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Review Article

Intracranial Hemorrhage in Term Newborns: Management and Outcomes

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Child neurology is frequently a late player in the management of the term newborn with intracranial hemorrhage in the first neonatal week. It is crucial, however, that the child neurologist undertake a comprehensive evaluation by investigating etiology and management of the hemorrhage. Intracranial hemorrhage is usually associated with premature newborns. The literature on intracranial hemorrhage in term newborns is largely in the form of isolated case reports or a small series of cases, and mostly nonsystematic. Presented here is an evidence-based review of the incidence, risk factors, etiologies, and clinical management of intracranial hemorrhage in the first week after birth, with discussion of the role of neuroimaging and hematologic investigation. Consideration of these investigations along with documentation of every intervention or its explanation will reduce parental anxiety and will assure the best possible neurologic as well as legal outcomes of term newborns with intracranial hemorrhage.

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Introduction

Intracranial hemorrhage is defined as the pathologic accumulation of blood within the cranial vault. Intraventricular hemorrhage is the most common type of intracranial hemorrhage in preterm newborns (i.e., low birth weight infants weighing less than 1500 g) [1], but in term newborns intracranial hemorrhage is relatively uncommon and has a different location, etiology, clinical presentation, and neurologic outcome [2,3]. Intracranial hemorrhage in term neonates usually occurs in the vicinity of the falx and tentorium cerebelli, producing posterior fossa hemorrhage in the dural space, or it may occur within brain parenchyma. Giving such news, explaining the etiology, and predicting the neurologic outcome is difficult and challenging for the physician, as well as devastating for the parents. Learning that the intracranial hemorrhage is due to birth injury may generate feelings of guilt or bitter accusations of medical malpractice.

The following is an evidence-based review of term newborns with intracranial hemorrhage in the first week after birth, including a practical approach to clinical evaluation and outcomes.

Incidence

The incidence or prevalence of intracranial hemorrhage is not known. Only some term infants with intracranial hemorrhage present with clinical events, so the true incidence of intracranial hemorrhage is difficult to determine. The reported incidence of asymptomatic and symptomatic intracranial hemorrhage varies from study to study probably due to differences in populations studied and in the sensitivity and timing of diagnostic imaging used. A large prospective magnetic resonance imaging (0.2 T) study of asymptomatic term newborns found an 8% prevalence of subdural hemorrhage [4]. Out of 88 asymptomatic neonates born via vaginal delivery and undergoing cranial MRI (3 T) between the ages of 1 and 5 weeks, 17 term infants had intracranial hemorrhage, for a study prevalence of 26% [5]. Such findings suggest that asymptomatic intracranial hemorrhage in term newborns is much more frequent than previously thought.

The reported incidence of symptomatic intracranial hemorrhage is likewise variable. In one study, the estimated local

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Table 1. Summary of neuroanatomic-based intracranial hemorrhage in term newborns

Intracranial Hemorrhage Type*	Definition	Cranial Computed Tomographic Scan Characteristics	Comments or Pathogenesis
Epidural Hemorrhage	Blood between the skull and outside the dura	Lentiform hyperattenuation along inner side of calvarium	Rare, because the middle meningeal artery moves freely away from displacements of the skull
Subdural Hemorrhage	Blood between the dura and arachnoid membrane	Crescent-shaped hyperattenuation conforming to the adjacent brain	Most common, vertical molding of skull causing tearing of blood vessels of tentorium
Subarachnoid hemorrhage	Blood between the arachnoid and the pia membrane	Hyperattenuating fluid in basal subarachnoid spaces or along cerebral sulci	Most common type, tearing of bridging blood vessels or dural sinuses during labor
Intraventricular hemorrhage†	Blood in lateral, third or fourth ventricles	Hyperattenuating fluid typically seen as layering within the ventricles	Uncommon, hemorrhage of choroid plexuses, extension of thalamic or subependymal matrix
Intraparenchymal hemorrhage	Blood within brain (intra-axial) parenchyma	Hyperattenuating focus within the cerebral or cerebellar hemispheres, with varying amount of surrounding vasogenic edema	Less frequent, Primary hemorrhage must be distinguish from secondary intraparenchymal hemorrhage

* Location of intracranial hemorrhage may be supratentorial or infratentorial.
† Unlike term newborns, 80% of preterm with intraventricular hemorrhage are associated with germinal matrix hemorrhagic infarction. Occurrence of intraventricular hemorrhage in term newborns is a poor predictor of neurologic outcome.

incidence of symptomatic intracranial hemorrhage was 4.9/10,000 live births, with a regional incidence of 2.7/10,000 live births [2]. An average incidence of 3.8/10,000 live births is consistent with the authors' personal experience at their teaching hospital's neonatal intensive care unit. Probably the largest study available to date is one using a database that linked birth and death certificates with maternal and neonatal hospital discharge records in California [6]. Data analysis on nearly 600,000 average-weight infants (2500-4000 g) born to nulliparous women showed an incidence of intracranial hemorrhage associated with spontaneous delivery, vacuum extraction delivery, and forceps delivery of 1 per 1900, 1 per 860, and 1 per 664 births, respectively [6].

Type and Severity

Types

A summary of intracranial hemorrhage types, with definition and characteristics, is given in Table 1. Intracranial hemorrhage is classified compartmentally as epidural, subdural, subarachnoid, intraventricular, or intraparenchymal,

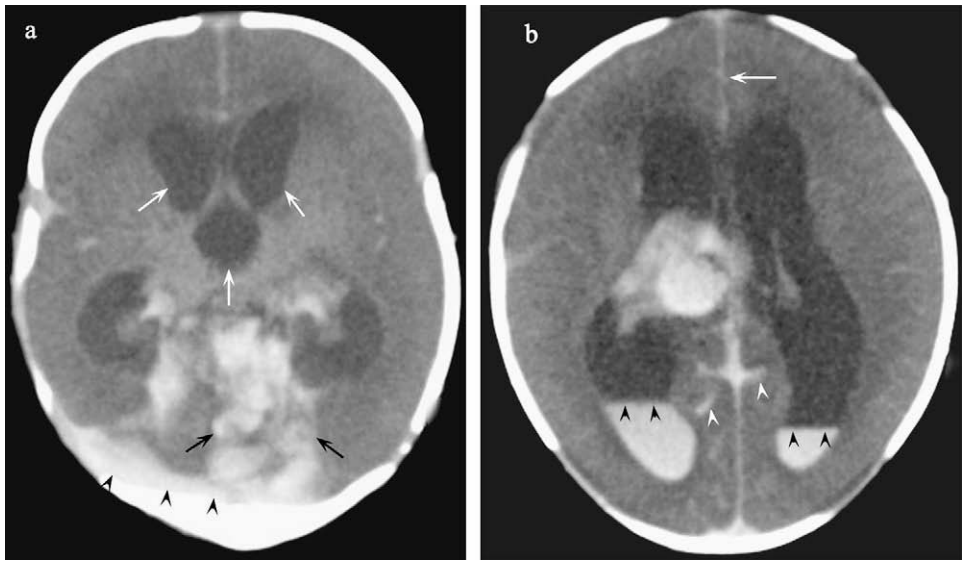

Figure 1. Cranial computed tomography performed within the first 24 hours after birth. All images are of the same term newborn. (a) The presence of three types of supratentorial intracranial hemorrhage (subdural hemorrhage, black arrow heads; intraparenchymal hemorrhage, black arrows; and ventricular enlargement, white arrows) points to a severe intracranial hemorrhage. (b) Subarachnoid hemorrhage of sulci (white arrow heads) or interhemispheric subarachnoid hemorrhage (white arrow), and intraventricular hemorrhage imaged as hyperattenuating fluid layering in dependent portions of the lateral ventricles (black arrow heads).

which may be supratentorial or infratentorial in location. In clinical practice, hemorrhage involving multiple compartments is not unusual [5]. An example of such multicompartment intracranial hemorrhage in a single term newborn is shown in Figure 1.

