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Sudden unexpected death in young adults with chronic hydrocephalus

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Abstract We present four cases of sudden unexpected death in young adults with chronic hydrocephalus. The patients were between 20 and 28 years of age and had suffered from aqueduct stenosis (two patients), spina bifida in combination with Arnold-Chiari malformation (type II) and fragile X-syndrome. The patients suddenly collapsed with cardiorespiratory failure and could not be resuscitated and none had a history of headache or seizures. The post-mortem examinations revealed no unusual findings and a definite cause of death could not be established. Neuropathological examination revealed chronically hydrocephalic brains without any signs of uncal or tonsillar herniation. We hypothesise that a sudden pressure-induced decompensation of cerebral neuronal pathways involving insular and limbic cortex, hypothalamus and brain stem nuclei, may have caused disturbances of the cardiopulmonary control centres in the reticular formation of the brain stem, which in turn may have led to instantaneous cardiorespiratory arrest resulting in sudden "neurogenic" cardiac death.

Keywords Sudden unexpected death · Chronic hydrocephalus · Intracranial pressure · Aqueduct stenosis · Arnold-Chiari malformation

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Introduction

According to the World Health Organisation, the definition of "sudden death" is one in which death occurs "within 24 h from onset of symptoms". In practice, however, pathologists and clinicians are more likely to use the term when the interval is shorter than 1 h or, more accurately and closer to the literal meaning of this term, even instantaneous. These cases are of great importance for medicolegal investigations by forensic pathologists as the cause of death has to be established and foul play has to be excluded. The most common cause of sudden unexpected death is cardiac disease while among intracranial causes epilepsy, spontaneous rupture of an aneurysm, intracerebral haematoma and acute hydrocephalus predominate (Graham and Black 1999).

Sudden death in the setting of acute hydrocephalus with rapid increase of the intracranial pressure, is a well recognised situation in which an underlying pathology or cause can be established in a number of cases consisting, for example, of acute blockage of the interventricular foramina or the aqueduct by colloid cysts of the third ventricle (Buttner et al. 1997; Shemie et al. 1997; Aronica et al. 1998), neoplasms (Shemie et al. 1997), lipomas (Zappi et al. 1993), pineal cysts (Milroy and Smith 1996; Mena et al. 1997) or other causes such as sarcoidosis (Maisel and Lynam 1996), neurocysticercosis (Verma et al. 1998), Dandy-Walker malformation (Elterman et al. 1995) and arachnoid cysts (Norman et al. 1995). These events are usually accompanied or preceded by neurological symptoms, most notably headaches, nausea or blurred vision.

We report four cases of young adults suffering from chronic hydrocephalus who died suddenly and unexpectedly without any preceding symptoms and discuss the potential influence of chronic hydrocephalus in the pathogenesis of sudden unexpected death.

