

## Prenatal Origins of Subdural Hemorrhage/Effusions and Related Seizures: Acute, or Crisis in a Chronic Condition?

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### Abstract

**Introduction:** Subdural haemorrhages and effusions are collections of blood or tissue fluid that appear in infants between the lining of the skull (Dura Mater) and the brain surface, with an incidence of 21 in 100,000.

**Method:** This study is further analysis of data in a case report of a dichorionic-dizygotic twin pregnancy in which one twin (Twin-A) presented three months postnatally with seizure. The other twin (Twin-B) developed normally and so became a control. The twins showed similar head growth up to 24 weeks but subsequently the rate of head growth of Twin-A exceeded that of Twin-B. Later, from 29 weeks, Twin-A's femur growth began to lag Twin-B's, but abdominal growths remained matched. Postnatally Twin-A's head growth rate continued to exceed that of Twin-B until at 3 months postnatal Twin-A presented with seizure

**Discussion:** This case suggests that a development defect exists in which cerebral venous vessel diameters fail to keep up with the rapidly increasing cerebral blood flow from late pregnancy into infancy. Forcing the increasing cerebral blood flow through inadequate venous vasculature will produce dangerous intracranial venous hypertension, which may lead to subdural and retinal hemorrhages. Venous effusion develops when lumen pressure markedly exceeds intracranial pressure, causing intracranial pressure to follow cerebral venous pressure. An acute crisis can arise at any time if intracranial pressure compresses veins sufficiently to further increase venous resistance. Thus the basic mechanism is not acute, it is chronic, but it has a potential for crisis.

**Conclusion:** There is a condition, caused by inadequate cerebral vein development, where cerebral vein pressure is raised excessively. Starting in late pregnancy and extending into infancy it may remain clinically silent (apart from macrocephaly) or suddenly result in acute bursting in venous vasculature. In this case enduring recovery was produced by fitting a Subdural-Peritoneal shunt.

**Keywords:** Subdural; Retinal; Hematoma; Twins; Seizure; Perinatal

### Introduction

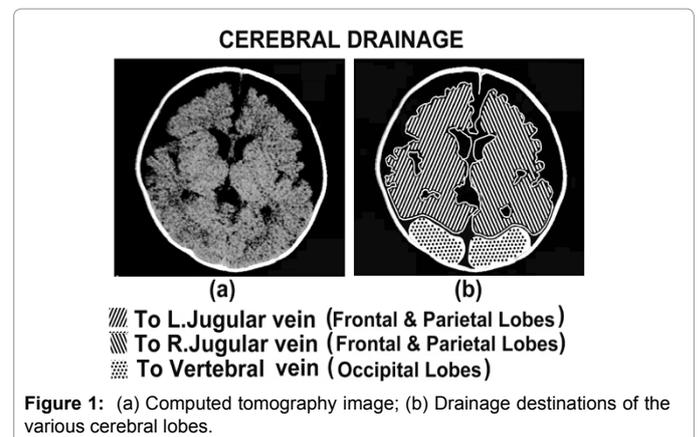
The term "Subdural" is used here in the general sense of including all features occurring between the Dura and the brain surface. Subdural haemorrhages and effusions are collections of blood or tissue fluid that appear in this space. They appear in infants with an incidence of 21 in 100,000 [1]. They come in three grades; acute which occur immediately following some injury, subacute which take a few days to develop, and chronic. In up to 55% of infants diagnosed with Chronic Subdural Hematoma/Effusion of Infancy, there is no culpable medical condition identified, and no recognised history of perinatal or postnatal trauma. Subdural Hematoma/Effusions (SDHE) is a familiar phenomenon but its mechanism is still controversial. This study was based upon data previously reported by a different author [2] in which one of non-identical twins presented at 3 months postnatal age with seizure. Up until then he had appeared normal, apart from an enlarged head. At presentation his haemoglobin level was 10.2 g 3 month mid range. Urine analysis was unremarkable, Blood, urine and subdural fluid cultures were negative [2].

