Chapter 5

Cerebrospinal fluid circulation and hydrocephalus

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Abstract

Hydrocephalus (HC) is classically defined as dynamic imbalance between the production and absorption of cerebrospinal fluid (CSF) leading to enlarged ventricles. Potential causative factors include various brain disorders like tumors causing obstruction of CSF flow within the ventricular system or the subarachnoid space. Classification of HC is based on the site of CSF flow obstruction guiding optimal treatment, with endoscopic third ventriculostomy in intraventricular obstruction and CSF shunt in communicating HC. Another clinically relevant classification is acute and chronic; the most frequent chronic form is idiopathic normal-pressure hydrocephalus (iNPH). The reported incidence of HC varies according to the study population and classification used. The incidence of congenital HC is approximately 0.4–0.6/1,000 newborns and the annual incidence of iNPH varies from 0.5/100,000 to 5.5/100,000. Radiologically, ventricular dilatation may be nonspecific, and differentiation of iNPH from other neurodegenerative diseases may be ambiguous. There are no known specific microscopic findings of HC but a systematic neuropathologic examination is needed to detect comorbid diseases and possible etiologic factors of HC. Depending on the etiology of HC, there are several nonspecific signs potentially to be seen.

Hydrocephalus (HC) is classically defined as dynamic imbalance between the production and absorption of cerebrospinal fluid (CSF), leading to enlarged ventricles. However, there are several disorders of CSF circulation not included in this definition. Furthermore, enlarged ventricles are often seen in radiologic imaging without classic symptoms of increased intracranial pressure (ICP). Normal ICP depends on posture, ranging from 5 to 15 mmHg in the supine and from −5 to +5 mmHg in the erect posture.

CSF circulation

In adults, CSF is formed at the rate of approximately 20 mL/hour or 500 mL/day (McComb, 1983). CSF is mostly formed in the choroid plexus (80%), by passive filtration across the capillary endothelium and regulated secretion across the choroid epithelium (Milhorat, 1975; McComb, 1983; Brinker et al., 2014). CSF is also formed by the ependymal lining of the ventricular system and the surrounding brain parenchyma (Milhorat, 1975; McComb, 1983; Brinker et al., 2014).

CSF, formed in the lateral ventricles, flows through the interventricular foramina of Monro to the third ventricle and through the cerebral aqueduct to the fourth ventricle (Milhorat, 1975). CSF exits the ventricular system through the median aperture (foramen of Magendie) and lateral apertures (foramina of Luschka) of the fourth ventricle into the subarachnoid space or through the obex.
into the central canal of the spinal cord (Milhorat, 1975). From the subarachnoid space, CSF is absorbed into the blood circulation via the villi of the arachnoid granulations that project into the venous sinuses (Milhorat, 1975; McComb, 1983; Brinker et al., 2014). The traditional view of CSF circulation has been challenged by the glymphatic circulation of the brain (Bulat and Klarica, 2011; Brinker et al., 2014, Ueno et al., 2016): CSF seems to drain into the cervical lymphatic vessels through the cribriform lamina (Kida et al., 1993), perivascular lymphatic drainage within the walls of cerebral capillaries and arteries (Weller et al., 2009; Carare et al., 2014), and dural lymphatic system (Aspelund et al., 2015; Louveau et al., 2015).

Normally, the rate of CSF formation and absorption is thought to be balanced. The total volume of CSF in adults is 90–200 mL (McComb, 1983; Kohn et al., 1991; Brinker et al., 2014) with up to 100 mL in the spinal canal (Edsbagge et al., 2011). In the pathologic states of CSF turnover, formation and absorption are in disequilibrium, leading to disproportionately enlarged volume of CSF, or HC. Potential causative factors include a papilloma of the choroid plexus (increased formation) and an obstruction of CSF flow within the ventricular system (Fig. 5.1) or in the subarachnoid space (decreased absorption) (Milhorat, 1975).