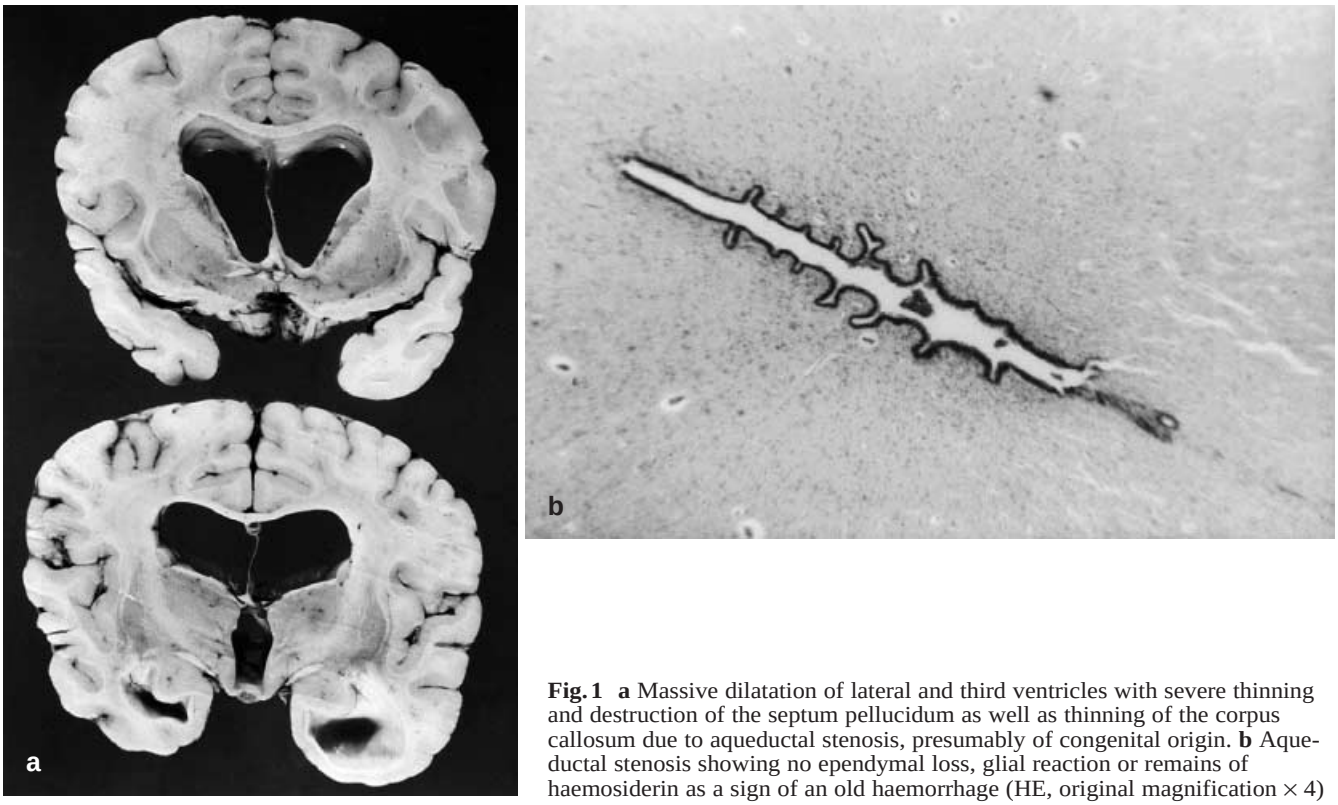

Fig. 1 **a** Massive dilatation of lateral and third ventricles with severe thinning and destruction of the septum pellucidum as well as thinning of the corpus callosum due to aqueductal stenosis, presumably of congenital origin. **b** Aqueductal stenosis showing no ependymal loss, glial reaction or remains of haemosiderin as a sign of an old haemorrhage (HE, original magnification × 4)

Case reports

Patient 1

Clinical history

A 20-year-old male with a history of mild bronchial asthma but no other serious previous diseases, collapsed suddenly during a game of football without showing any preceding symptoms. Resuscitation was started immediately by lay persons present at the scene. Upon arrival of the doctor, the patient's pupils were dilated and did not react to light. The ECG showed ventricular fibrillation and despite cardiovascular resuscitation attempts over 2 h, the patient was declared dead shortly after arrival at hospital. The patient had previously been attending a special school for pupils with learning difficulties where his performances were below average. Investigation of the patient's medical records showed no history of meningitis, seizures, or headaches. However, the patient had suffered concussion as a 9-year-old after a bike accident.

Pathology findings

The autopsy showed changes typical for bronchial asthma as well as signs of a cardiogenic shock with acute right-sided cardiac failure. Relevant macroscopic findings were a hypotonic dilatation of the right ventricle as well as a moderate peripheral emphysema. The remaining organs were unremarkable. Microscopically, hyperplasia of the bronchial epithelium, mucous membrane and musculature could be found as well as massive amounts of thick mucus in the bronchial lumen with bacteria, as well as neutrophilic and eosinophilic granulocytes. The other organs were unremarkable and in particular, no signs of pulmonary embolus or endocarditis could be found. Thus, findings consistent with bronchial asthma were detected, however, no definite cause of death could be established.