In the MRI study by Looney et al. [5], infratentorial subdural hemorrhage was the most frequent intracranial hemorrhage in a group of asymptomatic term newborns. Fenichel et al. [7] reported primary subarachnoid hemorrhage as the most common type of hemorrhage over a 5-year period among symptomatic term newborns ($n = 22$) in neonatal intensive care unit. Symmetric bithalamic and striatal nuclear hemorrhage after asphyxia at birth was first reported by Kotagal et al. [8]. The stated pattern of hemorrhage differs from the germinal matrix hemorrhage common in preterm newborn in having a later onset (between the 4th and 10th days after birth), and is also distinct from supratentorial subarachnoid hemorrhage or infratentorial subdural hemorrhage in the term newborn.

Intraparenchymal hemorrhage is less frequent than subdural hemorrhage and subarachnoid hemorrhage in term newborns. A review of neurosurgical computerized database spanning more than 40 years identified 11 cases of lobar hemorrhage [9]. In contrast to the paucity of cases reported in the literature, however, intraparenchymal hemorrhage is not uncommon in clinical practice.

Intraventricular hemorrhage is primarily a disorder of prematurity. The lower incidence of intraventricular hemorrhage in term newborns (4.6%) compared with preterm newborns (50%) is thought to be due to the greater maturity of the brain at term [10,11]. Unlike preterm intraventricular hemorrhage, intraventricular hemorrhage in term newborns has multiple etiologies and a more variable source of the origin of hemorrhage. In the term newborn, intraventricular hemorrhage commonly originates from the choroid plexus or as an extension of thalamic hemorrhage, in addition to bleeding originating in the capillaries of the subependymal germinal matrix [12,13].

The major causes of intraventricular hemorrhage are birth trauma or asphyxia [14]. Wu et al. [15] reported an incidence of 1.2% for intraventricular hemorrhage secondary to sinovenous thrombosis in a neonatal intensive care unit. In 25% of cases of intraventricular hemorrhage in term newborn, the cause remains unknown [16]. Cryptic hemangioma of the choroid plexus is probably responsible for a large number of these cases that are documented at autopsy [17].

In children and adults, the typical cause of epidural hemorrhage is skull fracture due to tearing of the middle meningeal artery in its groove within the temporal bone. Newborns and infants rarely develop epidural hemorrhage, because the middle meningeal artery, which is not yet encased within the bone, moves freely away from displacements of the skull. Extradural hemorrhage, however, may occur in the newborn, in absence of skull fracture, when an external blow causes the outer layer of the dura to detach from the inner table of the skull. This most often occurs with a difficult forceps extraction [17].

Severity

The severity of intracranial hemorrhage is classified as mild, moderate, or severe. Mild intracranial hemorrhage is defined as (a) hemorrhage involving only one compartment or one lobe, with a maximum midline shift of 0.5 cm, or as (b) intraventricular hemorrhage in only one ventricle with no hydrocephalus. Moderate intracranial hemorrhage is defined as (a) hemorrhage involving only one lobe and compartment with midline shift or as (b) intraventricular hemorrhage of more than one ventricle but no hydrocephalus; when two or more lobes are involved, midline shift is inconsequential. Severe intracranial hemorrhage is defined as (a) hemorrhage in more than one lobe and in more than one compartment or as (b) intraventricular hemorrhage with hydrocephalus [18]. The description of hemorrhage type and severity is not complete without considering the association between etiology and type, such as a large subdural hemorrhage being associated with ischemic brain injury. It is also important to distinguish between primary intraparenchymal hemorrhage and intraparenchymal hemorrhage caused by hemorrhagic transformation of an underlying cerebral infarction or arteriovenous malformation. Unlike the case for adults with intraparenchymal hemorrhage, in newborns with intracranial hemorrhage the clinical significance of volumetric measurement for the severity of intraparenchymal hemorrhage (small, <3 cm; medium, 3-6 cm; or large, >6 cm) or by using formula ($ABC/2$, where A and B are the largest perpendicular diameters of the hematoma in centimeters, and C is the number of vertical computed tomographic slices multiplied by the slice thickness in centimeters) is not known [19].

Role of Neuroimaging

Cranial ultrasound is often used as the first imaging modality for newborns. Instrument transportability, low cost of operation, absence of exposure to radiation, and the ease with which it can be performed in the neonatal intensive care unit setting has made this technique popular worldwide. In a study by Mercuri et al. [20], 177 asymptomatic newborns had cranial ultrasound between 6 and 48 hours after birth. Ultrasound abnormalities were present in 35/177 infants (20%). Ischemic lesions were the most common finding (8%) followed by hemorrhagic lesions (6%). The possible sequelae of antenatal hemorrhage, such as focal ventricular dilation or choroid cysts, were present in 6% infants. The authors concluded that ultrasound abnormalities are common even in the absence of antenatal or perinatal risk factor [20].

Ultrasound findings are likely to increase with presence of macrocephaly (33%), seizures (26%), or 1-minute and 5-minute Apgar scores of <7 (13%) [21]. Several studies have shown the superiority of computed tomography (CT) imaging over ultrasound in the detection of intracranial hemorrhage [22]. Other considerations that foster the use of cranial CT scanning in neonatology include the inability of cranial ultrasound to detect newborns with

retrocerebellar or posterior interhemispheric subdural hemorrhage, the low sensitivity (30%) of ultrasound in cases of acute arterial infarction [23-25], and better sensitivity of CT scan compared with ultrasound in detecting subarachnoid hemorrhage (100% vs. 0%), diffuse parenchymal abnormality (100% vs. 33%), and small intraventricular hemorrhage (100% vs. 0%) [26]. Use of cranial CT and MRI resulted in a change in clinical management and prognosis in 22.4% of neonates, or an increased confidence that the central nervous system was normal [22,27].

Because magnetic resonance images are multiplanar and have higher intrinsic contrast resolution, MRI is superior to CT in identifying hemorrhage, particularly for subacute to chronic hemorrhage and for extracerebral or posterior fossa (infratentorial) hemorrhages [5]. Because conventional MRI sequences can fail to detect hemorrhage, gradient echo sequence MRI is preferred for documenting hemorrhage. Furthermore, one may choose susceptibility-weighted imaging over conventional gradient echo sequence MRI to detect intraparenchymal hemorrhage in clinically suspected cases with smaller hemorrhage [28].

Unless structural anomalies such as cerebral aneurysm, cavernous malformation, arteriovenous malformation, venous infarction, or neoplasm or concomitant spinal (cervical) cord injury are suspected, cranial neuroimaging with MRI, magnetic resonance angiography and venography, or cerebral arteriography need not be undertaken as an urgent procedure in the neonatal intensive care unit [29]. The role of MRI or vasculography in CT-positive hemorrhage is to identify possible rare structural lesions and to guide surgical management.

Risk Factors

Several risk factors have been reported in term newborns with intracranial hemorrhage, but studies that have demonstrated a relationship between the proposed risk factors and intracranial hemorrhage have been few—usually in the form of a small series of cases. Pertinent risk factors leading to intracranial hemorrhage in term newborns are given in Table 2.

Method of Delivery

The normal birth process itself may be traumatic enough to cause intracranial hemorrhage in term newborns [25]. A retrospective case-control study in 66 term infants imaged within 7 days after birth showed an increased risk of intracranial hemorrhage with forceps-assisted delivery (vaginal delivery assisted by vacuum devices was not evaluated in this study) [18]. Whitby et al. [4] detected an increased risk for subdural hemorrhage for delivery with forceps after failed vacuum extraction delivery. Compared with successful vacuum extraction, the combination of vacuum extraction and forceps delivery increased the risk of subdural hemorrhage or subarachnoid hemorrhage from 1 per 854 to 1 per 277 births. Cesarean section performed after a failed attempt at vaginal delivery was also associated with an increased risk, compared with successful vacuum extraction. They concluded that if attempts at vaginal delivery fail, the risk of injury are increased no matter which method of delivery is chosen [30]. The important conclusion from the study by Towner et al. [6] was that successful vaginal delivery with the use of either vacuum extraction or forceps appeared to carry no excess risk of intracranial hemorrhage, compared with cesarean section during labor. They hypothesized that a substantial portion of morbidity previously thought to be a function of operative vaginal delivery might actually be due to the process of labor [6]. Benedetti et al. [30] stressed the fact that the number of fetal injuries associated with labor is much more important as a risk factor than the method of delivery itself.