**CLASSIFICATION**

Clinically the most relevant classification is based on the site of CSF flow obstruction guiding the primary treatment modality (Rekate, 2011). Most frequent sites of intraventricular obstruction starting from the lateral ventricle are the foramen of Monroe (typically caused by colloid cyst), third ventricle (Fig. 5.2), aqueduct of Sylvius (aqueduct stenosis, Fig. 5.3), and fourth ventricle (typically tumor, Fig. 5.4). Although extraventricular obstruction is traditionally classified as communicating HC, extraventricular (but subconvexity) obstruction is also thought to occur (Fritsch et al., 2014). Accurate neuroimaging techniques are needed to demonstrate CSF pathways precisely.

Based on the symptoms HC can be classified as acute or chronic. Both forms can be either communicating or obstructive.

Nonobstructive HC can be classified also based on the etiology. Up to 95% of HC is thought to be caused by impaired absorption of CSF. Choroid plexus tumors (Fig. 5.2) are the rare cause of potentially increased formation of CSF. Increased CSF pressure can occur without enlargement of brain ventricles and without obvious etiology such as idiopathic intracranial hypertension (IIH).

Fig. 5.1. Acute obstructive hydrocephalus (*) caused by bilateral cerebellar infarction (arrows) in an elderly man.

Fig. 5.2. Nine-month-old boy with rapidly growing head and tense fontanel but no obvious clinical symptoms. Choroid plexus papilloma (homogeneous contrast enhancement and no infiltration into brain parenchyma) fulfilling third ventricle and causing obstructive hydrocephalus.
Chronic hydrocephalus

Adult chronic HC is often called normal-pressure HC (NPH). NPH is classically characterized with a clinical triad of symptoms, including cognitive impairment, gait difficulty, and urinary incontinence. Enlarged brain ventricles usually occur with obliterated parasagittal cortical sulci (Relkin et al., 2005). When predisposing factors such as subarachnoid hemorrhage or brain trauma are obvious, the NPH is regarded as secondary (sNPH) (Relkin et al., 2005). NPH is regarded as idiopathic (iNPH) in the absence of known predisposing factors. NPH can also be classified according to disproportionately enlarged subarachnoid space HC (DESH) as DESH and non-DESH (Kitagaki et al., 1998; Mori et al., 2012). Long-standing overt ventriculomegaly in adults (LOVA) is separated from iNPH, occurs with even larger ventricles, and may have an obstructive etiology (Oi et al., 2000).

EPIDEMIOLOGY

Since HC is not an easily determined simple disease but rather a divergent continuum of various conditions, the epidemiologic literature is rather scarce and the reported numbers vary according to the study population and classification used.

Hydrocephalus in children

The incidence of congenital HC is approximately 0.4–0.6/1,000 newborns (Fernell et al., 1994; Garne et al., 2010; Jeng et al., 2011), with a slight downward trend (Massimi et al., 2009; Sun et al., 2011). Premature babies are at increased risk of intraventricular hemorrhage, which is the most frequent cause of HC in infants. Later, tumors (most often in the posterior fossa, especially in the fourth ventricle causing obstructive HC) become the most frequent cause of HC. Some of the potential etiologic factors of HC in children are listed.
in Table 5.1. Still in the time of magnetic resonance imaging (MRI), idiopathic HC counts for approximately 10%. In MRI, obstructive membranes in CSF pathways, especially in the fourth ventricular exit foramina, may be revealed by three-dimensional constructive interference in steady state (3D-CISS) sequences at 3.0 T, while conventional images remain insensitive (Dincer et al., 2009). HC itself is a treatable condition and thus seldom fatal, leading to its gradually increasing prevalence with age. The mortality is mostly caused by malignant etiologies or severe congenital malformations.