Neuropathology findings

Macroscopically, the brain showed mild cerebral oedema (brain weight after formalin fixation 1,508 g) with moderate uncal and tonsillar grooving but without signs of upper or lower herniation; the gyration pattern was normal. In the latero-polar portion of the left frontal lobe, a brown induration 1.5×0.5 cm in size, consistent with an old contusion, i.e. remains of an old head trauma, was found. The floor of the third ventricle appeared paper-thin and ballooned. Coronal sections of the brain showed a massive dilatation of the lateral and third ventricles with severe thinning and destruction of the septum pellucidum as well as thinning of the corpus callosum (Fig. 1a); however, the fourth ventricle was not dilated. Sections of the brain stem revealed an aqueductal stenosis with a very small residual lumen. There was no sign of congestion or haemorrhage. Histologically, the aqueductal stenosis showed no ependymal loss, glial reaction or remains of haemosiderin as a sign of an old haemorrhage (Fig. 1b). However, ependymal loss and subependymal gliosis were found in the massively dilated lateral and third ventricles. The neuropathological diagnosis was subtotal aqueductal stenosis with massive internal hydrocephalus, most likely of congenital origin.

Patient 2

Clinical history

The 25-year-old obese female collapsed suddenly on the toilet at home. On arrival of the doctor the ECG showed asystole and cardiovascular resuscitation attempts over 40 min were unsuccessful. The patient had recently emigrated from Russia and records about the previous medical history were not available. However, it could be established from relatives that the patient had been suffering from psycho-motoric retardation with learning difficulties since childhood, but as far as was known there was no history of previous serious diseases, headaches or seizures.

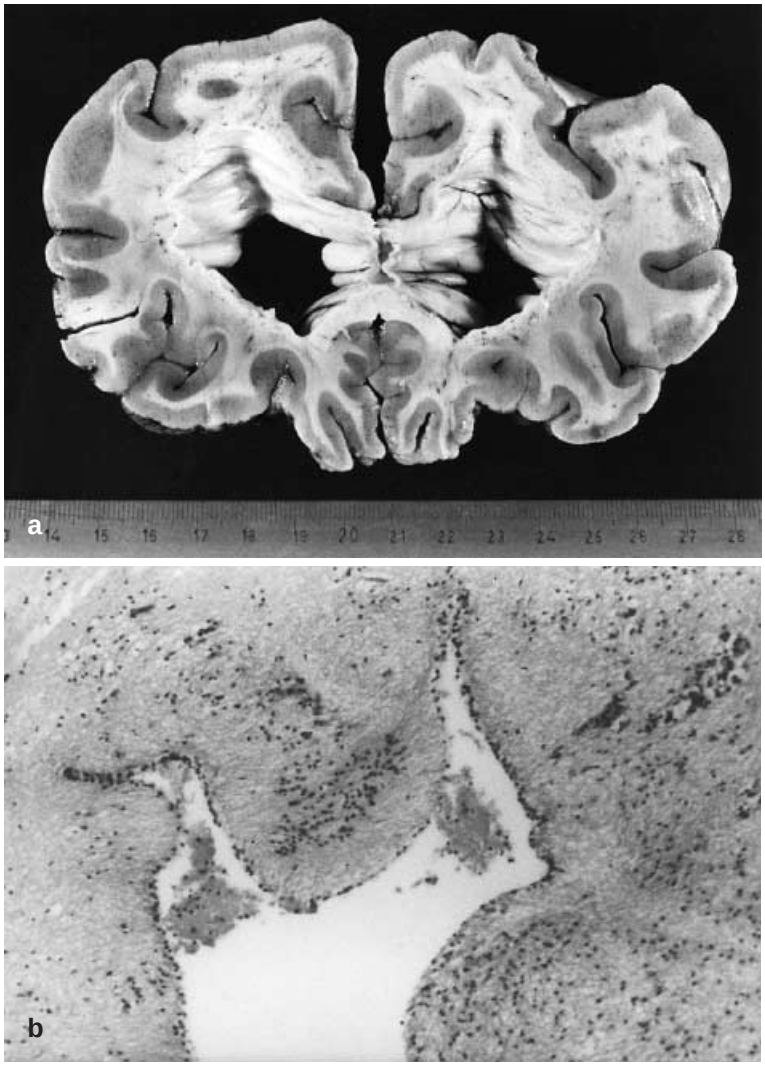

Fig. 2 **a** Internal hydrocephalus due to aqueductal stenosis with dilatation of the frontal horns of the lateral ventricles showing granular ependymopathia, presumably of post-infectious origin. **b** Granular ependymopathia of the lateral ventricle with ependymal loss and subependymal gliosis (HE, original magnification × 32)