Risk of intracranial hemorrhage is likely to increase in hemophiliac infants born via assisted vaginal delivery as opposed to cesarean delivery [31].

Prenatal Factors

Maternal hypertension and obstetric pathologies such as abruption of the placenta are well-recognized risk factors for intracranial hemorrhage in term newborns. Sims et al.

Table 2. Risk factors for intracranial hemorrhage (ICH) in term newborns in the first neonatal week*

Maternal risk factor causing ICH in newborn	Perinatal risk factor†	
	Newborn	Labor and delivery
Usage of drugs such as aspirin (acetylsalicylic acid) or street drugs such as cocaine	Birth trauma	Spontaneous vaginal delivery‡
Pregnancy-induced hypertension	Low Apgar scores	Prolonged labor
Placental abruption	Resuscitation at birth; thrombocytopenia	Forceps delivery
Autoimmune disorders	Breast fed infants who received no vitamin K	Suction cup
Platelet alloimmunization	Inherited coagulopathy	Cesarean-section, some times
	Disseminated intravascular coagulopathy	Multiple risk factors or combination of the above interventions may be associated with intracranial hemorrhage
	Increased cerebral venous pressure	

* No risk factor is identified in the majority of term newborns with intracranial hemorrhage. Rarely, cerebral neuronal or vascular abnormality may cause intracranial hemorrhage in the term newborns.

† Sims et al. [21] hypothesized that many of the stresses contributing to brain injury in the intrapartum or neonatal period may exist prenatally.

‡ Normal (uncomplicated) birth process itself may be traumatic enough to cause intracranial hemorrhage [25].

[21] hypothesized that many of the stresses contributing to brain injury in the intrapartum or neonatal period may exist prenatally.

Low Apgar Scores and Perinatal Asphyxia

Hypoxic-ischemic injury and hemorrhagic injury, in both preterm and term newborns, often occur concomitantly, share many pathophysiological and etiological factors, and have similar clinical features [32]. Takahashi et al. [33] prospectively studied the effect of fetal distress on the neonatal brain by monitoring fetal heart rate during second-stage labor. Among 11 cases of term neonates, intracranial hemorrhage was evidenced in all 3 of the infants who had 5-minute Apgar score of 7 or less [33]. Jhawar et al. [18] also reported that low Apgar scores, with and without requirement for resuscitation at birth, are risk factors for intracranial hemorrhage. Because intracranial hemorrhage itself may cause respiratory distress, it is difficult to ascertain if perinatal hypoxia is a causative factor in intracranial hemorrhage [18].

Hematologic Risk Factors

Intracranial hemorrhage due to a bleeding disorder is rare in the term newborn, but tends to be more severe and devastating, which underscores the importance of early detection of bleeding problems. From analysis of a neurosurgical database spanning four decades, Sandberg et al. [9] identified 11 term newborns with spontaneous intraparenchymal hemorrhage; coagulopathy was noted in 3 of the 11.

Thrombocytopenia is the most common condition leading to intracranial hemorrhage in term newborns [18]. Thrombocytopenia has multiple causes; it may be drug-induced, infectious, genetic, or immune-related, or due to disseminated intravascular coagulation, or placental insufficiency [34]. The risk for intracranial hemorrhage increases with severity of thrombocytopenia. Most cases occur with platelet counts of less than 30,000/mm^3. Neonatal alloimmune thrombocytopenia is a particularly important risk for intracranial hemorrhage: 7-26% of affected neonates develop intracranial hemorrhage [35]. Neonatal alloimmune thrombocytopenia occurs when mothers lacking the most common human platelet antigen among European origin (HPA-1a) become sensitized to that antigen present on fetal platelets. Unlike rhesus hemolytic disease of the newborn, a first-born may be affected, and there are no routine tests to predict its occurrence [36]. Disseminated intravascular coagulation can also lead to severe thrombocytopenia and intracranial hemorrhage in the term newborn, but this occurs in the sick newborn, usually in the neonatal intensive care unit setting.

Coagulopathies (i.e., increased tendency for bleeding due to coagulation factor deficiency) have been implicated in newborns with intracranial hemorrhage. Vitamin K is essential for the final carboxylation of coagulation factors II, VII, IX, and X. Its deficiency can lead to hemorrhagic disease of the newborn, which is rare in the United States because of routine administration of vitamin K—but there are reports of intracranial hemorrhage with this deficiency [37]. It is most common in exclusively breast-fed infants who received no vitamin K after birth, and also in infants with mothers taking various antiepileptic drugs [38], analgesics [39,40], or street drugs.

Most coagulation problems are acquired, but a number of inherited conditions may present in the newborn period as intracranial hemorrhage. Hemophilia A and B (deficiency of factor VIII and factor IX) are the most common severe inherited coagulopathies. Hemophilia C (deficiency of factor XI) is much less common. The estimated incidence of intracranial hemorrhage in hemophiliac newborns is approximately 3% [41,42]. Smith et al. [43] found intracranial hemorrhage in 3/20 newborns with hemophilia A or B when screened by ultrasound of the head or cranial CT in the first neonatal week; all three cases of intracranial hemorrhage occurred in newborns delivered with instrument assistance [43]. Intracranial hemorrhage in newborn with von Willebrand disease is infrequent, because a physiologic increase in von Willebrand factor levels at birth protects most patients from bleeding [44]. Other rare bleeding disorders are inherited as an autosomal recessive deficiency of one of the following factors: fibrinogen, factor X, factor VII, or factor XIII. Due to their mode of inheritance, these bleeding disorders occur more frequently in populations where consanguineous marriage is common.

Sinovenous thrombosis increases the risk for intraventricular hemorrhage. In a retrospective study, 31% of neonates (≥36 weeks gestation) who had intraventricular hemorrhage also had sinovenous thrombosis [15], which occurs most commonly due to nonhematological conditions such as hypoxia, congenital heart disease, extracorporeal membrane oxygenation therapy, and birth trauma. Disseminated intravascular coagulation due to sepsis or other medical conditions, as well as thrombophilia (i.e., an inherited tendency for thrombosis) can also cause sinovenous thrombosis in term newborns.

Neurologic Factors

Fortunately, primary cerebral clinical entities leading to intracranial hemorrhage are rare in the first week. However, the clinical presentation of a symptomatic newborn with no known risk factor or discernable cause for hemorrhage or the presence of focal subarachnoid hemorrhage should alert the physician to look for a cerebral structural abnormality. Several vascular malformations of the cerebral circulation may become symptomatic beyond the neonatal period, but only malformation of the great vein of Galen becomes symptomatic in the term newborn at birth and may present as cardiac failure rather than as intracranial hemorrhage [45].

Clinical Features

Unlike the presentation of intracranial hemorrhage later in childhood, newborns at birth do not present with features

such as headache, papilledema, or focal neurologic signs. Like preterm newborns, term newborns with intracranial hemorrhage may manifest with a neonatal seizure, decreased level of consciousness, or both. Such a clinical presentation should prompt one to seek specific information pertaining to the possibility of an intracranial abnormality. The newborn's history, including the setting in which the presentation occurs, maternal history and family history, and perinatal risk factors may suggest the diagnosis of intracranial hemorrhage.

An important initial consideration is whether the newborn was sick before the presentation. The occurrence of recognizable encephalopathic features may suggest hypoxemia or infection. Disseminated intravascular coagulation leading to thrombocytopenia is particularly common in the sick newborn in the neonatal intensive care unit setting. Newborns with alloimmune thrombocytopenia or inherited coagulopathy appear to be well until the onset of intracranial hemorrhage. A history of a previous sibling with neonatal bleeding suggests alloimmune thrombocytopenia or inherited coagulopathy; consanguinity and family history of bleeding problems strongly suggest inherited coagulopathy. Maternal history can also offer clues to a hematological cause of intracranial hemorrhage. Maternal history may reveal use of drugs such as aspirin that can cause hemorrhage due to action on cyclooxygenase in the newborns [39,40]. The mother's intake of cocaine leading to intracranial hemorrhage in the newborn has been reported [46]. During pregnancy, maternal hypertension or placental insufficiency may cause neonatal thrombocytopenia. Thrombocytopenia or autoimmune disorders (e.g., systemic lupus erythematosus or idiopathic thrombocytopenic purpura) suggest that the newborn may have maternal platelet-induced autoantibodies resulting in isoimmune thrombocytopenia. Isoimmune thrombocytopenia is less common than alloimmune thrombocytopenia as a cause of intracranial hemorrhage [47].

