

Something about neurology

ICU grand round 18/11/14

Dr. CT Lun

Dr. SO So

- F/54
- PMH:
 - bipolar affective disorder FU PSY
 - DM/ hyperlipidaemia/ HT/ obesity
 - Lacunar infarct at right pons and right frontal lobe in Sept 2007, presenting with dysarthria and left sided weakness, satisfactory recovery with independent ADL

HPI

- Admitted in medical ward for decreased sensorium
- Last seen well at 9 pm on 15/7/14, but found unarousable at 4 pm by husband (19 hours later)
- noted patient yell once at 0300 on 16/7/14 and then fell asleep again
- No convulsion witnessed but saliva drooling
- Some psychiatry medications seen on table
- Patient husband claim not in low mood, not voice out wish to commit suicide, but very poor drug compliance
- Noted to have hypoglycemia (undetectable) in ambulance and given dextrose, H'stix 8.7 in AED

Physical examination

- Afebrile 36.5 degrees
- GCS: E4V1M2 on admission
- Pupils 3mm bilaterally, reactive to light
- Neck soft, no abnormal limb movement , No myoclonus
- Left sided hypertonia and hyperreflexia
- Bilateral upgoing plantar
- CVS/ RES/ ABD: NAD

Investigations

- ABG: 7.46/3.6/13/19.2
- Mildly impaired renal function:
 - 139/5.1/23.9/170
- Liver function normal, CPK normal
- CT brain: no ICH, old Right pons infract, similar to CT brain 2007
- Empirically given ceftriaxone / acyclovir

17/7/14

- Electively intubated for airway protection and transferred to ICU
- Put on midazolam and morphine
- Differential diagnoses:
 - Drug
 - Metabolic causes
 - Stroke
 - CNS infection
 - Non-convulsive seizure

CNS infection

- Lumbar puncture done:
 - opening pressure 14 cm H₂O
 - Clear CSF
 - Protein 0.31g/ L
 - Glucose 6.1 mmol/L (serum glucose 11.7)
 - WBC 0

Metabolic cause

- Ammonia level normal
- TSH normal
- Urine x porphyrins: no excess
- Blood x ANA, anti-ds DNA -ve
- CPK normal
- H'stix stable during stay in ICU

? Drug

- Husband claim no illicit drug but DO not certain and possible
- Current medication before admission

Artane	Zestril
Quetiapine	Moduretic
Epilim chrono	Atenolol
Aspirin	Diamicron
	zocor

- Blood and urine toxicology
 - Drug(s) detected: Atenolol, Metformin and Morphine, Benzhexol, Gliclazide
- Blood x valproate level 323(within normal range)
- Blood x salicylate/ paracetamol/ ethanol –ve

EEG on 18/7/14

- 1st EEG (day 3)
 - No epileptic activity
 - Background slow waves
 - But patient in sedatives
 - ? Under drug effect

Progress in ICU

- Patient remained unconscious despite all sedatives were stopped on 18/7/14
- Sensorium around E4VtM2-3
- No eye contact
- Sometimes eyes deviated to right
- Brisk jerks over left upper and lower limbs
- Hypertonia over left side

Stroke?

- Repeated CT brain 21/7
 - The hypodensity at the Rt pons is again similar, could represent old infarct or prominent perivascular space.
- Repeated EEG 23/7 (day 8 and 4 days after sedatives stopped):
 - bilateral temporal slow wave background rhythm with occasional non-specific sharp waves, no epileptiform activity

- MRI 25/7 (day 10):
 - T2 hyperintense lesions suggestive of old infarcts are seen in right temporal cortex, right side of pons, and inferior aspect of right frontal cortex.
 - They show no interval increase in extent comparing with previous MRI scan 2009
 - There is no new intracranial lesion detected.
 - MRA (circle of Willis) show no significant arterial stenosis or occlusion