Pathology findings

The autopsy showed an acute biventricular dilatation of the heart and pulmonary oedema secondary to resuscitation efforts. Furthermore, a medioabdominal scar of 15 cm with bilateral tube ligation was present. The other organs were unremarkable and in particular, no signs of pulmonary embolus or endocarditis could be found. In conclusion, no definite cause of death could be established, however, the findings were compatible with sudden cardiorespiratory failure of unknown aetiology.

Neuropathology findings

Macroscopically, the brain showed a mild cerebral oedema (brain weight after formalin fixation 1,340 g) with moderate uncal and tonsillar grooving but without signs of upper or lower herniation; the gyration pattern was normal. The floor of the third ventricle was paper-thin and ballooned. Coronal sections showed a massive dilatation of the lateral, third and fourth ventricles with severe thinning of the septum pellucidum and corpus callosum and all ventricles presented granular ependymopathy (Fig. 2a). Furthermore, a persisting cavum septi pellucidi measuring $1.0 \times 1.0 \times 0.3$ cm was found. Sections of the brain stem revealed a short aqueductal stenosis in the rostral part with small residual lumen. Histologically, the granular ependymopathy of the aqueduct and floor of the fourth ventricle was pronounced, in the remaining ventricles moderate; furthermore, there was ependymal loss and subependymal gliosis in the lateral and third ventricles (Fig. 2b). The subtotal aqueductal stenosis showed ependymal loss and subependymal nodular glial scarring. The diagnosis was subtotal aqueductal stenosis with massive internal hydrocephalus, possibly of post-infection (possibly post-meningitis) origin. Apart from the presence of a non-communicating hydrocephalus, the dilatation of the fourth ventricle was indicative of an additionally impaired subarachnoidal CSF resorption, also consistent with a possible history of meningitis.

Patient 3

Clinical history

A 22-year-old asthenic and mentally retarded male with Martin-Bell syndrome (fragile X-syndrome) was found lifeless on his bed with a TV remote control in his hand after he had last been seen alive several hours previously. When medical assistance arrived, the patient was asystolic with dilated pupils which did not react to light. Cardiovascular resuscitation attempts over 35 min were unsuccessful. The patient had been living in an institution for mentally and physically handicapped, but was otherwise healthy with no

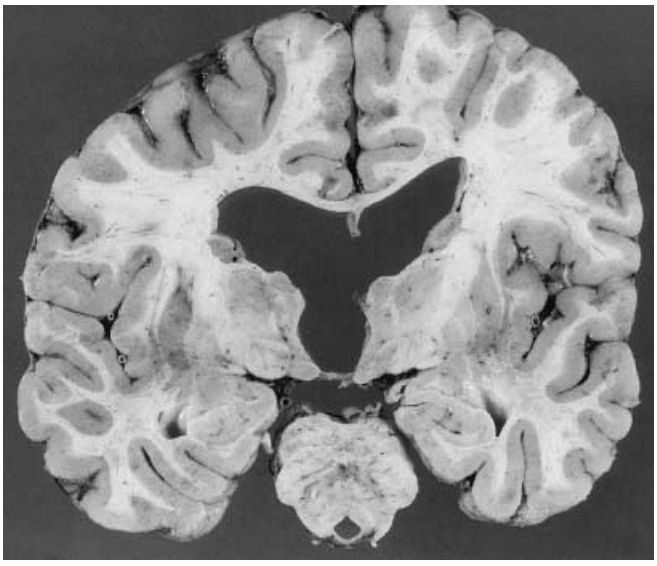

Fig. 3 Massive macrocephaly (brain weight 2,080 g) with dilatation of lateral, third and fourth ventricles as well as of the aqueduct with thinning and destruction of the septum pellucidum and thinning of the corpus callosum in a patient suffering from fragile-X syndrome