The majority of neonates with intracranial hemorrhage have no clinical symptoms, including some with moderate to severe hemorrhages [5]. Thus, only a few newborns with intracranial hemorrhage come to clinical attention before discharge from the neonatal nursery. Any one or a combination of the core symptoms in child neurology (e.g., decreased level of consciousness, generalized hypotonia, or seizure) may mark the presentation of intracranial hemorrhage. These manifestations are not specific to intracranial hemorrhage. Although primary cerebral etiology causing intracranial hemorrhage is uncommon, neurologic manifestations are the most common presentation of intracranial hemorrhage in term newborns.

Clinical presentation depends on the etiology and compartment of the cranium involved with the hemorrhage or the pace with which intracranial pressure rises. Hematoma location may be an important determinant of symptoms, because peritentorial subdural hemorrhage occurs frequently and without immediate clinical consequences [4,5]. Alternatively, subdural hemorrhage in the posterior fossa may lead to obstructive hydrocephalus or an elevated intracranial pressure. Seizures or signs and symptoms related to abnormally high intracranial pressure are constant features of intracranial hemorrhage. Thus, it is not surprising that increased intracranial pressure is a common presentation of intracranial hemorrhage in term newborns [23]. Decreased level of consciousness is more likely to occur when there is elevated intracranial pressure due to mass effect. In addition, Kotagal et al. [8] reported a prolonged period of obtundation after asphyxia at birth; they concluded that the interruption of the thalamocortical arousal mechanisms was the cause for prolonged obtundation.

It is not unusual for term newborns with intracranial hemorrhage to present with neurologic signs. For example, seizure was the most common presenting symptom of intracranial hemorrhage in 7/11 term newborns [9]. Indeed, intracranial hemorrhage is a common cause of neonatal seizures. The seizure occurrence, type, and severity are variable in term newborns. Seizure may occur soon after birth or after an extended period of normality. Most term newborns with intracranial hemorrhage present with seizure within the first 2 days after birth [9]. Neonatal seizures may prove difficult to differentiate from normal movement, or may have variable presentations, ranging from a subtle seizure such as apnea to a more apparent seizure to status epilepticus [48].

A retrospective analysis of 33 term infants with intracranial hemorrhage revealed that 24/33 infants (72.3%) presented with seizure, respiratory distress, or apnea [2]. At times, apnea may be the only presentation of a neonatal seizure, with or without risk factors for intracranial hemorrhage; however, it is more likely that apnea is secondary to brainstem immaturity, sepsis, gastroesophageal reflux, pulmonary disease, or arrhythmias rather than to intracranial hemorrhage. Too often, apnea is suspected to be the manifestation of a neonatal seizure—but seizures presenting as apnea may also be overlooked. Apnea, as a manifestation of seizure activity, is usually associated with tachycardia, increased blood pressure, or hypoxia. In addition, if apnea is accompanied with tonic eye deviation, this should leave no doubt that the apnea is a manifestation of neonatal seizure [49]. Apnea of any duration associated with significant tachycardia or bradycardia in a newborn who is otherwise apparently well should prompt the physician to consider intracranial abnormalities such as intracranial hemorrhage. Temporal lobe hemorrhage with apneic seizures in term neonates, although uncommon, has been reported [50,51]. On the other hand, apnea with bradycardia may be a manifestation of elevated intracranial pressure [49].

Hemorrhagic disease of the newborn with intracranial hemorrhage usually has concomitant bleeding in the skin or other organs, which may manifest as early as the first day after birth. In a German series, Sutor et al. [52] found intracranial hemorrhage in 58% of newborns. Newborns with vitamin K deficiency often present with gastrointestinal bleeding [53].

Examination

Once the clinical history is seen to be suggestive of a cerebral insult, the physician should perform a quick and focused examination, both general and neurologic. The physical examination should include vital signs, state of consciousness, and abnormal posture or movement. General examination may reveal subtle or obvious clues about the hematologic etiology of hemorrhage. Congenital infections causing hepatosplenomegaly may have thrombocytopenia related to those infections. Forearm or thumb anomalies may indicate thrombocytopenia–absent radii syndrome or Fanconi anemia. A bulging anterior fontanelle (in seated position) or rapidly increasing head circumference measurements may suggest elevated intracranial pressure.

Assessment of consciousness level in the newborn may be challenging in the presence of seizure and with anticonvulsant administration, mechanical ventilation, or other interventions in the neonatal intensive care unit setting. Deficits of topographical brain involvement such as parasagittal or central (thalamus or basal ganglia) regions secondary to intracranial hemorrhage or hypoxic-ischemic injury may be difficult to recognize in the newborn. The lack of symmetric movement of extremities either spontaneously or in response to stimulation (Moro reflex) may suggest a clavicle fracture, brachial nerve injury, or spinal cord injury. A history of birth injury should prompt an investigation for intracranial hemorrhage when evaluating a seizure or signs of an elevated intracranial pressure.

Eye examination may be invaluable, but often is difficult, warranting an ophthalmologic consultation. Funduscopic examination may reveal retinal hemorrhages, which have been observed in 20-40% of newborns following vaginal delivery without obvious perinatal difficulties or neurologic injury [54]. It may also reveal additional findings such as prematurity of the retina, which helps in estimating the gestational age of the newborn.

Differential Diagnosis

Differential diagnosis of the term newborn with intracranial hemorrhage should include underlying cerebral infarction, which may be associated with focal subarachnoid hemorrhage, and sinus venous thrombosis, which may present as a deep intracranial hemorrhage or intraventricular hemorrhage.

Neonatal herpes simplex encephalitis should be considered when an encephalopathic newborn presents with fever or neonatal seizure. Note, however, that neonatal herpes simplex virus-2 encephalitis has a variable imaging appearance, and that encephalitic hemorrhage may not be limited to the frontotemporal lobe in infants [55]. Clinical entities such as glutaric aciduria type 1 or Menkes disease usually do not present in the first week [56,57], but may be considered in appropriate clinical situations.

Investigations

Laboratory Investigation

The goals of initial laboratory investigation of term neonates with intracranial hemorrhage are multiple: (1) to confirm the clinical suspicion of intracranial abnormality such as hemorrhage, (2) to define the type and the severity of the intracranial hemorrhage, (3) to entertain evidence-based etiologic and clinical differential diagnosis for the hemorrhage, (4) to consider possible neurosurgical intervention in newborns with worsening intracranial pressure, (5) to obtain a baseline study for the immediate and long-term follow-up, and, most importantly, (6) to seek clues suggesting an underlying cerebral abnormality specifically in those with apparently spontaneous intracranial hemorrhage or of focal subarachnoid hemorrhage.

To achieve these multiple goals, when faced with a newborn with neurologic manifestation, a noncontrast CT scan of the brain is preferred as the first investigation. This should be undertaken as soon as possible, to document any intracranial hemorrhage. Cranial ultrasound should be obtained if the medical condition of the newborn does not allow safe transfer to the diagnostic imaging area. Because clinical evaluation may not provide evidence-based diagnostic or prognostic information, neuroimaging is indicated in the absence of a discernable cause for decreased level of alertness or seizure irrespective of risk factors. In the neonatal intensive care unit, CT scanning of the brain provides an interobserver-independent baseline study for the reassessment of intracranial pressure, which may direct neurosurgical planning and intervention. If the infant makes an uneventful recovery, this will be useful for long-term follow-up.

If the CT scan is normal, inconclusive, or not consistent with the clinical presentation but the suspicion of intracranial pathology remains, lumber puncture may be considered. Lumber puncture is most likely to be performed to rule out sepsis. Red blood cells are often found in the cerebrospinal fluid of newborns with intracranial hemorrhage [54]. Lumber puncture is not usually undertaken for the sole purpose of confirming intracranial hemorrhage.