### Postnatal Intracranial Pressure Indications

At presentation Twin-A was recorded as having a tense, bulging anterior fontanel and "sunset sign" of the eyes [3]. His head was large and its shape was abnormal with bi-parietal bulges. Retinal hemorrhages were noted by ophthalmology the day after hospital admission. MRI scans showed chronic subdural hematomas with small areas of acute blood. A CT scan taken on the day of admission, (Figure 1a), showed fluid collections around the frontal and parietal lobes but not under the occipital lobes.

Something was happening to those lobes draining into the jugular veins (Figure 1b), which was not happening to the occipital lobes

draining into the vertebral veins. When surgical drainage and shunt placement were undertaken, xanthochromic fluid with some fresh blood escaped under very high pressure. Following shunt placement he made a complete and lasting recovery.



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## Methods and Results

### In utero ultrasound dimension measurements

Ultrasound scans and clinical records were plotted, Figure 2, to provide a history of dimensions in pregnancy. Ultrasound measurements are plotted against gestational age for Twin-A in grey and Twin-B in black. From 20 to 24 weeks Twin-A and Twin-B show similar head bi-parietal diameter (BPD), abdominal circumference and femur growth rates, their traces are parallel. In Figure 2a the BPD of Twin-A is marginally greater than Twin-B which is reasonable for non-identical same sex twins. From 24 to 29 weeks Twin-A head growth rate increased over that of Twin-B, and during weeks 33 to 37 the difference clearly was accelerating. However their abdominal circumferences, (Figure 2b), remained closely matched throughout pregnancy suggesting that nutrition was not a problem. Limb (femur) growths, (c), showed matching growth rates up to 29 weeks. Then Twin-A femoral length started to lag behind that of Twin-B. This might suggest some inadequacy of blood flow rather than blood quality since abdominal growths (b) remained closely matched. Dividing head BPD by femoral length produces an index of Head/Body proportion. Figure 2d are plots of this asymmetry growth index, (BPD/FL). There is an increasing divergence of these indices with fetal age.

### The chronic nature of this condition

In Figure 3, the plots of in utero BPD are a repeat of Figure 2a. Postnatally, Twin-A's BPD is derived from head circumference figures in reference [2], by dividing by the ratio of the circumference of a circle to its diameter, "Pi" (3.142). Values for Twin-B were calculated from

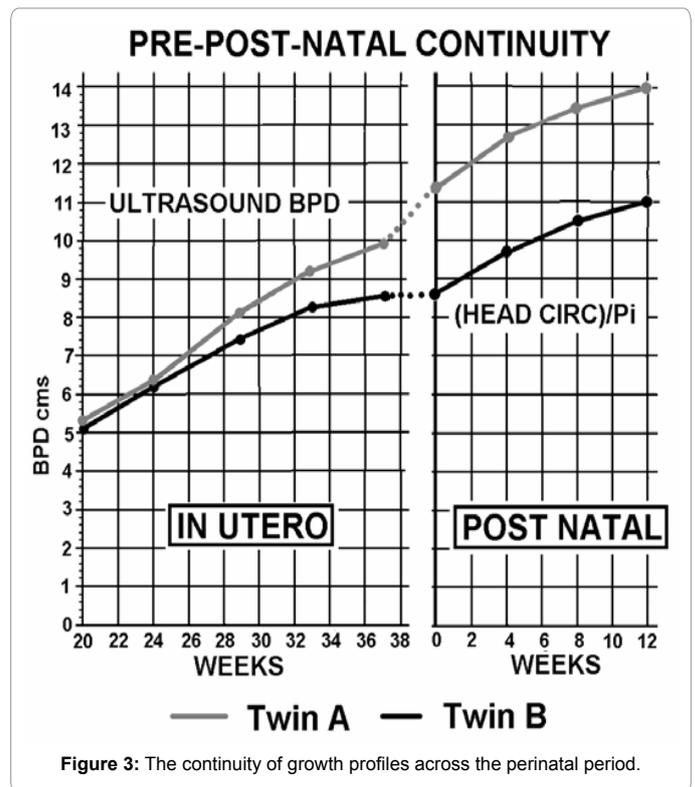


Figure 3: The continuity of growth profiles across the perinatal period.