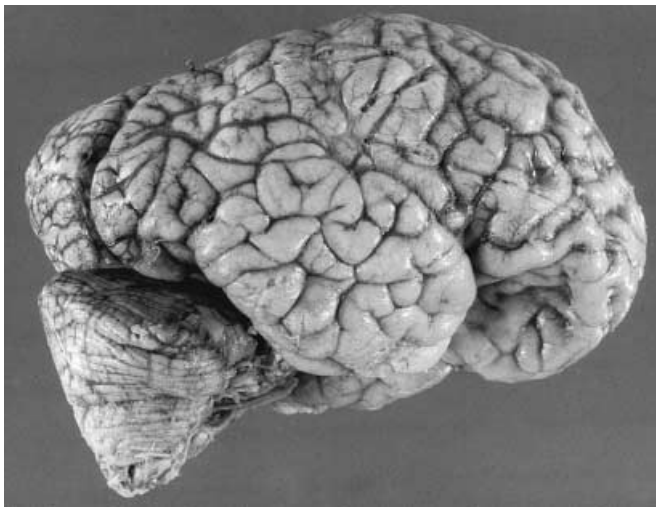

Fig. 4 Arnold-Chiari type II malformation with caudal displacement of the lower vermis and bilateral prominent cerebellar tonsils. Further processing revealed S-shaped antero-posterior kinking of the medulla, a moderate dilatation of all ventricles and the aqueduct as well as a closed median ventricular aperture

history of serious previous diseases and in particular no history of headaches or seizures.

Pathology findings

The autopsy showed macrocephaly and a high palate. Macroscopically, there was acute biventricular cardiac dilatation and pulmonary oedema. The other organs were unremarkable, in particular no sign of pulmonary embolus or endocarditis was found. No definite cause of death could be established, but the findings were compatible with sudden cardiorespiratory failure of unknown aetiology.

Neuropathology findings

Macroscopically, the brain showed a massive macrocephaly (brain weight after formalin fixation 2,080 g) with moderate uncal and tonsillar grooving but without signs of upper or lower herniation (Fig. 3). There was moderate cerebral oedema but no pathological gyration. The floor of the third ventricle was paper-thin and ballooned. Coronal sections of the brain showed a massive dilatation of the lateral, third and fourth ventricles as well as of the aqueduct (lumen 0.4×0.4 cm) with thinning and destruction of the septum pellucidum and thinning of the corpus callosum (Fig. 3). Histologically, there was a moderate ependymal loss and mild subependymal gliosis in all the ventricles. The architecture of grey and white matter was normal. The diagnosis was extensive macrocephaly with communicating internal hydrocephalus, compatible with Martin-Bell syndrome (fragile X-syndrome).

Patient 4

Clinical history

The 28-year-old paraplegic and wheelchair-bound male suffering from spina bifida, experienced sudden cardiac failure while undergoing a trans-oesophageal ECG. In spite of immediate cardiovascular resuscitation attempts under intensive care conditions, the patient could not be revived. He had a history of cystectomy after neurogenic bladder dysfunction and left-sided nephrectomy because of chronic vesico-ureteral reflux due to complications in the course of the underlying neurological condition. He was also known to have suffered from light-chain gammopathy. Shortly before death, he had been admitted to hospital for treatment of a nephrotic syndrome. After admission, he showed high levels of inflammation parameters so that a transoesophageal ECG was performed in order to exclude endocarditis. The patient was intellectually deficient, attended a school for special needs and was living in a care facility. As a child, the patient had received a ventriculo-peritoneal shunt. Unfortunately, no information was available as to where and when this shunt had been placed, what type of shunt and valve it was or whether it had been patent. According to the medical records available for the last 10 years of the patient's life, no shunt corrections or checks had been performed. However, there was no known history of headaches, neurological deficits or seizures and the patient had been neurologically normal on hospital admission.