Conventional T_1- and T_2-weighted MRI of the brain is useful to further explore a CT finding of hypodense brain parenchyma for its exact spatial location, extent, and associated cerebral finding. Because superficial hemorrhage is common in birth trauma or with instrument-assisted delivery, and deep hemorrhage is common in nontraumatic hemorrhage, the distinction between these two types of intracranial hemorrhage is useful for directing laboratory investigation (e.g., coagulation testing for cases of deep intracranial hemorrhage) [58]. In most cases, an urgent MRI of the brain is not pursued in the assessment of intracranial hemorrhage, but it is indicated once the urgency of the initial intracranial hemorrhage evaluation is past. The goal for delayed MRI of the brain is to define the full extent of posthemorrhagic cerebral injury. The confirmation of intracranial hemorrhage with either MRI or

CT neuroimaging will allow for prompt management and an expedited search for the etiology.

Hematologic Investigation

An initial hematology laboratory investigation should include a complete blood count and a baseline coagulation screen with prothrombin time and activated partial prothrombin time. Anemia or decreasing hemoglobin values may indicate internal hemorrhage, including possible intracranial hemorrhage (e.g., a large subdural hemorrhage). Platelet counts in the term newborn are usually in the same range as in older children, but the coagulation screening laboratory tests (and particularly the activated partial prothrombin time) need to be interpreted using age-adjusted norms, because the times are physiologically prolonged at birth.

A platelet count that is severely decreased as well as prolonged in duration in an otherwise healthy newborn strongly suggests alloimmune thrombocytopenia. Maternal platelet values should be reviewed; maternal thrombocytopenia may indicate maternal autoimmune disorders, such as lupus or idiopathic thrombocytopenic purpura, that can affect the newborn's platelet count as well. Prolonged prothrombin time suggests vitamin K deficiency or, rarely, factor VII deficiency. Prolonged activated partial prothrombin time suggests hemophilia A or B or, rarely, severe hemophilia C (factor XI deficiency). If any of the inherited factor deficiencies is suggested by family history or by prolonged activated partial prothrombin time, specific factor assays may be obtained. Factor XIII deficiency does not cause prolongation of prothrombin time or activated partial prothrombin time, so a clot stability test and factor XIII levels should be obtained if this disorder is suspected based on family history and clinical presentation. Factor assays in the newborn need to be interpreted using age-appropriate ranges, because some factors are physiologically decreased at birth [59].

Electroencephalography

Electroencephalography (EEG) should be performed as soon as it can be arranged. The diagnosis of seizures is clinical; however, if there is clinical uncertainty or if a nonconvulsive seizure is suspected, EEG is useful for documenting the epileptic focus and providing information regarding the functional integrity of the rest of the brain [60,61]. The EEG may reveal epileptiform activity, with or without background slowing. Background EEG patterns remain a powerful prognostic factor [62]. A normal age-appropriate background EEG pattern will attest to the focal nature of intracranial hemorrhage and will assure that the newborn's brain has not sustained a global insult. This finding will contribute to an evidence-based discussion with parents regarding prognosis. Continuous video-EEG monitoring, if needed, may help improve the medical management of newborns with intracranial hemorrhage [63]. Therefore, early detection of intracranial hemorrhage (with or without seizure activity) and timely management of the newborn remain pivotal in the practice of neonatal neurology.

Management

Management of a sick newborn in the neonatal intensive care unit setting begins with confirmation of the diagnosis of intracranial hemorrhage. Any treatable etiological factor (e.g., sepsis, dehydration, thrombocytopenia, vitamin K deficiency, or coagulopathy) should be identified and treated promptly.

Prevention

The single most important primary prevention is to gather all available data in order to determine that a vaginal delivery can be accomplished successfully with the obstetrics instrument chosen. Despite the limitations of the data reported by Towner et al. [6], it appears that attempts at vaginal delivery with the use of either forceps or a vacuum device, if successful, carry no procedure-specific risk of intracranial hemorrhage. When the chances of successful operative delivery are thought to be low, however, it should probably not be attempted, nor should repeated attempts at vaginal delivery be made if either vacuum extraction or forceps delivery has failed [6,30]. Medical interventions should be implemented on the very first clinical suspicion of intracranial hemorrhage.

The secondary prevention is to limit the extent of parenchymal injury to the brain due to neurosurgery or hematoma [64].

Treatment

A multidisciplinary team of physicians best serves the most immediate management of intracranial hemorrhage in newborns. In addition to neonatology, the team should involve neuroradiology, pediatric hematology, pediatric neurology, and pediatric neurosurgery, as well as an experienced social worker. Once a complicated prenatal or perinatal course is anticipated, the social worker should be involved in monitoring the expectant mother.

In the majority of newborns with intracranial hemorrhage, medical therapy is the primary mode of therapy. The immediate goal of medical therapy is to provide adequate ventilation, prevent metabolic acidosis, and to keep the newborn's vital organs well perfused, including the brain. Any needed treatment for clinical sepsis or neonatal seizures should preferably be instituted before diagnostic procedures. If seizures are present, the focus of treatment should be controlling seizure activity with the least dosage and number of anticonvulsants. Phenobarbital is the preferred drug in this age group, but decreased alertness may be a prominent symptom, which at times may hinder seizure control by limiting the desired upward titration of antiepileptic drug therapy.

Newborns with intracranial hemorrhage should be monitored closely for the development of delayed cerebral edema or syndrome of inappropriate antidiuretic hormone [65]. Use of cerebral function monitoring for intracranial

pressure [66] or intracerebral microdialysis to remove excess lactate or pyruvate should be carefully justified in selected newborns with intracranial hemorrhage [67].

Hematologic Management

Once intracranial hemorrhage is identified, it is important to monitor hemoglobin levels and to transfuse the newborn if necessary. If hemorrhage related to vitamin K-deficiency is suspected, the newborn should be given 1 mg of vitamin K intravenously. In newborns with intracranial hemorrhage and thrombocytopenia, it is important to promptly transfuse with platelets. The response to platelet transfusion may further clarify the diagnosis. In newborns without bleeding but with platelet counts of $<30{,}000/mm^3$, it is nonetheless prudent to transfuse with platelets to prevent intracranial hemorrhage [68]. If alloimmune thrombocytopenia is suspected because of a poor response to random donor platelet, washed maternal platelets should be given if possible. Intravenous immunoglobulin may also be given to the newborn, but the platelet response may take 24-72 hours [69]. Treatment of disseminated intravascular coagulation should be targeted at correcting any underlying etiologic conditions. Transfusion with fresh frozen plasma and platelets may be beneficial in actively bleeding sick newborn with disseminated intravascular coagulation.

If a coagulopathy is suspected but there is no specific diagnosis, transfusion with fresh-frozen plasma (after obtaining laboratory coagulation tests) is appropriate, to prevent further bleeding. Fresh-frozen plasma contains all blood clotting factors, but at variable concentrations. There are also case reports of treatment of neonatal life-threatening hemorrhage with recombinant activated factor VII; however, this remains a novel therapeutic approach, and one that needs further study [70]. Once a specific hematologic diagnosis is established, therapy with specific factor concentrates can be initiated. For expectant mothers with known hemophilia carrier status, the optimal mode of delivery remains controversial. It appears, however, that instrumental and spontaneous vaginal delivery increases the risk of hemorrhages (intra- and extracranial), compared with cesarean delivery [31].

Neurosurgical Considerations

Most symptomatic newborns with intracranial hemorrhage do not require neurosurgical intervention. In a retrospective study by Hanigan et al. [2], neurosurgical intervention was limited to 3% of the cases: one infant with massive intracranial hemorrhage and one child with posthemorrhagic hydrocephalus. Neurosurgical intervention could, however, be lifesaving in a situation in which there is a sudden clinical deterioration primarily due to a precipitous rise in intracranial pressure, and it should therefore be seriously considered. A neurosurgical procedure in a carefully selected case, performed by an experienced neurosurgical team, is considered safe.