circumference at birth and the shape of the normal growth curves described in reference [2] as "subsequent growth followed the 30-40th percentile growth curves". There appears to be continuity of the growth curves for both twins, from 24 fetal weeks until 12 weeks post natal, when Twin-A suffered seizure. There was some interruption around birth as might be expected. Clearly the mechanism that led to macrocephaly, blood proteins in the CSF, and eventually, to seizure in Twin-A, started in utero at about 24 weeks fetal age, i.e. the mechanism was chronic.

## Discussion

### Implications and Hypothetical mechanism

Striking features noted at Twin-A's presentation were his "bulging tense" anterior fontanel, the "setting-sun" eye sign, retinal haemorrhages in the eyes, and the release of yellow fluid with some fresh blood under "very high pressure" when placement of a shunt was undertaken. These facts all show that the excess fluid was at an abnormally high pressure. The first question is obviously what was causing the high pressure?

### Elevated cerebral venous pressure

There appears to be a close parallel between the observations in this case and the rat model used by Mayhan and Heistad [4]. Their study was of the role of cerebral venous pressure in disruption of the Blood-Brain Barrier (BBB). They used the tracer Fluorescein isothiocyanate, FITC dextran (mol.wt.=70,000) to measure leakage through the Blood Brain Barrier (BBB). In one set of experiments they produced elevated cerebral venous pressure by occluding the vena cavae. They found that this raised cerebral venous pressure from  $7 \pm 1$  to  $28 \pm 2$  mmHg. Rat arterial pressure is nominally 110/70 [5] so SVC occlusion raised cerebral venous pressure to a quarter of arterial pressure. They also observed this caused pial venous diameter to be stretched from  $59 \pm 7$  to  $73 \pm 8$  um, and venule/venous leakage to rise from 0.02 to  $3.10 \text{ ml/sec} \times 10^{-6}$ ,

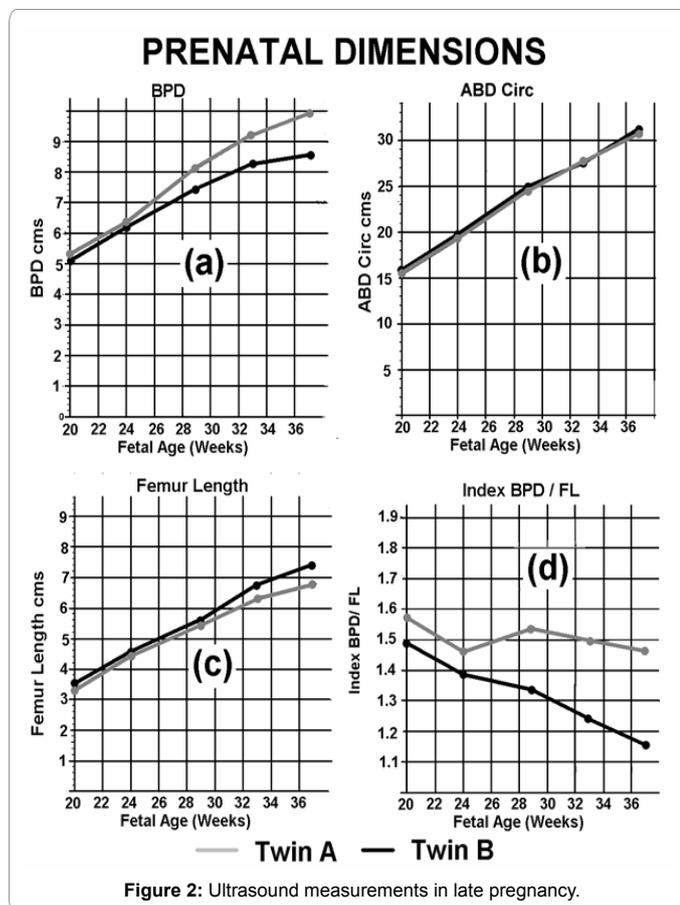


Figure 2: Ultrasound measurements in late pregnancy.

