Intraventricular Hemorrhage in Premature Newborns: Causes and Treatment

See online here

Intraventricular hemorrhage within the subependymal germinal matrix is a disease that is significantly more common in premature infants, especially those born before the age of 32 weeks of gestation. Infants with intraventricular hemorrhage are usually asymptomatic but might develop non-specific symptoms and signs of anemia. Hypotonia, coma, seizures, and death can occur in more severe cases of intraventricular hemorrhage. Cranial ultrasonography is the diagnostic modality of choice for establishing the diagnosis and for follow-up. Treatment mainly consists of cardiovascular and respiratory support, surgical intervention for posthemorrhagic hydrocephalus and the use of acetazolamide to treat progressive hydrocephalus.

Overview
Pre-term delivery is associated with several complications that can be life-threatening or cause long-term disability and sequelae in the patient. Periventricular and intraventricular hemorrhage is a commonly acquired lesion of the central nervous system that specifically affects premature infants.

The condition is characterized by hemorrhage into the intraventricular space and the periventricular white matter. The involvement of the periventricular white matter is associated with long-term disability due to the proximity of the lesion to the motor tracts (see image).

**Epidemiology**
The most important risk factors for intraventricular hemorrhage in newborns are very low birth weight and delivery at a gestational age of less than 35 weeks. The estimated incidence can range from 20%-50%.

Intraventricular hemorrhage in premature infants is associated with significant mortality, with an estimated rate that can be as high as 50%. The most important risk factor for increased mortality is the extent of hemorrhage. Patients with low-grade hemorrhage have the lowest mortality rate, at approximately 5%.

Differences in the incidence of intraventricular hemorrhage between males and females have not been observed; however, recent studies of indomethacin prophylaxis for intraventricular hemorrhage in premature babies have shown improved efficacy in male infants.

Intraventricular hemorrhage is more common in neonates born before the 32nd week of gestation (see image). Most cases occur within the first 72 hours of life, but some cases can happen as late as 7 days post-delivery; therefore, screening programs for intraventricular hemorrhage in premature infants have been recommended to continue until the age of 1 week.

Risk Factors

- Extreme prematurity
- Hypotension, hypothermia, metabolic acidosis, and thrombocytopenia

Pathophysiology

Intraventricular hemorrhage originates from a capillary network that supplies the subependymal germinal matrix.

The subependymal germinal matrix is responsible for neuronal proliferation, neuroblast division, and neuronal cell migration into the cerebral parenchyma within the developing brain of the fetus. Neuronal proliferation usually ends at 20 weeks of gestation; glial cell proliferation ends at 32 weeks.

After 32 weeks, the subependymal germinal matrix has almost completely regressed, which is why intraventricular hemorrhage is much more common in premature newborns born before 32 weeks of gestation.

The anatomical classification of the location and extent of the intraventricular hemorrhage are important for prognosis. Grade I periventricular or intraventricular hemorrhage is defined as subependymal and germinal matrix hemorrhage. Grade II is the same as grade I but with the extension of hemorrhage into the lateral ventricles without ventricular enlargement.

Grade III hemorrhage is associated with ventricular enlargement. Grade IV hemorrhage involves the cerebral parenchyma and is not confined to the subependymal and germinal matrix.

The most important pathogenic mechanism of periventricular hemorrhage and
intraventricular hemorrhage in premature newborns is the **loss of autoregulation**. Premature infants with **pulmonary disease** are more prone to **impaired cerebral blood flow and pressure autoregulation**, which explains the increased incidence of intraventricular hemorrhage in this subgroup of patients.

Additionally, **birth, tracheal suctioning**, and the use of **intravascular fluids** for resuscitation are also known to alter cerebral blood flow and intracranial pressure in premature infants who have poorly developed cerebral blood flow autoregulation.

![Image: Cortical infarction with low hemorrhage. By: Hellerhoff. License: CC BY-SA 3.0](https://example.com/image)

This mechanism of impaired autoregulation and increased cerebral blood perfusion in the fragile capillaries of the germinal matrix is thought to be responsible for grades I, II, and III hemorrhages. Grade IV hemorrhage is caused by **cerebral infarction** due to increased venous pressure.

The most likely cause of **increased cerebral venous pressure** is the ongoing hemorrhage from the germinal matrix into the lateral ventricles and the enlargement of the ventricles, which can cause venous engorgement (see image). The term **periventricular hemorrhagic infarction** can be used interchangeably with grade IV hemorrhage.

Due to the **destruction of the motor tracts** by the hemorrhagic incident, infants who survive usually have **cerebral palsy**. The involvement of the cortex can result in **seizures** and/or **cognitive impairments**.

**Post-hemorrhagic hydrocephalus** usually occurs in infants who survive and is caused by decreased absorption of the cerebrospinal fluid and obstruction of the cerebrospinal fluid circulation.

### Clinical Presentation

Premature babies usually present as **ill** and therefore intraventricular hemorrhage is rarely associated with any significant changes in the clinical picture of the infant.

Due to the relatively large ratio of the head to the body of the infant and the ability of the
head to expand, infants with intraventricular hemorrhage may develop symptoms and signs of anemia. Pallor, increased capillary refill time, or shock can be observed.

Infants with severe intraventricular hemorrhage may also develop metabolic or respiratory acidosis, apnea, hypotonia, and stupor, and may go into a coma. The fontanels are usually full and firm to palpation due to the increased intracranial pressure. Seizures occur in a minority of patients. Children with grades III and IV hemorrhage may die, and therefore the diagnosis can only be confirmed on autopsy.

Diagnostic Workup

Laboratory investigations are rarely useful in infants with intraventricular hemorrhage unless the hemorrhage is severe enough to cause metabolic acidosis or respiratory acidosis. Lymphocytosis and lymphopenia have been observed in infants with intraventricular hemorrhage.

Imaging studies are the mainstay diagnostic tool for the screening, confirmation, and follow-up of intraventricular hemorrhage. Premature newborns, especially if born at less than 30 weeks of gestation, should undergo cranial ultrasonography at the age of 1 week post-natally. Cranial ultrasonography should be repeated at 36–40 weeks’ postmenstrual age in all premature babies.

If at any point the diagnosis of intraventricular hemorrhage is confirmed by cranial ultrasonography, follow-up serial ultrasonographies are indicated and should be repeated on a weekly basis. They are used to detect the progression of hemorrhage and the development of post-hemorrhagic hydrocephalus (see image).

Computed tomography scanning and magnetic resonance imaging have a limited role in the diagnosis of intraventricular hemorrhage because of the excellent sensitivity and specificity of cranial ultrasonography.

Treatment

Infants with intraventricular hemorrhage may have hemorrhagic shock, metabolic disturbances, and/or respiratory distress; therefore, cardiovascular and respiratory support are indicated.

Anemia and metabolic acidosis can occur in infants with severe intraventricular hemorrhage. In these patients, acute correction of anemia with blood transfusions may be indicated. Serial lumbar puncture has been shown to be ineffective in the prevention of progressive hydrocephalus.
Infants who develop late or progressive **hydrocephalus** should receive **acetazolamide** to decrease the production of cerebrospinal fluid. **Post-hemorrhagic hydrocephalus** may require a **ventriculoperitoneal or ventriculostribaleal shunt placement**.

**Indomethacin prophylaxis** has been shown to improve the cognitive profile of infants who develop intraventricular hemorrhage, especially males, but not motor function outcome. This effect was preserved and still able to be observed until the children were school-aged.

**References**


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