In a single large referral-based retrospective study of neurosurgery, 8/11 patients (73%) patients underwent surgical hematoma evacuation [9]. There were no subsequent hemorrhages or deaths during a mean follow-up period of 4.5 years. The study concluded that radiographic evidence of mass effect or signs of elevated intracranial pressure may necessitate surgical hematoma evacuation [9]. Surgical decompression of posterior fossa subdural hemorrhage is indicated only in the presence of acute hydrocephalus or signs of brainstem compression [71]. Palliative surgery in the form of surgical placement of an external ventricular tube to relieve increasing intracranial pressure or to drain out hemorrhagic ventricular cerebrospinal fluid should be considered. Rarely, a permanent ventriculoperitoneal shunt is needed for posthemorrhagic hydrocephalus [2,21].

Surgery should be avoided if the intracranial hemorrhage is thought to be the result of venous or arterial infarction. Not performing surgery in such cases may limit surgery-related brain injury, particularly in the case of the neonatal brain [72].

Neurologic Outcomes

Parental concerns for future outcome are best addressed by clinical judgment inferred from medical or surgical treatments needed in the management of hemorrhage. Most of us who deal with intracranial hemorrhage in newborns are aware that the clinical outcome is usually surprisingly good with conservative medical treatment, despite extensive hemorrhage observed on the initial CT scan. Intracranial hemorrhage in term newborns, however, has the potential for serious neurologic outcome, including death or lifelong disability.

A summary of five selected studies of term newborns with intracranial hemorrhage and the neurologic outcomes is given in Table 3 [2,9,12,73,74].

There is no single predictor of intracranial hemorrhage outcome in term newborns. However, the extent (compartmental, lobar, or both), the severity, and the etiology of intracranial hemorrhage may influence the prognosis. In addition, low gestational age (i.e., prematurity), early occurrence of recurrent seizures or status epilepticus, and the need for multiple anticonvulsants to control seizures were associated with poor outcome [75,76]. A normal neonatal period and neurologic examination and a normal or mildly abnormal neonatal EEG predict a favorable outcome, particularly if neonatal neuroimaging is normal. Abnormal examination lacks predictive specificity [62].

The majority of newborns with spontaneous subarachnoid hemorrhage will make a complete recovery. Disability is more likely to occur in a newborn with frontal lobe hemorrhage or when multiple intracranial compartments are involved. Although intraventricular hemorrhage without severe perinatal asphyxia is rare in term infants, its occurrence suggests poor prognosis. In a study by d'Allest et al. [77], five term neonates were admitted to the neonatal intensive care unit for new onset of seizures; three of whom

Table 3. Summary of five selected studies of term newborns with intracranial hemorrhage (ICH) and their neurologic outcomes

Reference	Sample size	Study characteristics	Follow-up duration, mean (range)	Predictor or neurologic outcome	
				Favorable	Poor
Hanigan et al., 1995 [2]	$n = 32$	Symptomatic ICH admitted to a regional NICU	3.4 years (1-6.5)	Newborn with uncomplicated ICH	2 (6%) died, HII had high risk of developmental delay
Sandberg et al., 2001 [9]	$n = 11$	8 neonates (73%) had surgery, IPH from surgical database	4.5 years (1-16)	4 (36%) were normal; no death reported	4 (36%) with motor deficits, 1 (9%) with cognitive delay
Nanba et al., 1984 [12]	$n = 13$	CT correlation of idiopathic ICH and location outcome	Not available	None suggested	SDH with cerebral low density on CT
Guardia et al., 1986 [73]	$n = 62$	Diagnostic and prognostic value of CT in HII	Not available	SAH or cerebral edema	Less favorable when cranial CT scan shows signs of necrosis
Jhawar et al., 2005 [74]	$n = 66$	To define the physical and cognitive deficits	3 years (1.0-10.9)	Most with no physical and cognitive deficits	7 (11%) died, most (19%) with SAH during the first week

Abbreviations:
CT = Computed tomography
HII = Hypoxic-ischemic injury
IPH = Intraparenchymal hemorrhage
NICU = Neonatal intensive care unit
SAH = Subarachnoid hemorrhage
SDH = Subdural hemorrhage

developed status epilepticus. Cranial CT scans showed unilateral or bilateral intraventricular hemorrhage. Of the five infants, four died during the neonatal period. Low birth weight and status epilepticus were independent predictors of poor outcome [77].

Intracranial hemorrhage remains a major cause of morbidity and mortality in hemophiliac newborns. Psychomotor retardation and cerebral palsy were reported in the majority of hemophiliac patients with intracranial hemorrhage (30 cases, including 11 newborns) [78].

Medicolegal Implication

Term newborns with intracranial hemorrhage at birth should be considered a potential legal liability in the practice of neonatal neurology. Delayed diagnosis, lack of verifiable etiology for hemorrhage, and clinical limitations in assessing the sick newborn are a few of the difficulties that become the source of medicolegal liability. This is further compounded by the difficulty in separating antenatal events from those occurring during labor, delivery, and resuscitation. Stoddard et al. [79] discussed the medicolegal implications in a case of antenatally diagnosed intracranial lesions, including intraparenchymal hemorrhage, in an otherwise physically normal infant.

Fortunately, the steps needed to minimize legal risks and complications are the same as those for minimizing unfavorable neurologic outcomes. Medicolegal risks can be decreased by taking precautions such as (1) earliest possible documentation of high-risk pregnancy, difficult labor delivery, or prenatal diagnosis of intracranial abnormalities, to avoid a bitter accusation of birth-injuries such as intracranial hemorrhage; (2) an astute search for any treatable clinical condition; (3) early involvement of a social worker and counseling to reduce parental anxiety in a timely manner; (4) providing evidence-based clinical information to the parents and applying clinical judgment inferred from specific medical or surgical treatments needed in the management of the newborn with intracranial hemorrhage; and, most importantly, (5) avoiding therapies not shown to improve medical care and choosing therapies that are well linked to evidence. Clinical guidelines always need to be interpreted sensibly and applied with discretion [80].

Directions for Future Research

Too little is known about developmental changes in cerebrovascular physiology in infants with intracranial hemorrhage. Studies examining age- and sex-related differences in cerebral blood flow, cerebral autoregulation, and cerebral metabolic rate in healthy neonates are needed, to provide reference data for better understanding. Prospective studies should investigate the association between management in labor or delivery and the risk of intracranial hemorrhage, and should address the question of how intracranial hemorrhage in newborns can be prevented. There is a high prevalence of children with developmental and speech delays of unknown etiology. Some of these children may have asymptomatic intracranial hemorrhage. Studies using susceptibility-weighted MRI should explore the association

between term newborns with intracranial hemorrhage and developmental delay of unknown etiology.

Summary

Intracranial hemorrhage is a heterogeneous disorder with variable risk factors, etiologies, and neurologic and medicolegal outcomes. Fortunately, symptomatic intracranial hemorrhage in term newborns is rare, but its occurrence presents numerous challenges. In term newborns, subdural hemorrhage appears to be more frequent than subarachnoid hemorrhage, intraventricular hemorrhage, intraparenchymal hemorrhage, and epidural hemorrhage. Clinical presentation of intracranial hemorrhage is nonspecific, but usually limited to neurologic manifestations. Prompt detection of intracranial hemorrhage is facilitated by selection of appropriate neuroimaging, a quick identification of the treatable etiologies (e.g., sepsis or thrombocytopenia), and management directed to limit secondary brain injury due to intracranial hemorrhage.

The treatment of intracranial hemorrhage is primarily medical and conservative. Occasionally, neurosurgical intervention is needed, and may prove lifesaving. When attempting to predict outcome, one must realize that even severe intracranial hemorrhage may have a relatively good outcome. A poor outcome, however, is suggested by intraventricular hemorrhage, status epilepticus, difficulty to control seizure, or recognition of a congenital coagulopathy.

Like other birth-related neurologic injuries, intracranial hemorrhage has potential legal implications. Providing the evidence-based optimal medical or surgical therapies and early parental counseling along with documentation of every intervention can ensure the best possible neurologic or legal outcomes in term newborns with intracranial hemorrhage in the first week.