### Idiopathic intracranial hypertension

In Israel, the annual incidence of IIH was observed to be 3.17 per 100,000 for women and 0.85 per 100,000 for men. The incidence rate in females of child-bearing age (18–45 years) was 5.49 per 100,000. The female-to-male ratio for individuals >17 years old was 6.1:1 (252 females and 41 males) and 2.1:1 (60 females and 28 males) for ages 11–17 years. Obesity was documented in 83.4% of patients and the incidence of IIH seems to be increasing, probably due to increasing obesity (Kesler et al., 2014).

### CLINICAL PHENOTYPES AND IMAGING

Symptoms of acutely increased ICP include typically headache, nausea, vomiting, and eventually coma. Frequent symptoms are also visual disturbance (gaze paresis, reduced vision) and dizziness. Acutely computed tomography (CT) indicates or excludes HC. For etiologic evaluation MRI (also MR angiography is considered) is usually needed (Fig. 5.5). Acute HC can be either communicating or obstructive. MRI should also be advocated in children and adolescents as well as in follow-up examinations after, for example, CSF shunting for radiation protection reasons.

### Idiopathic intracranial hypertension

The classic sign of IIH is papillary edema and the most severe consequence is loss of vision. Another typical symptom is headache. Thus, these patients should be carefully evaluated by ophthalmologist and neurologist. The primary treatment is most often acetazolamide but if the effect of medication is inadequate or the medication is intolerable, the treatment of choice is either ventricular or lumbar CSF shunt. The etiology of IIH is still open but obesity and female gender seem to be obvious risk factors (Johnston et al., 2007). The preferred imaging method is MRI, which excludes any secondary etiologies and classic HC. In IIH, the ventricles are small and in general the imaging findings are otherwise normal but optic nerve sheet can be dilated and an empty sella can be observed (Fig. 5.6). Obstruction in venous sinuses has been proposed as a potential etiology in a subgroup of patients (Higgins et al., 2002). Thus venous angiography is indicated and, in cases of obstruction, venous dilatation with or without stenting could be attempted; however, this treatment is still considered experimental and has the potential for severe complications.

#### Table 5.1

<table>
<thead>
<tr>
<th>Etiology</th>
<th>n (total 80)</th>
<th>%</th>
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<tbody>
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<td>Intraventricular hemorrhage</td>
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<tr>
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<td>Arachnoid cyst</td>
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<td>Meningitis</td>
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<tr>
<td>Trauma</td>
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</tr>
<tr>
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<td>27.5</td>
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<td>Congenital – total</td>
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<td></td>
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<tr>
<td>Clover-leaf skull</td>
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<td></td>
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<tr>
<td>Dandy–Walker syndrome</td>
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<td>Encephalocoele</td>
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<td>Holoprosencephaly</td>
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<tr>
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<td>Porencephalic cyst</td>
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<tr>
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<tr>
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</tr>
<tr>
<td>Idiopathic hydrocephalus</td>
<td>7</td>
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</tr>
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</table>

The most common form of adult HC is iNPH. iNPH is seldom seen under the age of 60 (when it is usually due to a known etiology, i.e., sNPH); after that the incidence increases gradually with aging, the median age of diagnosis being over 70. The reported annual incidence of iNPH varies from 0.5/100,000 to 5.5/100,000 (Vanneste et al., 1992; Brean and Eide, 2008). The estimated prevalence is 22/100,000, increasing with age and varying in elderly populations from 0.5% up to 5.9% (Brean and Eide, 2008; Iseki et al., 2009; Tanaka et al., 2009; Jaraj et al., 2014). The female-to-male ratio is close to equal. iNPH is probably underdiagnosed since higher incidence is reported in population-based studies. The incidence of sNPH is less studied but is estimated to include approximately half of cases.
Chronic hydrocephalus – normal-pressure hydrocephalus

The classic Hakim triad of NPH includes gait difficulty (magnetic gait with broad base and short step length), cognitive decline (typically decline in frontal executive functions, including amnesia, apraxia, and psychomotor slowing), and urinary incontinence. The triad is full only in around 50% of cases and in contrast dizziness, headache, and various psychiatric symptoms are rather frequently observed (Relkin et al., 2005; Williams and Relkin, 2013). The only effective treatment so far alleviating symptoms, including cognitive decline, is CSF shunt (Kazui et al., 2015). It is noteworthy that a careful selection of patients for surgery is crucial since comorbid diseases like Alzheimer disease (AD) often hamper the treatment effect (Koivisto et al., 2013; Malm et al., 2013; Fritsch et al., 2014; Pomeraniec et al., 2016).

