Unilateral cortical necrosis following status epilepticus with hypoglycemia

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Abstract

Isolated status epilepticus or severe hypoglycemia rarely causes irreversible focal neurologic deficits in children. We describe three children who presented with status epilepticus and prolonged hypoglycemia resulting in hemiplegia due to unilateral hemispheric damage. The non-vascular cortical topography of the lesions is consistent with selective neuronal necrosis, confirmed by histopathology in one patient. This suggests increased neuronal vulnerability to necrosis secondary to energy failure resulting from combination of hypoglycemia and status epilepticus.

Keywords: Cortical necrosis; Hypoglycemia; Seizures; Status epilepticus

1. Introduction

Hypoglycemia, even when severe and leading to coma, does not usually result in irreversible focal neurologic sequelae [1–3]. Likewise, status epilepticus (SE) rarely leads to permanent focal neurologic deficits in children [4,5]. However, certain clinical situations are associated with an increased risk of irreversible cerebral damage following SE. For instance, children younger than 4 years may experience prolonged clonic seizures with unilateral predominance in the course of a febrile illness, followed by long-lasting hemiplegia and partial epilepsy, referred to as the hemiconvulsion-hemiplegia-epilepsy or HHE syndrome [6]. Increased cerebral metabolism associated with pyrexia [7] could cause an imbalance between energy demand and supply and potentially account for the neurologic sequelae. Similar effects might be expected from energy depletion. We describe three children with unihemispheric damage following SE in combination with hypoglycemia.

2. Case reports

2.1. Patient 1

An 8-year-old girl was admitted in coma, having been found unconscious 1 h earlier by her grandmother. She was born at term following normal pregnancy. Past medical history was unremarkable. The mother had type 1 diabetes mellitus and untreated depression. During ambulance transfer the patient had a brief right-sided seizure. On admission she was unresponsive with a Glasgow coma score of 7/15. She had prolonged right-sided clonic seizures with secondary generalization. Postictally she showed decerebrate posturing. Hemogram, electrolytes, liver enzymes and arterial blood gases were normal. Venous blood sugar was low at 10 mg/dl (0.5 mmol/l). There was no clinical or biological evidence of infection. Hypoglycemia was treated with an intravenous bolus of 40 ml of a 10% glucose solution followed by an equivalent infusion over 30 min. Seizure activity lasted 3 h without recovery of consciousness in spite of treatment, which consisted of intravenous diazepam (two doses at 0.5 mg/kg) and phenobarbital (20 mg/kg) and phenytoin (20 mg/kg). Blood sugar stabilization proved difficult, necessitating subcutaneous glucagon injection (1 mg). Steady normogly-
cemia was achieved about 10 h after admission. Intermittent seizure activity refractory to standard therapy led to artificial ventilation. Interictal electroencephalogram (EEG) showed diffuse high amplitude delta activity over the left side. Focal right-sided seizures persisted during 72 h then stopped. The patient’s mother subsequently admitted to having injected her daughter subcutaneously with 40 IU of rapid-acting insulin (Actrapid, Novo Nordisk) six times during the preceding 24 h. Administration of near-lethal doses of insulin was in the context of ‘Munchausen by proxy’ type of child abuse, the patient not being diabetic.

Cerebral computed tomography (CT) at 48 h showed loss of gray-white matter differentiation with generalized decreased density of left hemispheric cortex and slight midline displacement. Cerebral magnetic resonance imaging (MRI) performed 2 weeks later showed swelling and diffuse low intensity of entire left hemispheric cortex with discrete mass effect on T1-weighted sequence (Fig. 1A). Post-contrast MRI showed enhancement of left leptomeningeal vessels. Proton density and T2 sequences (Fig. 1B) showed diffuse hyperintensity of entire left cortical mantle with sparing of basal ganglia, brainstem and cerebellum. On discharge 4 weeks later the young girl had right-sided hemiplegia, expressive aphasia and severe cognitive impairment. Seizure control was satisfactory on phenobarbital. Cerebral positron emission tomography (PET) scan obtained 2 months after the event using F18-fluorodeoxyglucose (FDG) showed diffuse left cortical hypometabolism.