that is by over 1000 times, They say “During SVC occlusion ... disruption of the BBB was always venular. Leaky sites were not observed in arterioles or capillaries. Leaky sites occurred in venules 25-40  $\mu\text{m}$  diameter. More diffuse leaky sites were observed in discrete areas of larger veins (>50  $\mu\text{m}$ ) within 5 mins during SVC occlusion. The excessive leakage continued for at least 40 minutes subsequent to release of the occlusion although the venular pressure had returned to normal ( $6 \pm 1$  mmHg), indicating that the damage was chronic. So, raised cerebral venous outflow resistance can raise cerebral venous pressure to a value that causes venules and veins to leak. Lesser venous hypertension, though insufficient to cause vessel damage, may cause local edema sufficient to interfere with neuron function. This interference will cease if the excessive venous pressure is removed. Neurons will recover as edemous fluid disperses. Hinchey et al. [6] studied this phenomena in adults suffering from a variety of disorders which produce vascular hypertension. They described it as “Reversible Posterior Leukoencephalopathy Syndrome”. They describe the symptoms as ranging from “drowsiness to stupor, seizures, vomiting, mental abnormalities including confusion and diminished spontaneity and speech, and abnormalities of visual perception. The onset is usually subacute but may be heralded by a seizure. Seizures are common at the onset of neurologic symptoms but can also develop later”. When the source of hypertension was identified and removed their patients typically made a gradual full recovery within two weeks. Their cases mostly appear to have involved arterial hypertension. In the present study hypertension would only be produced in cerebral veins, but the local edema considerations equally apply. This would explain why Twin-A recovered following fitting of the shunt.

### Fluid Accumulations; Fluid effusions

Twin-A's CT scan at admission, Figure 1a, shows that fluid effusions had accumulated around the frontal and parietal lobes, but not under the occipital lobes. At shunt placement this effusion fluid was found to be at high pressure. This would stretch or tear the trabeculae linking the cortex through the arachnoid to the dura. So, why had that not happened under the occipital lobe? Figure 1b maps the lobes of the brain shown in Figure 1a according to the veins draining them into their ipsilateral brachiocephalic veins. Fluid is abundant around the frontal and parietal lobes but the occipital lobes remain tight against the inner skull table. It might be thought that one possible reason for this could be the weight of the brain pressing down at the time of supine examination. However, in vivo, the brain is only slightly denser than the CSF. Its buoyancy means that in the adult, a brain weight of 1,400 gm in air is reduced to 50 g in CSF [7]. An alternative explanation offered by this case is that the separation of the cortex and the arachnoid membrane is produced by effusion from venules within the cortex, driven by high venous lumen pressure. Very little flow from the frontal, parietal and temporal lobes reaches the vertebral veins so similar pressure rises will not occur in vertebral vein pressure. Since the occipital lobe venous pressure will not be affected there will be no venous effusion to push the occipital lobe away from the occiput. It will remain attached to the skull by its arachnoid trabeculae of normal length as in Figure 1a. This fluid distribution shows that this condition is related to cerebral venous flow, not systemic pressure.