Pathology findings

The autopsy revealed gross obesity (weight 140 kg, height 162 cm) and severe scoliosis as well as a bilateral pes equinovarus due to spina bifida. Macroscopically, a moderate emphysema, bronchiectasia and mild pulmonary arteriosclerosis with mild right ventricular hypertrophy (thickness of the wall: 0.4 cm) and dilatation was found, as well as a splenomegaly (weight 610 g). Microscopically, the chronic obstructive lung disease was confirmed, furthermore, abundant amyloid deposits were found in renal blood vessels, especially the glomeruli and in the spleen. No definite cause of death could be established, however, the findings were compatible with sudden cardiorespiratory failure through vagal reflex.

Neuropathology findings

Macroscopically, the brain showed moderate cerebral oedema (brain weight after formalin fixation 1,522 g) with moderate uncal and tonsillar grooving but without signs of upper or lower herniation and without pathological gyration. However, an Arnold-Chiari type II malformation with caudal displacement of the lower vermis and prominent cerebellar tonsils with *s*-shaped antero-posterior kink-

ing of the medulla as well as a flattened cerebellar base was found (Fig. 4). Furthermore, a channel stretching from the right frontal pole to the right lateral ventricle could be traced, however, the shunt had been removed at autopsy. Coronal sections of the brain showed a moderate dilatation of the lateral, third and fourth ventricles as well as of the aqueduct with thinning of both the septum pellucidum and corpus callosum. Sectioning of the cerebellum and brain stem revealed a closed median ventricular aperture (Magendie). Furthermore, a cavernous haemangioma in the right frontal lobe was found. Histologically, no pathological features were present. The diagnosis was an Arnold-Chiari type II malformation with internal hydrocephalus.

Discussion

Hydrocephalus is defined as an enlargement of the internal and/or external cerebro-spinal fluid (CSF) compartments, i.e. the ventricles and aqueduct as well as the subarachnoid space in which the intracranial pressure can be raised or normal (Rickert 2001). With the rare exception of CSF over-production caused by choroid plexus hypertrophy and tumours, hydrocephalus is usually of an obstructive nature caused by a disturbance of CSF flow due to a blockage of the natural intracerebral CSF pathways (internal or non-communicating hydrocephalus) or a hampered resorption of CSF (external or communicating hydrocephalus). This results in a discrepancy between CSF production and elimination leading to a net gain in CSF volume and thus the creation of an acute or chronic hydrocephalus (McComb and Davis 1991; Rickert 2001). While the typical symptom of acute hydrocephalus is headaches, chronic hydrocephalus is clinically milder and characterised by insufficient school results in children and young adults as well as impaired intellectual performance and altered behaviour. In 30–50% of paediatric patients the IQ is normal, however, intellectual deficits are encountered with increasing intracranial pressure and decreasing thickness of the cerebral mantle. While the IQ was found to be lower than 80 in patients with a cerebral mantle of under 2 cm, the IQ was normal at a thickness of more than 2.8 cm (Detwiler et al. 1999). All of our patients showed varying degrees of intellectual deficits or mental retardation which can be attributed to the presence of long-standing hydrocephalus, post-infection state (meningitis) or the underlying syndrome or malformation (Arnold-Chiari and fragile-X syndrome), the latter being a defect located on chromosome Xq27.3 and characterised by macrocephaly and mental retardation (Sabaratnam 2000).

Hydrocephalus can arise in a plethora of settings and be variably classified in terms of time of onset (congenital vs acquired), pathomechanism (obstructive vs hypersecretory), temporal course (acute vs chronic; progressive vs arrested) as well as pressure (tension-hydrocephalus vs normal pressure hydrocephalus) (Mori 1995). The most common causes for hydrocephalus in children and young adults are malformations (ca. 40%, including aqueductal stenosis and Arnold-Chiari Type II), tumours (ca. 20%), idiopathic (ca. 10–15%), post-haemorrhagic (ca. 10–15%), post-infection (ca. 9%) and X-chromosomal (ca. 2%, including fragile-X syndrome) (Detwiler et al. 1999).