Right-sided seizures were refractory to various combinations of antiepileptic drugs including carbamazepine, valproic acid, phenytoin, phenobarbital and benzodiazepines. Left hemispheric atrophy was seen on a control MRI. The patient underwent left functional hemispherectomy 1 year after the acute event. Histology showed extensive spongiform necrosis. No neurons were seen in the entire left hemispheric cerebral cortex. Astrocytes were abnormally plump with fibrillary gliosis in the superficial cortical layers. Deep cortical layers and subcortical white matter contained large vacuoles (50–500 μm) interspersed with plump astrocytes and fat-laden cells. Complete absence of cortical neurons in the presence of reactive gliosis was confirmed by immunohistochemical staining with anti-neuron-specific enolase. Basal ganglia, brainstem and cerebellum seemed intact. Postoperative course was uneventful. The patient has been seizure-free since (7 year follow-up).

2.2. Patient 2

A 4 year-old girl was admitted in uncontrolled generalized SE that started 70 min earlier at school. Past medical history was unavailable at the time. She was born at term following an uneventful pregnancy. Right microphthalmia was noted at birth. Right optic nerve coloboma was present without hypoplasia. Neonatal period was marked by several episodes of hypoglycemia. Diagnostic work-up showed panhypopituitarism. MRI of sella turcica showed complete absence of anterior pituitary with normal stalk and posterior pituitary. She was treated with hormone replacement therapy (thyroxine, growth hormone and hydrocortisone). A germline retrotransposition insertion event disrupting the homeodomain of HESX1 was subsequently identified in this patient and a sibling who also had anterior pituitary aplasia [8]. Our patient’s development was normal. During
the current admission intrarectal diazepam followed by intravenous infusions of phenobarbital (20 mg/kg) and phenytoin (20 mg/kg) failed to control seizures that lasted 2 h. Initial electrolytes, glycemia (70 mg/dl, 3.8 mmol/l) and cerebrospinal fluid analysis were normal. Left-sided clonic seizures with secondary generalization appeared after about 5 h. These were refractory to repeat infusions of benzodiazepines, phenobarbital and phenytoin but responded to pentobarbital 3 h after seizure onset. Repeat biochemistry showed blood sugar level of 10 mg/dl (0.5 mmol/l). At that point her past medical history became known and hydrocortisone was given together with intravenous glucose (2 ml/kg of a 10% dextrose solution). After pentobarbital withdrawal, EEG showed low amplitude delta activity over the right hemisphere and high amplitude over the left. Cerebral CT scan showed decreased attenuation of right hemisphere with effacement of overlying sulci. T1-weighted MRI sequence 5 days later showed loss of gray-white matter differentiation, slight mass effect and cortical tumefaction of entire right hemisphere with post-contrast scans showing hyperaemia of overlying leptomeningeal vessels (Fig. 2A). Proton density and T2-weighted (Fig. 2B) sequences showed right cortical hyperintensity consistent with diffuse right hemispheric cortical edema and/or cortical necrosis without involvement of basal ganglia, brainstem and cerebellar structures. Two months later repeat MRI showed atrophy of right hemisphere, right ventricular ex-vacuo dilatation and spontaneous ribbon-like cortical hyperintensity on T1 pre-contrast sequences (Fig. 2C), post-contrast scans showing diffuse cortical enhancement (Fig. 2D). T2 sequences showed diffuse cortical and subcortical hyperintensity of right hemisphere, consistent with necrosis (Fig. 2E). Two months later, FDG-PET scan showed diffuse right cortical hypometabolism. Anticonvulsant therapy was discontinued after 2 years of seizure freedom. The patient has a persistent left hemiplegia.

