

Severe neonatal hypoglycemia in the newborn despite prenatal diagnosed cerebral midline malformations – A review of three cases

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Background:

- Brain abnormalities like cerebral midline malformations (CMM) can be accompanied by endocrine insufficiencies due to hypopituitarism, which can lead to severe neonatal hypoglycemia
- Symptomatic neonatal hypoglycemia can cause irreparable fatal brain injury resulting in hypoglycemic encephalopathy.
- Usually CMM can be detected by fetal ultrasound or fetal MRI scan
- Postnatal glucose monitoring is usually performed only within the first hours after birth

Case report:

- 3 cases of term eutrophic newborns, which all
- ... were born vaginally and immediately breastfed after normal postnatal adaption
 - ... were diagnosed suffering from a CMM prenatally
 - ... were scanned postnatally for hypoglycemia
 - ... presented with symptomatic hypoglycemia
 - ... were now suffering from a developmental delay (ranging from mild to severe), which could be associated with the undergone severe hypoglycemia

(See Fig. A / Table A)

Discussion:

- Target blood glucose levels:**
- Following the guidelines of the American Academy of Pediatrics (AAP) and the Pediatric Endocrine Society (PES) the threshold for neonatal hypoglycemia in symptomatic patients are :
 - 2.8 mmol/L (50 mg/dL) for patients aged < 48 hours
 - 3.3 mmol/L (60 mg/dL) for patients aged > 48 hours
 - as older a newborn, as lower is the neurological tolerance for hypoglycemia
 - In patients with confirmed or suggested genetical / cerebral disorders the goal is to maintain plasma glucose level > 3.9 mmol/L, because the risk of harm due to lowered hypoglycemia is significant

(Avatapalle HB et al. Abnormal Neurodevelopmental Outcomes are Common in Children with transient Congenital Hyperinsulinism Front Endocrinol (Lausanne)) 2013;4:60)

Definition and timing of evaluation in persistent / late onset hypoglycemia :

- The three cases show, that in particular disorders – like CMM - a severe hypoglycemia after a long period of euglycemia can occur
- Facing the fact, that every symptomatic hypoglycemia can result in brain injury, a prolonged monitoring of both – glucose concentration and clinical condition should be performed in patients of CMM.
- All of these patients were suffering from an endocrinological disorder → explicit diagnostics for neonatal endocrinopathies should be performed – even if the glucose monitoring of the patients remains normal.

Conclusion

Prenatal diagnosis of CMM should urge caring physicians to plan delivery in centres with paediatric endocrine experience. Neonatal glucose monitoring should be performed not only within the first hours after birth, but over a longer period in these particular cases. The threshold of cerebral damage due to hypoglycemia alters with age in the neonatal period. The threshold of patients with known CMM should be adapted and therapeutical intervention should be discussed early. The cases show, that the symptoms of the hypoglycemia are the same in these patients even after a longer time lag after birth. Endocrine assessment is required within the first days in order to test for congenital partial or total hypopituitarism. Close collaboration between gynecologists, neonatologists and endocrinologists may prevent bad neurological outcome.

Table A: Overview over the findings, symptoma and follow – up of the three reported cases with severe hypoglycemia

	Case I	Case II	Case III
Prenatal Ultrasound / MRI:	Septo-optic dysplasia	Agenesis of the corpus callosum	Agenesis of the septum pellucidum
Lowest measured blood glucose level (mmol/L) (NR: 3.5 – 5.5)	0.6 (after 8 hrs)	1.4 (after 32 hrs.)	1.6 (after 14 hrs.)
Clinical findings in hypoglycemia	Shivering / Seizures	Seizure	Tachycardia / Shivering
Clinical course	Multicystic encephalopathy, seizures, short stature, severe developmental delay	Microdeletion syndrome (46, XY, del(18)(21.2); Cryptorchidism, short stature, Developmental delay	Short stature
Endocrine failure	Panhypopituitarism	Panhypopituitarism	Isolated GH deficiency

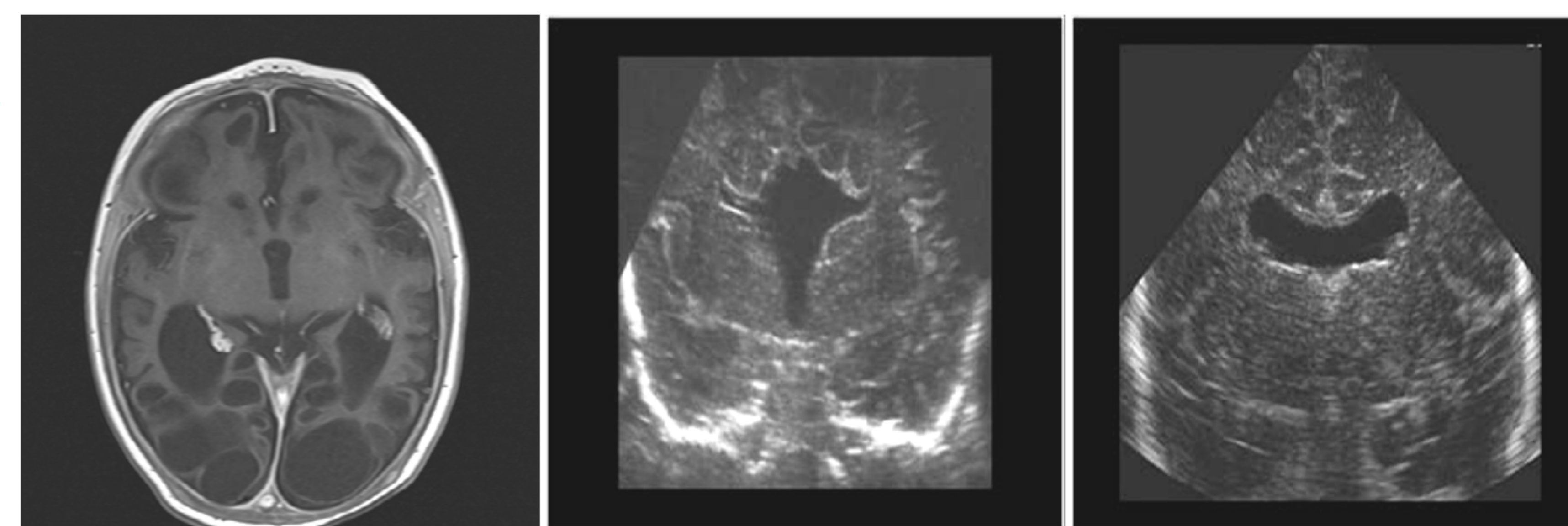


Fig. A: I.) MRI scan of case I, revealing the multicystic encephalopathy
 II.) Ultrasound scan of case II, showing the agenesis of the corpus callosum
 III.) Ultrasound image of case III, picturing the absence of the septum pellucidum