Apart from dilated ventricles, chronically hydrocephalic brains show compression of the periventricular white matter as well as a thinning of the corpus callosum, septum pellucidum and the floor of the third ventricle. Histologically, the ependyma is flattened or partially missing with loss of cilia and microvilli while there is also periventricular subependymal reactive gliosis and atrophy of the choroid plexus epithelium (Del Bigio 1993). All of these morphological changes were present in the brains of our case examples and thus consistent with long-standing chronic tension-hydrocephalus, however, only patient 4 was previously known to have suffered from hydrocephalus.

Sudden unexpected death in the setting of acute hydrocephalus with rapid increase of intracranial pressure and severe headaches, is a well recognised scenario and typically found in acute blockage of the interventricular foramina or aqueduct by cysts or tumours. However, sudden unexpected deaths have also been encountered in individuals with chronic hydrocephalus, even occurring without any signs of uncal or tonsillar herniation or medullary, i.e. cardiorespiratory compromise, which is the usually proposed mechanism for hydrocephalus-associated deaths. The presence and degree of these findings are variable, and cases with chronic hydrocephalus have been reported with acute cardiorespiratory arrest but without previous life-threatening elevation of intracranial pressure, impairment of consciousness or signs usually associated with progressive worsening of hydrocephalus (Garvey and Laureno 1998). Also in our cases, no signs of uncal or tonsillar herniation were present and the midbrains were free of necrosis or haemorrhages. Furthermore, none of our patients had suffered from epilepsy which is found in 12–30% of patients with long-standing hydrocephalus (Piatt and Carlson 1996).

Chronic hydrocephalus represents a precarious equilibrium between CSF production and absorption and there is a point at which the limits of compensation may be reached and any volume expansion or additional rise in intracranial pressure, which in itself might be insignificant for a healthy individual, may be catastrophic. This is partly due to the fact that in hydrocephalus, the damaging effect of raised intracranial pressure does not only depend on the absolute CSF pressure but also on the ventricular surface area on which the pressure is exerted. Therefore, slight increases in intracranial pressure in patients with already dilated ventricles, i.e. in chronic hydrocephalus, are more clinically relevant and deleterious than high intracranial pressure in patients with narrow ventricles (Hakim et al. 1976). The final destabilising event may be an additional element of obstruction, an increase in secretion of CSF, e.g. through raised central venous pressure, cerebral oedema, an episode of cerebral hypoxia or a minor traumatic episode (Leestma 1988). While the intracranial pressure usually lies between 0 and 15 mmHg in a resting person, it can vary substantially depending on exertion and position and can rise to 120 mmHg under increased intra-abdominal, intrathoracic and aortic pressure as brought on by exercise, isometric contraction and coughing, sneezing, laughing, pressing or straining (Dickerman et al. 1999; Rickert

2001). This mechanism might have played a role in three of our patients who were undergoing situations known to raise intracranial pressure: patient 1 was playing football, patient 2 was straining while emptying the bowels and patient 4 was undergoing a stressful procedure which might have raised intracranial pressure; otherwise, the position of the patient's head and neck may have played a role as shown in Chiari I malformation with hydrocephalus where syncopes were frequently encountered which were related to coughing, laughing and straining while the presence of tonsillar herniation and bony malformations around the foramen magnum was reported to be associated with sudden unexpected deaths (James 1995; Wolf et al. 1998). Furthermore, syncopal episodes have even been induced by modest exertion and were attributed to transient increases in intracranial pressure causing dysfunction of the ascending reticular system (Dobkin 1978). Death can be instantaneous, as reported in a patient who collapsed in the middle of a conversation and was found to have a parainfectious aqueductal stenosis but had not shown any signs of raised intracranial pressure prior to cardiorespiratory arrest (Yanofsky et al. 1981). This is corroborated in three of our cases where the collapse and sudden death was witnessed by relatives or bystanders (patients 1, 2 and 4) while an equally unexpected and instantaneous demise has to be presumed for patient 3 who was found dead on his bed still holding the television remote control.