2.3. Patient 3

A 3 month-old boy presented with fever, hypotonia and unconsciousness. Pregnancy and full-term delivery were normal. Family history was unremarkable. He was found cyanosed, his cot sheet stained with regurgitated milk. On admission he was febrile (40°C) and tachypneic (70/min) with tonic eye deviation and bilateral basal crackles. Blood analysis showed leukocytosis (27 000/mm³), normal C-reactive protein, lactic acidosis (serum lactate 100 mg/dl, 11 mmol/l) and glucose level of 60 mg/dl (3.3 mmol/l). He received an intravenous bolus of glucose (10 ml of a 10% dextrose solution) and a loading dose of phenobarbital (20 mg/kg). Consciousness improved after 30 min. An hour later intermittent right-sided clonic seizures with secondary generalization appeared, lasting over 30 min despite intravenous midazolam (bolus of 100 µg/kg followed by infusion of 50 µg/kg per h). Repeat glycemia was 24 mg/dl (1.3 mmol/l) with serum lactate of 30 mg/dl (3.5 mmol/l). Cerebrospinal fluid analysis with glucose level of 80 mg/dl (4.4 mmol/l) was normal. Ictal EEG showed continuous left-hemispheric spike and wave activity. Cerebral ultrasound scans showed no abnormalities. Seizure control required increasing doses of benzodiazepines necessitating artificial ventilation. Further boluses of glucose were given to treat hypoglycemia. The patient developed acute renal failure, abnormal clotting and raised liver enzymes in the context of multi-organ failure that gradually improved over 48 h. Consistent normoglycemia was difficult to achieve during that time, with blood glucose levels in the range 10–85 mg/dl (0.5–4.7 mmol/l). Detailed metabolic work-up was negative. T2-weighted cerebral MRI performed 5 days after admission showed left cortical and subcortical white matter hyperintensity extending from parietal to occipital region, pararolandic areas being most involved. T1-weighted post contrast scans showed left hemispheric leptomeningeal enhancement. The patient was discharged 4 weeks later with right-sided hemiplegia and seizure-free on phenobarbital. Two months later diffuse areas of left cortical hypometabolism were seen on FDG-PET scan. Currently at the age of 6 he has mild learning difficulties, persistent right-sided hemiplegia and has been off antiepileptic therapy for 3 years.

3. Discussion

We present three children with SE and hypoglycemia who develop unihemispheric damage. While in the first case SE could be attributed to hypoglycemia, which preceded it, in the other cases hypoglycemia was documented after the onset of SE. Sustained hypoglycemia was due to: insulin injection in Patient 1, lack of anti-insulin effect of corticosteroids secondary to panhypopituitarism in Patient 2 and to a combination of increased substrate requirements, inadequate counter-regulatory hormones and insufficient glycogen mobilization in Patient 3 in the context of multi-organ failure. In all three cases normoglycemia was difficult to achieve for several hours. Neuroimaging findings were similar, with initial diffuse cortical involvement confined to one hemisphere and sparing of basal ganglia and cerebellum.

Acute hypoglycemia can impair neurological function as the brain is normally dependent on glucose for oxidative metabolism. While mild hypoglycemia triggers an autonomic response through hypothalamic activation [9], more profound glucose deprivation may induce significant cortical dysfunction, ultimately coma and death [10]. In treated diabetes mellitus, recurrent hypoglycemia may manifest as transient hemiplegia in adults [11] and children [2,3,12]. There is no specific glucose level below which hemiplegia occurs, most studies reporting a range of 15–40 mg/dl [12]. The importance of duration of hypoglycemia was demonstrated in non-human primates [13]. Permanent neurological damage after profound hypoglycemia lasting 6 h was seen in 73% of cases, with a mortality rate of 14%. Mechanisms of
cortical dysfunction during hypoglycemia are not fully understood, although N-methyl-d-aspartate (NMDA) receptor-mediated mechanisms have been implicated in irreversible lesions [14]. Available clinical data on hypoglycemic coma concern mostly adults, pediatric reports consisting of specific situations such as diabetes mellitus, cerebral

Fig. 2. MRI sequences showing evolution in patient 2. (A) MRI T1 sequence showing right hemispheric cortical tumefaction with loss of gray-white matter differentiation, slight mass effect and leptomeningeal enhancement. (B) T2 sequence showing diffuse right hemispheric cortical hyperintensity. Two months later: (C) T1 sequence showing cortical atrophy and spontaneous ribbon-like cortical hyperintensity of right hemisphere and right ventricular ex-vacuo dilatation. (D) T1 post-contrast scan showing in addition diffuse right hemispheric cortical enhancement. (E) T2 sequence showing diffuse cortical and subcortical hyperintensity of right hemisphere.
malaria or acute intoxication. Neuropathological changes described in hypoglycemia include neuronal necrosis of the cerebral cortex [15].