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References

[1] **Osborn** DA, Evans N, Kluckow M. Hemodynamic and antecedent risk factors of early and late periventricular/intraventricular hemorrhage in premature infants. Pediatrics 2003;112:33-9.

[2] **Hanigan** WC, Powell FC, Miller TC, Wright RM. Symptomatic intracranial hemorrhage in full-term infants. Childs Nerv Syst 1995;11: 698-707.

[3] **Højberg** AS, Ebbesen F, Lund EB, Agerholm H. Neurodevelopmental outcome in full-term infants with symptomatic intracranial haemorrhage of unknown aetiology. Dan Med Bull 1997;44:439-42.

[4] **Whitby** EH, Griffiths PD, Rutter S, et al. Frequency and natural history of subdural haemorrhages in babies and relation to obstetric factors. Lancet 2004;363:846-51.

[5] **Looney** CB, Smith JK, Merck LH, et al. Intracranial hemorrhage in asymptomatic neonates: prevalence on MR images and relationship to obstetric and neonatal risk factors. Radiology 2007;242:535-41.

[6] **Towner** D, Castro MA, Eby-Wilkens E, Gilbert WM. Effect of mode of delivery in nulliparous women on neonatal intracranial injury. N Engl J Med 1999;341:1709-14.

[7] **Fenichel** GM, Webster DL, Wong WK. Intracranial hemorrhage in the term newborn. Arch Neurol 1984;41:30-4.

[8] **Kotagal** S, Toce SS, Kotagal P, Archer CR. Symmetric bithalamic and striatal hemorrhage following perinatal hypoxia in a term infant. J Comput Assist Tomogr 1983;7:353-5.

[9] **Sandberg** DI, Lamberti-Pasculli M, Drake JM, Humphreys RP, Rutka JT. Spontaneous intraparenchymal hemorrhage in full-term neonates. Neurosurgery 2001;48:1042-8.

[10] **Hayden** CK Jr, Shattuck KE, Richardson CJ, Ahrendt DK, House R, Swischuk LE. Subependymal hemorrhage in full-term neonates. Pediatrics 1985;75:714-8.

[11] **Trounce** JQ, Rutter N, Levene MI. Periventricular leucomalacia and intraventricular haemorrhage in the preterm neonate. Arch Dis Child 1986;61:1196-202.

[12] **Nanba** E, Eda I, Takashima S, Ohta S, Ohtani K, Takeshita K. Intracranial hemorrhage in the full-term neonate and young infant: correlation of the location and outcome. Brain Dev 1984;6:435-43.

[13] **Mitchell** W, O'Tuama L. Cerebral intraventricular hemorrhages in infants: a widening age spectrum. Pediatrics 1980;65:35-9.

[14] **Volpe** JJ. Intracranial hemorrhage: subdural, primary subarachnoid, intracerebellar, intraventricular (term infant), and miscellaneous. In: Neurology of the newborn. 4th ed. Philadelphia: WB Saunders, 2001:397-423.

[15] **Wu** YW, Hamrick SE, Miller SP, et al. Intraventricular hemorrhage in term neonates caused by sinovenous thrombosis. Ann Neurol 2003;54:123-6.

[16] **Menkes** JH, Sarnat HB. Perinatal Asphyxia and Trauma: Intracranial hemorrhage. In: Child Neurology. 7th edition. Philadelphia: LWW, 2006:387-91.

[17] **Doe** FD, Shuangshoti S, Netsky MG. Cryptic hemangioma of the choroid plexus: a cause of intraventricular hemorrhage. Neurology 1972; 22:1232-9.

[18] **Jhawar** BS, Ranger A, Steven D, Del Maestro RF. Risk factors for intracranial hemorrhage among full-term infants: a case-control study. Neurosurgery 2003;52:581-90.

[19] **Adeoye** O, Broderick JP. Intracerebral hemorrhage: recent developments and future directions. Pract Neurol 2008;4:33-6.

[20] **Mercuri** E, Dubowitz L, Brown SP, Cowan F. Incidence of cranial ultrasound abnormalities in apparently well neonates on a postnatal ward: correlation with antenatal and perinatal factors and neurological status. Arch Dis Child Fetal Neonatal Ed 1998;79:F185-9.

[21] **Sims** ME, Halterman G, Jasani N, Vachon L, Wu PY. Indications for routine cranial ultrasound scanning in the nursery. J Clin Ultrasound 1986;14:443-7.

[22] **Blankenberg** FG, Norbash AM, Lane B, Stevenson DK, Bracci PM, Enzmann DR. Neonatal intracranial ischemia and hemorrhage: diagnosis with US, CT, and MR imaging. Radiology 1996;199:253-9.

[23] **Huang** CC, Shen EY. Tentorial subdural hemorrhage in term newborns: ultrasonographic diagnosis and clinical correlates. Pediatr Neurol 1991;7:171-7.

[24] **Golomb** MR, Dick PT, MacGregor DL, Armstrong DC, DeVeber GA. Cranial ultrasonography has a low sensitivity for detecting arterial ischemic stroke in term neonates. J Child Neurol 2003;18:98-103.

[25] **Avrahami** E, Amzel S, Katz R, Frishman E, Osviatzov I. CT demonstration of intracranial bleeding in term newborns with mild clinical symptoms. Clin Radiol 1996;51:31-4.

[26] **Siegel** MJ, Patel J, Gado MH, Shackelford GD. Cranial computed tomography and real-time sonography in full-term neonates and infants. Radiology 1983;149:111-6.

[27] **Blankenberg** FG, Loh NN, Bracci P, et al. Sonography, CT, and MRI imaging: A prospective comparison of neonates with suspected intracranial ischemia and hemorrhage. AJNR Am J Neuroradiol 2000; 21:213-8.

[28] **Haacke** EM. Images of the month. Clin Neurol News 2008;4:20.

[29] **Bergman** I, Bauer RE, Barmada MA, et al. Intracerebral hemorrhage in the full-term neonatal infant. Pediatrics 1985;75:488-96.

[30] **Benedetti** TJ. Birth injury and method of delivery. N Engl J Med 1999;341:1758-9.

[31] **MacLean** PE, Fijnvandraat K, Beijlevelt M, Peters M. The impact of unaware carriership on the clinical presentation of haemophilia. Haemophilia 2004;10:560-4.

[32] **Fenichel** GM. Neonatal hypoxic-ischemic and hemorrhagic cerebral injury. In: Neonatal neurology. 4th ed. Philadelphia: Churchill Livingstone Elsevier, 2007:69-87.

[33] **Takahashi** Y, Ukita M, Nakada E. Intrapartum FHR monitoring and neonatal CT brain scan [In Japanese]. Nippon Sanka Fujinka Gakkai Zasshi 1982;34:2133-42.

[34] **Sola** MC. Evaluation and treatment of severe and prolonged thrombocytopenia in neonates. Clin Perinatol 2004;31:1-14.

[35] **Mueller-Eckhardt** C, Kiefel V, Grubert A, et al. 348 cases of suspected neonatal alloimmune thrombocytopenia. Lancet 1989;1:363-6.

[36] **Bussel** JB. Primiani A fetal and neonatal alloimmune thrombocytopenia: progress and ongoing debates. Blood Rev 2008;22:33-52.

[37] **Hubbard** D, Tobias JD. Intracerebral hemorrhage due to hemorrhagic disease of the newborn and failure to administer vitamin K at birth. South Med J 2006;99:1216-20.

[38] **Cornelissen** M, Steegers-Theunissen R, Kollée L, Eskes T, Motohara K, Monnens L. Supplementation of vitamin K in pregnant women receiving anticonvulsant therapy prevents neonatal vitamin K deficiency. Am J Obstet Gynecol 1993;168:884-8.

[39] **Sasidharan** CK, Kutty PM, Ajithkumar, Sajith N. Fetal intracranial hemorrhage due to antenatal low dose aspirin intake. Indian J Pediatr 2001;68:1071-2.

[40] **Karlowicz** MG, White LE. Severe intracranial hemorrhage in a term neonate associated with maternal acetylsalicylic acid ingestion. Clin Pediatr (Phila) 1993;32:740-3.