MRI is the primary imaging modality for patients with memory problems. MRI defines changes seen in amnestic disorders with higher accuracy than CT (Figs 5.7 and 5.8). Accordingly, patients with presumed NPH should always undergo an MRI scan. DESH is indicative of suprasylvian block in CSF absorption (Kitagaki et al., 1998; Mori et al., 2012).

Long-standing overt ventriculomegaly in adults

A subgroup of LOVA is usually noncommunicating (Oi et al., 2000; Fritsch et al., 2014). The ventricles are larger than in typical communicating NPH and patients have increased risk of over-drainage-related complication with shunt and thus the primarily recommended treatment is endoscopic third ventriculostomy followed by

Fig. 5.5. Acute obstructive hydrocephalus in a 9-year-old boy, detected after mild trauma and headaches. Magnetic resonance imaging with constructive interference in steady state (CISS) sequence reveals a tumor inside the aqueduct (grade II oligodendroglioma in biopsy).

Fig. 5.6. Signs indicative of idiopathic intracranial hypertension in a 10-year-old boy with headaches. Distended perioptic subarachnoid space and flattening of posterior sclera, together with elongation and kinking of the left optic nerve (left), a partially empty sella (middle), and hypoplastic left transversal sinus together with a stenotic right sigmoid sinus in venous magnetic resonance angiography (right).
CSF shunt if there is no response to endoscopic third ventriculostomy.

**NEUROPATHOLOGY**

**Macroscopy**

Macroscopic evaluation in HC, including NPH, shows enlarged ventricles and usually relatively well-preserved cerebral cortex (Fig. 5.9). The angles of the lateral ventricles can be blunted (Lowe et al., 2008). In sNPH lesions related to subarachnoid hemorrhage, brain trauma, or other predisposing factors can be seen. Cerebrovascular lesions are frequently seen also in patients with presumed iNPH (Leinonen et al., 2012).

**Microscopy/immunohistochemistry**

There are no known specific microscopic findings of HC but a systematic neuropathologic examination is needed to detect comorbid diseases and possible etiologic factors of HC. Depending on the etiology of HC, there are several nonspecific signs potentially to be seen. In chronic HC, frequent pathologic findings include lesions and changes related to neurodegeneration such as amyloid-β (Aβ) aggregates and hyperphosphorylated tau (Figs 5.10–5.12) to a variable extent but usually not severe enough to fulfill the accepted diagnostic criteria for AD or other known neurodegenerative diseases. The minimal immunohistochemical staining should include antibodies for Aβ and hyperphosphorylated tau. The use of p62 is also recommended as a screening immunohistochemistry stain. In addition, vascular alterations and nonspecific findings, such as gliosis, poorly staining periventricular myelin on periventricular white matter, chronic meningitis, meningeal and arachnoid fibrosis, and meningeal thickening, can be observed (Bech et al., 1999; Lowe et al., 2008).

**Overview of the diagnostic approach**

Esiri and Rosenberg (2004) described neuropathologic findings in hydrocephalic dementia. Based on their recommendations the principal goal is exclusion of defined neuropathologic entities. The alterations observed include ventricular dilatation with preserved cerebral cortex, fragmented ependymal lining of the lateral ventricles, variable gliosis of subependymal tissue, and leptomeningeal thickening without inflammation. AD-related neurodegenerative lesions such as neuritic plaques and/or neurofibrillary tangles may appear, although insufficiently for the diagnosis of AD. In Esiri and Rosenberg’s series, only 1 patient was shunted, i.e., the diagnosis of HC was set postmortem. Furthermore, in the early reports most of the patients died shortly after diagnosis, hampering the determination of the response to shunt treatment (Leinonen et al., 2012).