Most probably, death in our four cases occurred as a result of sudden cardiorespiratory failure, however, its aetiology and pathomechanism has to be elucidated, especially in view of the absence of clinical prodromes and lack of uncal or tonsillar herniation at autopsy. Interestingly, patients with known chronic hydrocephalus suffering acute cardiorespiratory arrest without previous life-threatening elevation of intracranial pressure or clinical prodromes, showed obliterated perimesencephalic cisterns on CT scans which were related to brain stem dysfunction (Klug et al. 1984) and regarded to be a serious risk factor for sudden death in hydrocephalic patients (Garvey and Laureno 1998). Experimental studies confirm that partial occlusion of the pre-pontine and perimesencephalic cisterns causes cardiorespiratory dysfunction while increased compression of the posterior fossa contents, including obliteration of the cisterna magna, coincides with apnoea (Thuomas et al. 1993). Presumably, these changes resulted from pressure on the tractus solitarius in the medulla, a site known to be involved in cardiovascular and respiratory control (Ryder et al. 1986).

Control of cardiac function is thought to occur through an integrated circuitry connecting insular cortex (the stimulation of which is experimentally known to cause heart block and asystole), hypothalamus and brain stem nuclei, e.g. dorsal vagal nucleus, nucleus ambiguus, arcuate nucleus, nucleus tractus solitarius, ventrolateral medulla, raphe nucleus and infralimbic cortex (Natelson and Chang 1993; Rossi 1999). The nerve supply to the heart originates in the limbic cortex (cingulate gyrus) and descends to the hypothalamus, possibly via the basal ganglia, but most likely via the amygdala. From the hypothalamus, the two limbs of the autonomic nervous system descend with intermediate synapses in cardiopulmonary control centres in the reticular formation of the brain stem where a number of reflexes are likely to be mediated. Changes within this chain may lead to reflex disturbance and thus life-threatening and lethal arrhythmia, e.g. due to reflex mechanisms centred within bulbo-spinal structures in the domain of baro-mechano-chemoreflexes which notoriously respond to variations in blood pressure and chemical breathing-dependent components of blood and cerebrospinal fluid (Rossi 1999), or due to the repolarisation change which increases the vulnerable period during which an extrasystole would be likely to result in ventricular tachycardia or fibrillation (Samuels 1993). As the hypothalamus is thus involved in neurally mediated cardiovascular control, the possibility that intracranial pressure affects its regulatory centres is intriguing. It has been shown that stimulation of the anterior hypothalamus elicits a substantial drop in blood pressure by inhibition of sympathetic tone and these effects are possibly more devastating in the setting of hydrocephalus (Ryder et al. 1986). Two further, albeit more hypothetical, pathomechanisms are impingement of the corpus callosum and supracallosal hippocampal formation by the rigid free surface of the falx cerebri, possibly resulting in variable axonal dysfunction ranging from decreased to increased neurophysiological activity (Jinkins 2000), as well as subendocardial myofibrillary degeneration potentially involving the cardiac conducting system and thus predisposing to arrhythmia and sudden death. These have been generated experimentally by stimulation of the limbic cortex and mesencephalic reticular formation (Samuels 1993). However, no macro- or microscopic myocardial changes could be found in our cases. Interestingly, one study found the average age of death in fragile-X syndrome to be about 12 years lower than in the general population with cardiovascular death being the most common cause; however, no explanation for this fact was given by the authors and no connection to the cerebral changes was drawn (Partington et al. 1992).

In conclusion, there is evidence that sudden unexpected death in the setting of raised intracranial pressure can occur in ways other than uncal or tonsillar herniation. A potential mechanism is by sudden pressure-induced decompensation of cerebral neuronal pathways involving insular and limbic cortex, hypothalamus and brain stem nuclei causing adverse reflex disturbances of cardiopulmonary control centres in the reticular formation of the brain stem. This in turn may lead to instantaneous cardiorespiratory arrest and thus result in sudden "neurogenic" cardiac death. Aware that these changes are of a predominantly functional nature and therefore lack physical evidence, we hypothesise that this pathophysiological chain of events may be implicated in or the cause of sudden unexpected death in patients with chronic hydrocephalus. However, future investigations on relevant brain structures may elucidate morphological information on the localisation and extent of the acute damage during sudden decompensation of chronic hydrocephalus, as shown in a recent study on the immunohistochemical expression of

the early gene product c-fos in brain stem neurons stimulated by asphyxia (Nogami et al. 1999).

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