[41] **Kulkarni** R, Lusher JM. Intracranial and extracranial hemorrhages in newborns with hemophilia: a review of the literature. J Pediatr Hematol Oncol 1999;21:289-95.

[42] **Tarantino** MD, Gupta SL, Brusky RM. The incidence and outcome of intracranial haemorrhage in newborns with haemophilia: analysis of the Nationwide Inpatient Sample database. Haemophilia 2007;13:380-2.

[43] **Smith** AR, Leonard N, Kurth MH. Intracranial hemorrhage in newborns with hemophilia: the role of screening radiologic studies in the first 7 days of life. J Pediatr Hematol Oncol 2008;30:81-4.

[44] **Chalmers** EA. Neonatal coagulation problems. Arch Dis Child Fetal Neonatal 2004;89:F475-8.

[45] **Fenichel** GM. Increased intracranial pressure. In: Clinical pediatric neurology: a signs and symptoms approach. 5th ed. Philadelphia: Elsevier/Saunders, 2005:104-5.

[46] **Spires** MC, Gordon EF, Choudhuri M, Maldonado E, Chan R. Intracranial hemorrhage in a neonate following prenatal cocaine exposure. Pediatr Neurol 1989;5:324-6.

[47] **Primiani** A, Bussel JB. Fetal and neonatal alloimmune thrombocytopenia: progress and ongoing debates. Blood Rev 2008;22:33-52.

[48] **Blanc** JF, Langue J, Bochu M, Dutruge J, Salle B. Intracranial hemorrhage in infants born at term [In French]. Arch Fr Pediatr 1982;39:251-3.

[49] **Fenichel** GM. Paroxysmal disorders, Clinical pediatric neurology: a signs and symptoms approach. 5th ed. Philadelphia: Elsevier/Saunders, 2005. 1-5.

[50] **Sirsi** D, Nadiminti L, Packard MA, Engel M, Solomon GE. Apneic seizures: a sign of temporal lobe hemorrhage in full-term neonates. Pediatr Neurol 2007;37:366-70.

[51] **Tramonte** JJ, Goodkin HP. Temporal lobe hemorrhage in the full-term neonate presenting as apneic seizures. J Perinatol 2004;24:726-9.

[52] **Sutor** AH, Dagres N, Niederhoff H. Late form of vitamin K deficiency bleeding in Germany. Klin Padiatr 1995;207:89-97.

[53] **Greenbaum** LA. Vitamin K deficiency. In: Kliegman RM, Behrman RE, Jensen HB, Stanton BF, editors. Nelson textbook of pediatrics. 18th edition. Philadelphia: W.B. Saunders, 2007:264-5.

[54] **Holden** KR, Titus MO, Van Tassel P. Cranial magnetic resonance imaging examination of normal term neonates: a pilot study. J Child Neurol 1999;14:708-10.

[55] **Vossough** A, Zimmerman RA, Bilaniuk LT, Schwartz EM. Imaging findings of neonatal herpes simplex virus type 2 encephalitis. Neuroradiology 2008;50:355-66.

[56] **Bishop** FS, Liu JK, McCall TD, Brockmeyer DL. Glutaric aciduria type 1 presenting as bilateral subdural hematomas mimicking nonaccidental trauma: case report and review of the literature. J Neurosurg 2007;106:222-6.

[57] **Nassogne** MC, Sharrard M, Hertz-Pannier L, et al. Massive subdural haematomas in Menkes disease mimicking shaken baby syndrome. Childs Nerv Syst 2002;18:729-31.

[58] **Hill** A. Discussion: Risk factors for intracranial hemorrhage among full-term infants: a case-control study. Neurosurgery 2003;52:589-90.

[59] **Ghevaert** C, Campbell K, Walton J, et al. Management and outcome of 200 cases of fetomaternal alloimmune thrombocytopenia. Transfusion 2007;47:901-10.

[60] **Maganti** R, Gerber P, Drees C, Chung S. Nonconvulsive status epilepticus. Epilepsy Behav 2008;12:572-86.

[61] **Tay** SK, Hirsch LJ, Leary L, Jette N, Wittman J, Akman CI. Nonconvulsive status epilepticus in children: clinical and EEG characteristics. Epilepsia 2006;47:1504-9.

[62] **Tekgul** H, Gauvreau K, Soul J, et al. The current etiologic profile and neurodevelopmental outcome of seizures in term newborn infants. Pediatrics 2006;117:1270-80.

[63] **Connell** J, Oozeer R, de Vries L, Dubowitz LM, Dubowitz V. Continuous EEG monitoring of neonatal seizures: diagnostic and prognostic considerations. Arch Dis Child 1989;64:452-8.

[64] **Nilsson** OG, Polito A, Säveland H, Ungerstedt U, Nordström CH. Are primary supratentorial intracerebral hemorrhages surrounded by a biochemical penumbra? A microdialysis study. Neurosurgery 2006;59:521-8.

[65] **Bussmann** C, Bast T, Rating D. Hyponatraemia in children with acute CNS disease: SIADH or cerebral salt wasting? Childs Nerv Syst 2001;17:58-62.

[66] **Klebermass** K, Kuhle S, Kohlhauser-Vollmuth C, Pollak A, Weninger M. Evaluation of the Cerebral Function Monitor as a tool for neurophysiological surveillance in neonatal intensive care patients. Childs Nerv Syst 2001;17:544-50.

[67] **Hillman** J, Milos P, Yu ZQ, Sjögren F, Anderson C, Mellergård P. Intracerebral microdialysis in neurosurgical intensive care patients utilising catheters with different molecular cut-off (20 and 100 kD). Acta Neurochir (Wien) 2006;148:319-24.

[68] **Murray** NA. Evaluation and treatment of thrombocytopenia in the neonatal intensive care unit. Actae Paediatr Suppl 2002;91:74-81.

[69] **Stockman** JA. Diseases of the blood. In: Behrman RE, Kliegman RM, Vaughan VC 3rd, editors. Nelson textbook of pediatrics. 14th ed. Philadelphia: WB Saunders, 1992:1229-30.

[70] **Veldman** A, Fischer D, Voigt B, et al. Life-threatening hemorrhage in neonates: management with recombinant activated factor VII. Intensive Care Med 2002;28:1635-7.

[71] **Margalith** D, Mogilner BM, Gadoth N. Posterior fossa subdural hematoma in a normally delivered full-term newborn. Surg Neurol 1980;14:405-9.

[72] **Derek** AB. Discussion: Spontaneous intraparenchymal hemorrhage in full-term neonates. Neurosurgery 2001;48:1048-9.

[73] **Guardia** E, Demestre X, Raspall F, et al. Perinatal hypoxic-ischaemic syndrome: diagnostic and prognostic value of computed tomography. Acta Radiol Suppl 1986;369:667-70.

[74] **Jhawar** BS, Ranger A, Steven DA, Del Maestro RF. A follow-up study of infants with intracranial hemorrhage at full-term. Can J Neurol Sci 2005;32:332-9.

[75] **Painter** MJ, Bergman I, Crumrine P. Neonatal seizures. Pediatr Clin North Am 1986;33:91-109.

[76] **Pisani** F, Cerminara C, Fusco C, Sisti L. Neonatal status epilepticus vs recurrent neonatal seizures: clinical findings and outcome. Neurology 2007;69:2177-85.

[77] **d'Allest** AM, Navelet Y, Nedelcoux H, Dehan M, Huault G. Intraventricular hemorrhage and parenchymatous ischemia in the newborn at term: report of five cases [In French]. Neurophysiol Clin 1997;27:129-38.

[78] **Klinge** J, Auberger K, Auerswald G, Brackmann HH, Mauz-Körholz C, Kreuz W. Prevalence and outcome of intracranial hemorrhage in hemophiliacs: a survey of the Paediatric Group of the German Society of Thrombosis and Haemostasis (GTH). Eur J Paediatr 1999;158:1162-5.

[79] **Stoddard** RA, Clark SL, Minton SD. In utero ischemic injury: sonographic diagnosis and medicolegal implications. Am J Obstet Gynecol 1988;159:23-5.

[80] **Hurwitz** B. Legal and political considerations of clinical practice guidelines. BMJ 1999;318:661-4.