Obviously, patients with shunt-responsive iNPH may have several concomitant brain pathologies, especially vascular and AD-related lesions. All studies published so far have failed to detect any novel neuropathologic features specific for hydrocephalic dementia (Cabral et al., 2011; Leinonen et al., 2012; Del Bigio, 2014).
Fig. 5.8. (A–C) Clinical symptoms indicative of normal-pressure hydrocephalus correspond with neuroradiologic findings of ventricular enlargement disproportionate to the size of the sulci of cerebral convexity. Vascular degenerative changes (C) are frequent but periventricular lucency caused by leakage of cerebrospinal fluid into the parenchyma (G) could mimic these changes and should be noted. Enlargement of temporal horns (D) may lead to overestimation of hippocampal atrophy (E). Evan’s index (F) is calculated as $a/b$. Flow void is measured from aqueduct (H). Callosal angle is measured from the level of posterior commissura (I and J). (Reprinted with permission from Kojoukhova M, Koivisto AM, Korhonen R, et al. (2015) Feasibility of radiological markers in idiopathic normal pressure hydrocephalus. Acta Neurochir (Wien) 157: 1709–1719.)
General limitations in all reported series of chronic HC are small number of cases, selection of the material, and various protocols in brain sampling. It is noteworthy that none of the patients autopsied so far have had iNPH as the only final clinical diagnosis. Based on the clinical follow-up of the basic study cohort (Koivisto et al., 2013, 2016), we argue that there are selected iNPH cases with dementia but without clinical signs, neuroradiologic and brain biopsy findings of any other known dementing disease. Thus, iNPH can be a distinct pathologic entity.

However, most of the cases have mixed pathologies and furthermore the clinical syndrome of iNPH may have several initiating pathologies.

Sampling of meninges, including dural sinuses and fresh frozen samples, is heavily encouraged.

In case there is any suspicion of CSF shunt obstruction/malfunction, the whole shunt system should be evaluated to find unexpected mechanical disruptions potentially not noticed in the clinical evaluation (Fig. 5.13).
Diagnostic criteria

As discussed above, in chronic HC AD-related changes, vascular alterations, and nonspecific findings such as gliosis and meningeal thickening have been observed. In a neuropathologic series of 10 patients with presumed NPH vascular pathology was frequent in patients with cognitive impairment (Leinonen et al., 2012; Del Bigio, 2014). It is noteworthy that specific NPH lesions have not been identified by current methodologies.

Autopsy studies of chronic HC with and without dementia are still urgently needed. Furthermore, the protocol with extensive sampling (including meninges) beyond standard neuropathology for dementia is preferred.

PATHOGENESIS, EXPERIMENTAL MODELS, AND BIOCHEMISTRY

The clinical syndrome of hydrocephalic brain dysfunction is thought to occur due to subcortical disconnection. Enlargement of the cerebral ventricles causes gradual destruction of periventricular white-matter axons. Secondary changes occur in neuronal cell bodies and synapses, but with minimal death of neurons. Destroyed axons cannot be restored, but some of the brain dysfunction is reversible by CSF shunting, probably through restoration of cerebral blood flow and normalization of the extracellular environment (Del Bigio, 2010a, b).