### The hydrodynamic origins of excessive cerebral and cranial pressures

It is well known that obstruction of transverse or subarachnoid sinuses results in cerebral venous hypertension. Yang et al., concluded that *children with abnormal venous outflow are predisposed to develop external hydrocephalus* [8]. When a vessel dilates, flow increases with both the increase in cross section area (radius<sup>2</sup>) and of flow rate. (Fluid

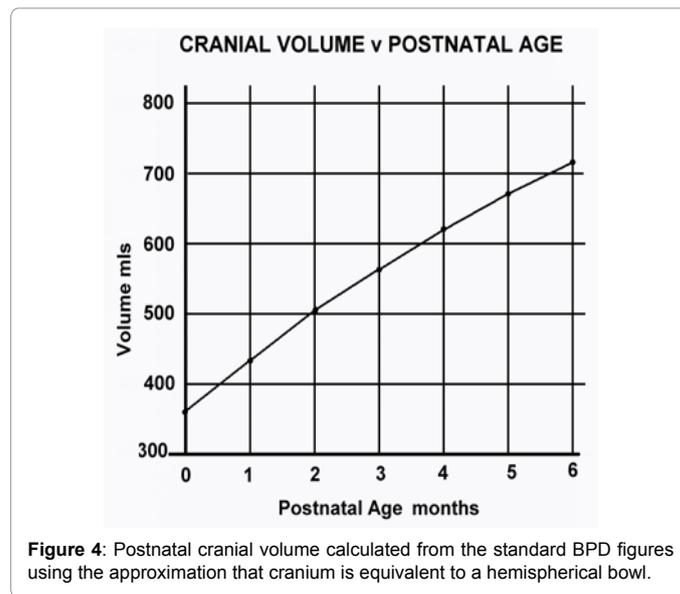


Figure 4: Postnatal cranial volume calculated from the standard BPD figures using the approximation that cranium is equivalent to a hemispherical bowl.

travels faster because there are more layers sliding over each other, a viscous effect.) Together that means that flow increases as radius<sup>4</sup> [9]. In practical terms, if a vessel constricts flow is halved for a decrease of only 19% of radius. Thus flow resistance can be very sensitive to inadequate vessel diameter. It is not suggested that in Twin-A the SVC was actually obstructed, only that the cerebral veins were not adequately enlarged to accommodate the increasing blood flow as the cerebrum developed. Figure 4 is constructed from standard curves for postnatal infant head circumference [10] by treating the cranium as a hemisphere of the same radius. Making the approximation that most of the intracranial space is taken up with cerebral tissue, and that the total required blood flow is proportional cerebral tissue volume, cerebral blood flow has to rise by an additional 50% of newborn volume by 3 months postnatal age and to have doubled by 6 months.

Forcing this escalating flow through inadequate venous vasculature requires escalating pressure at the cerebral venule outflow point. As mentioned above [4] this is where leakage occurs under elevated lumen pressure. Once venules are damaged, flow out into the subarachnoid space will continue so long as current cerebral venous pressure is greater than subarachnoid space pressure. In effect, subarachnoid pressure will follow the rising cerebral venous pressure.

### Macrocephaly

During cranial ossification, cranial growth in infants is stimulated by stretch receptors in the dura beneath the sutures of the developing skull plates [11]. Tension in these receptors causes them to signal for cranial growth. This causes sutures to grow just fast enough to match the contained volume. At presentation at 3 month, Twin-A was noted to have a distinctly larger head than his twin. The high intracranial pressure noted at admission would account for this accelerated cranial growth.

### The cerebral venous crisis

So long as cerebral venous pressure remains below that which will damage venular walls, this disorder will remain quiescent, apart from possible macrocephally. However a crisis will arise if cerebral blood flow increases faster than the inner jugular/sinus vessels can accommodate for a reasonable pressure drop. If cerebral vein walls get damaged by this elevated pressure, blood fluids will seep out through damaged areas

into the subarachnoid space until intracranial pressure nearly equals the new cerebral venous pressure. This raised intracranial pressure will press on the sigmoid and transverse sinuses, which are in effect extensions of the jugular veins within the cranium, and narrow them further. Narrowing will then increase the cerebral venous resistance and exacerbate the cerebral venous pressure rise, a regenerative, positive feedback, effect. Rising cerebral venous pressure will then further increase cerebral edema and possibly facilitate bleeding. This would proceed to a crisis in which edema would derange neuron function, inducing seizure. Although inserting a shunt in this case would not have stopped leakage through the damaged areas, it would have broken this positive feedback effect and allowed the cerebral veins to expand to their current natural diameter. This, in turn, would have reduced cerebral venous pressure and hence the transmural fluid flow that was causing the cerebral edema.