Our patients had severe hypoglycemia in the course of their seizures. Its persistence probably contributed to perpetuating SE, further increasing the risk of cerebral damage. SE is characterized by increased cerebral metabolism with ATP depletion and lactate accumulation [16]. Ongoing epileptic activity induces excitotoxic mechanisms mediated by both NMDA and non-NMDA glutamate receptors resulting in calcium influx. Intracytoplasmic calcium plays a major role in immediate and delayed neuronal necrosis through apoptosis. Abrupt increase in oxygen and glucose utilization sustained throughout SE have been documented, with cerebral blood flow rising early on then falling especially in areas vulnerable to damage. In addition, SE in itself may lead to systemic hypoxia, shock, lactic acidosis, multi-organ failure and hypoglycemia [16]. This is illustrated by Patient 3 whose hypoglycemia appeared with multi-organ failure following SE. The cerebral effects of combined SE and hypoglycemia have been studied in animals [17]. Rats made hypoglycemic prior to seizure induction had increased volumes of cerebral damage compared to normo- or hyper- glyceric rats. Induced hypoglycemia was well below the range that typically produces hippocampal damage. This suggests that limited energy substrate availability directly compromises the ability of neurons to survive seizures. Given the increased metabolic load of a seizure, additional hypoglycemia could contribute further to a metabolism-substrate mismatch resulting in functional and structural disturbances of neurons. It is difficult to distinguish between cerebral damage due to hypoglycemia, SE or hypoxia/ischemia. Differences in patterns of cerebral involvement between SE and ischemia [18,19] have not been consistently documented. Certain similarities in MRI findings between partial status epilepticus in adults and ischemic stroke [20] have been described. These consisted of areas of decreased signal intensity on T1 with effacement of sulci, loss of gray-white matter differentiation and leptomeningeal enhancement in post contrast MRI. However in contrast to ischemia, the distribution of lesions following status epilepticus did not respect vascular territories, in accordance with our findings. Furthermore Lansberg et al. [20] noted marked cortical hyperintensity on T2 throughout the affected hemisphere in all cases, similar to our results. Post-contrast leptomeningeal enhancement in focal status epilepticus may reflect hyperaemia from vasodilatation of leptomeningeal vessels. Subsequent cortical enhancement is probably due to altered blood–brain barrier permeability, as demonstrated in a rat model [21] or in acute ischemic stroke [22]. Hyperperfusion of the affected hemisphere during SE is an ictal phenomenon in response to elevated metabolic demands usually followed by hypoperfusion and hypometabolism [20,23], as documented by our patients’ interictal PET findings. However while these abnormalities resolved in patients with isolated SE whose follow-up scans showed only mild residual volume loss [20], they persisted in the children we describe. Irreversibility of cerebral changes in the latter group could be due to a compound effect of persistent hypoglycemia, as documented in animal models [17]. Neuronal loss with reactive gliosis, as seen in Patient 1, has been described in severe hypoglycemia [24] with variable cortical involvement.

As in other general conditions with focal manifestations [25], the reason underlying the unilateral distribution of cerebral lesions following SE in association with hypoglycemia is not obvious. In diabetic patients with recurrent hypoglycemic hemiparesis theories include selective neuronal vulnerability, cerebral vasospasm and asymmetric cerebral blood flow with no consensus regarding true etiopathogenesis [2,3,12]. It could be hypothesized that our patients had preexisting cryptic lesions in the affected hemisphere. This could be the case with Patient 2 who had right microphthalmia.

Our cases suggest that prolonged seizure activity in combination with hypoglycemia may prove more detrimental to the brain than either condition in isolation. Limited substrate availability in the presence of increased energy demand and/or consumption could account for this. Our report also illustrates the possibility of asymmetric brain susceptibility to cerebral energy crisis.

References