White-matter rarefaction in iNPH can be caused both by gradual CSF leakage into brain tissue and continuing hypoperfusion (Edwards et al., 2004; Krauss and von Stuckrad-Barre, 2008). Gliosis, which is usually emphasized in periventricular white matter, is probably a continuum of this process. White-matter changes seen in NPH are also associated with vascular pathologies, which is in line with the assumption that decreased cerebral blood flow due to increased ICP is a potential pathophysiologic mechanism causing the symptoms of NPH (Brusa et al., 1991; Silverberg et al., 2010). Fragmented ependymal lining and subependymal gliosis are probably reactive changes to the long-standing increased pressure rather than predisposing factors leading to iNPH. Cilia structure and function are rarely studied in the clinical setting (Fig. 5.14). Nevertheless, all these nonspecific lesions are likely to be only secondary to the so far unknown pathophysiologic process causing the disease to be not yet determined (Fig. 5.15). On the other hand, metabolite transporter expression alterations at the blood–brain barrier, deterioration of blood–brain barrier integrity leading to protein leakage, CSF production and turnover decline, and vascular changes may all converge on the pathology of aging and the age-related dementias. Thus, all these changes seen in iNPH patients may be initiated by aging and therefore age-matched clinically asymptomatic autopsy controls would be of great importance when assessing the significance of those lesions.

Fig. 5.12. Amyloid-β aggregates in a cortical biopsy.

Fig. 5.13. Chronically dilated ventricles in a 29-year-old male with mental retardation and repeated shunt malfunctions (fluctuating headache) and consequent shunt revisions. Broken (probably intermittently drained) catheter (circled) noted from the old X-ray only after sudden death and then confirmed in a forensic autopsy.
Only few animal models of HC are available. The most often used is kaolin-induced HC. Genetic defects causing ciliopathies or ciliary dyskinesia cause severe or even fatal HC (Zang, 2014). The first gene (SFMBT1) potentially related to iNPH is expressed in choroid plexus (Kato et al., 2011). Aquaporins (AQPs) are plasma membrane proteins, which have a significant role in the water homeostasis of the CNS. AQP-1, expressed in the choroid plexus, is involved in CSF secretion and AQP-4 in CSF absorption (Papadopoulos and Verkman, 2013). Chronic HC potentially interferes with protein clearance. Aβ pathology seems to be related to disturbed CSF dynamics since accumulation of Aβ and hyperphosphorylated tau has been observed in experimental HC in elderly rats (Deren et al., 2009), but interestingly, not in young rats (Mawuenyega et al., 2010).

Brain biopsies during HC surgery may help in the differential diagnostics and detection of concomitant neurodegenerative diseases (Leinonen et al., 2012; Elobeid et al., 2015; Pomeraniec et al., 2016). Furthermore, they open a novel window for the pathobiologic research (Laiterä et al., 2015).

Secondary hydrocephalus

HC after subarachnoid hemorrhage has been reported to occur in 6–67% of cases (van Gijn et al., 1985; Tapaninaho et al., 1993; Vale et al., 1997). The acute phase can be self-limiting in some patients, while others will require CSF diversion by external ventricular drainage to alleviate HC symptoms (Tapaninaho et al., 1993). The mechanisms of HC development have not been fully elucidated, but studies have suggested deterioration of CSF dynamics as a cause. Other proposed mechanisms are obstruction due to blood products, a disrupted absorption process at the arachnoid granulations level, or possibly a result of inflammation and fibrosis (van Gijn et al., 1985; Auer and Mokry, 1990; Massicotte and Del Bigio, 1999), but resolving the exact mechanisms causing the disturbance of CSF circulation still requires further study (McAllister et al., 2015). After aneurysmal subarachnoid hemorrhage, ventricular and sulcal enlargement, together with reduced gray-matter volume, may also indicate general atrophy rather than HC. Enlarged CSF spaces have been shown to correlate with cognitive deficits after aneurysmal subarachnoid hemorrhage (Bendel et al., 2010).

Like acute subarachnoid hemorrhage, severe traumatic brain injury can lead to disturbance of CSF circulation both acutely and later on. Acute HC after subarachnoid hemorrhage or traumatic brain injury may require permanent shunt but also significantly increase the risk of later developing chronic HC. Also meningitis, both per se and related to invasive neurosurgical procedures like prolonged external ventricular drainage, may lead to HC. Interestingly, in some rare cases with long-standing need of external ventricular drainage, especially with concomitant meningitis, ventricles may enlarge and the patient may deteriorate and thus require CSF drainage despite normal or unexpectedly low ICP.
REFERENCES