If this condition is hovering just below the threshold pressure for venule damage apparently trivial factors may induce a crisis. The rapid increase in cerebral activity following birth will cause the cerebrum to demand increased blood flow. Coughing or the powerful vomiting associated with pyloric stenosis or pylorospasm will superimpose additional acute pressures. The yellow colouring of the escaping fluid when the shunt was fitted would be explained by vessel damage during previous minor hypertensive episodes. Briner and Bodensteiner [12] sampled subdural collections in asymptomatic macrocranial infants and found a protein content up to 2,000 mg/100 ml and red blood cell counts of 7,000 RBC/100 ml. Chazal et al. [13] located the source. They measured the protein concentration in macrocephalous cases in their lumbar CerebroSpinal Fluid (CSF), in the ventricles, and near cranial convexities. In a 2.5 month female infant they found 0.5 g/L lumbar, 0.42 g/L ventricular, but 12 g/L near a cerebral convexity. In a 4 month old male the figures were lumbar 1.6 g/L, ventricular 0.2 g/L and 10 g/L near convexities. This shows that in these macrocephalus, but otherwise asymptomatic, infants the protein came from damaged cerebral vessels. The yellow colouration signalled previous episodes of blood exudation through damaged vascular walls.

## Diagnosis and Prognosis

Oran et al. [14] suggest that dilated transcerebral and superior ophthalmic veins seen on ultrasound, (secondary to elevation of the cerebral venous pressure), might be a useful sign warning of rising cerebral venous pressure. This present case suggests that *in utero* development of macrocephaly may warn of increasing intracranial pressure. If excessive head growth continues postnatally it should be fully investigated, especially if accompanied by a raised fontanel, with a view to CSF drainage, or, if really severe, fitting of a shunt as in this case

It seems likely that *in utero* the cerebrum is relatively inactive compared to after birth. In the neonatal period one would expect many cerebral regions would be highly active and demanding large oxygen supply. The resultant increase in cerebral blood flow would then further raise cerebral venous pressure and might cause intracerebral bleeding in vulnerable patients. Theoretically some form of external drain of CSF to reduce intracranial pressure might be of value to prevent these crises, provided fluid balance was maintained. Loh et al., [15] treated twenty one infants, identified with acute subdural hematoma, with external drainage of the subdural hematoma. Of these 62% had a good recovery, 19% had moderate disability, 14% had severe disability and 5% died. Lin et al., [16] had similar success in a series of 36 infants, by providing continuous drainage for up to 9 days. At follow-up they found 63.9% made good recovery 13.9% had moderate disability, 8.3% had severe disability, 11.1% were vegetative and 2.8% died.

Given time, natural vessel growth factors may supply a corrective stimulus. Alberts et al. [17] state "Once a vessel has matured, signals from its endothelial cells to the surrounding connective tissue and smooth muscle cells play a crucial part in regulating the vessel function and structure.. For example, the endothelial cells have mechanoreceptors that sense the shear stress due to blood flow over their surface. By signalling this information they enable a blood vessel to adapt its diameter and wall thickness to suit the blood flow". Hence it would appear that if suitable palliative measures, (e.g. external drainage [16], evacuation, [15], or shunting to relieve intracranial pressure, as in this case) can maintain normal growth during this catch-up period, natural vessel growth mechanisms may produce appropriate vessel dimensions. If the high venous flow resistance is due to mechanical factors (e.g. absent or deformed vein of Galen etc) prognosis is harder to predict. It will depend on the development of collateral circulation etc.

## Conclusion

This case demonstrates that there exists a chronic condition, starting in late pregnancy and running into infancy (Figure 3), in which crises may occur that replicate the subdural and retinal bleeding commonly considered diagnostic of imposed trauma.

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