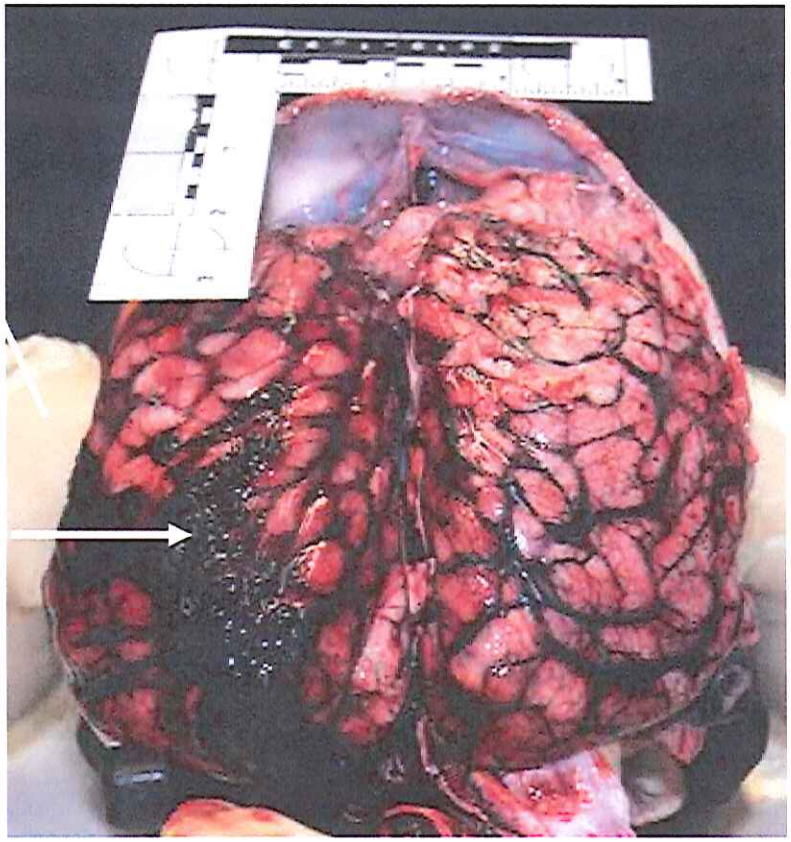


Figure 3

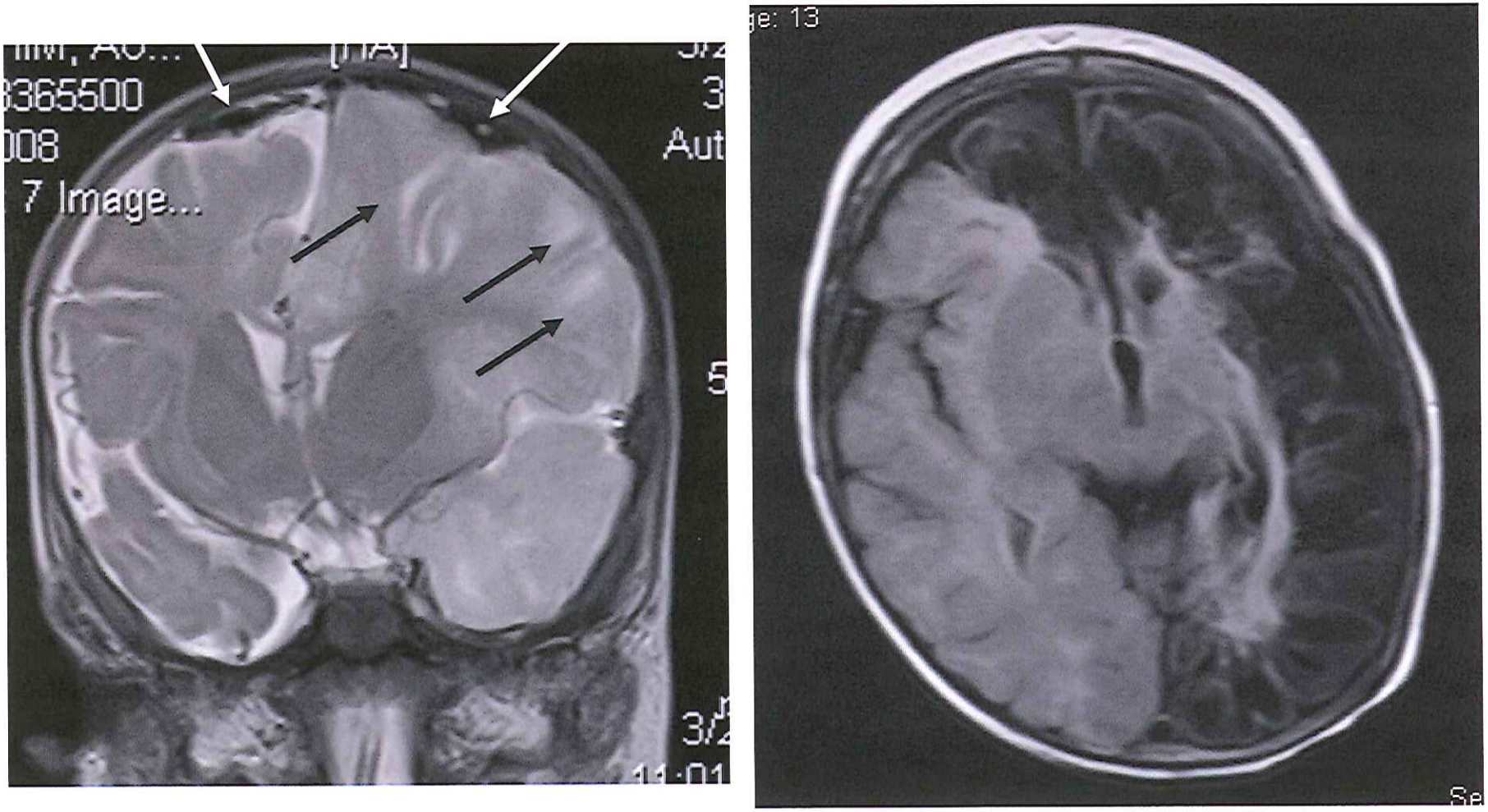
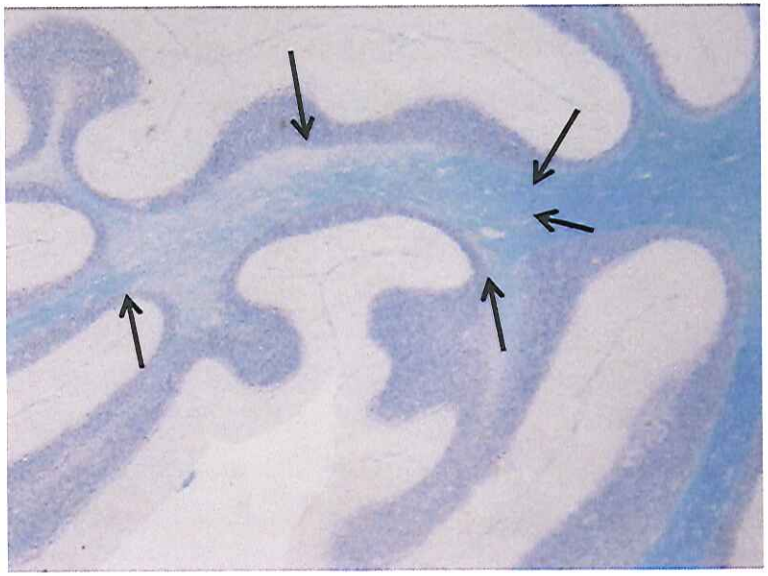
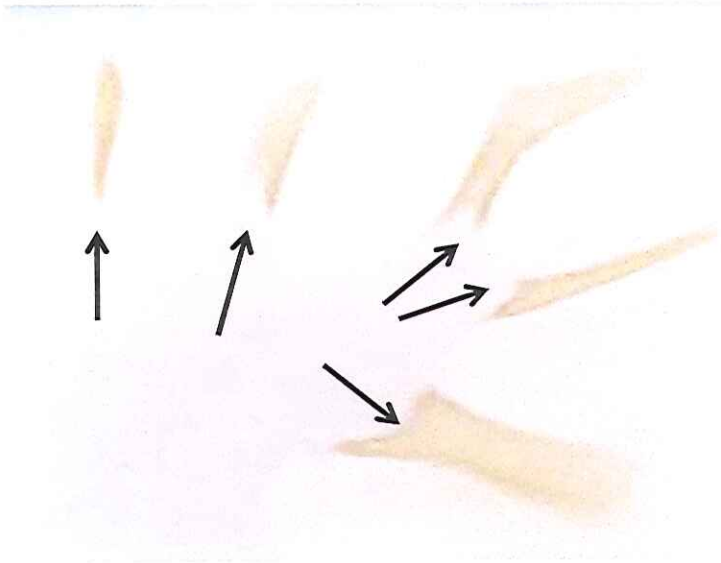
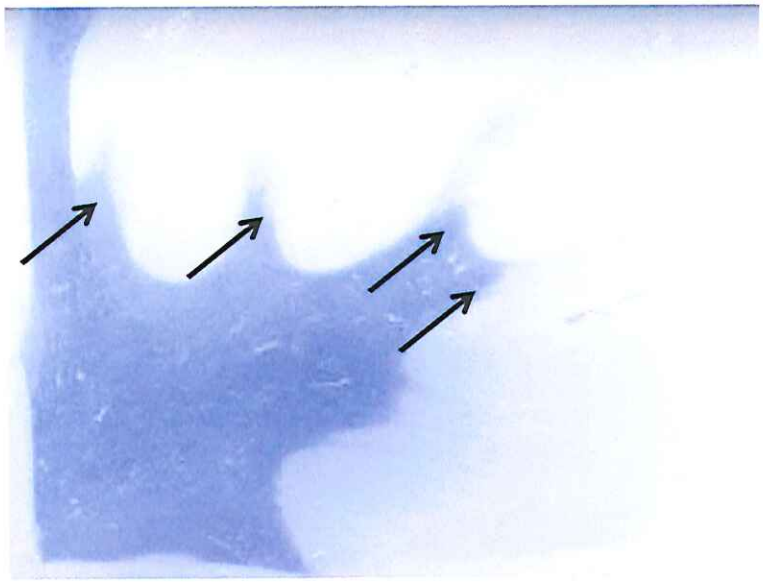


Figure 4







Three images from 2y 10 m female who died 22 days after an overdose of desmopressin. Demyelinated lesions are indicated by black arrows. Myelin stains blue (top left, bottom right). The brown stain shows macrophages in the damaged areas.