Consulted neurology

- Intracranial lesions not account for decreased sensorium
- Metabolic causes mostly ruled out by laboratory tests
- Suggest to repeat EEG with valium
- EEG with valium injection: No significant changes in signals or clinically with i.v. benzodiazepam

Non-Convulsive Status Epilepticus

- EEG manifestations reported in NCSE include continuous or virtually continuous spike wave discharge, discrete focal electrographic seizures, diffuse slow activity with or without spikes, and periodic or repetitive epileptiform discharges.
- Most other clinical situations in which NCSE occurs require EEG for diagnosis, which can be confirmed if the EEG shows continuous or virtually continuous paroxysmal activity, and preferably improvement simultaneous with clinical response to anticonvulsant medication such as intravenous/oral benzodiazepines

What this patient suffers from?

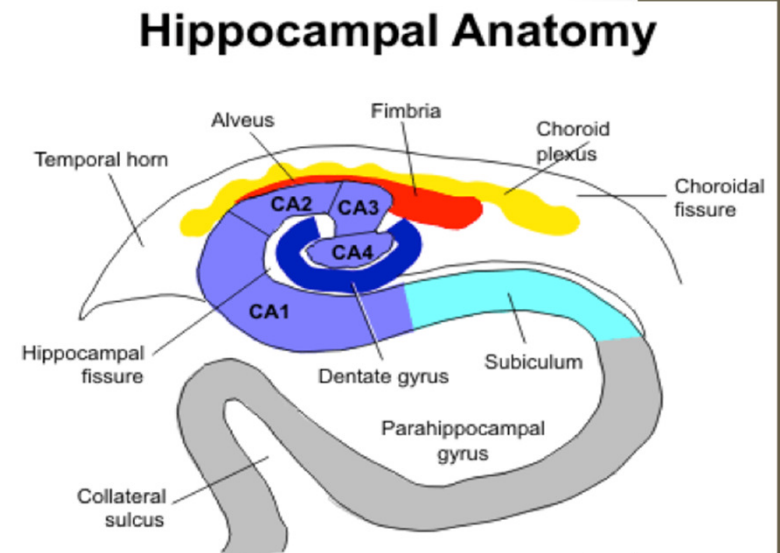
- CNS infection
 - The lumbar puncture not compatible with
- Stroke
 - Long tract signs over left signs compatible with old infarcts
 - MRI showed no new infarcts
- Metabolic causes
 - Normal liver/ thyroid function with negative urine porphyrins
- Non-convulsive seizure
 - No epileptiform activity by EEG,
 - No EEG signals or clinical improvement after i.v. benzodiazepine
- Hypoglycemic encephalopathy
 - Patient found hypoglycemia with undetectable H'stix in ambulance
 - Unknown duration of hypoglycemia

Hypoglycemic encephalopathy

- Unique energy utilisation of brain
- Very limited endogenous glycogen store 0.5-1.5g
- Brain accounts for 2% of body weight but utilise 25% of body's glucose
- Brain can use glycerols/ lactate/ ketone bodies during starvation, but cannot meet all of the metabolic demands of the brain
- Profound hypoglycemia can cause neuronal damage

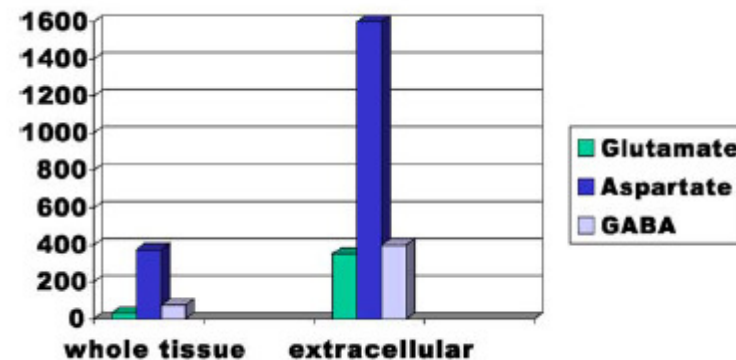
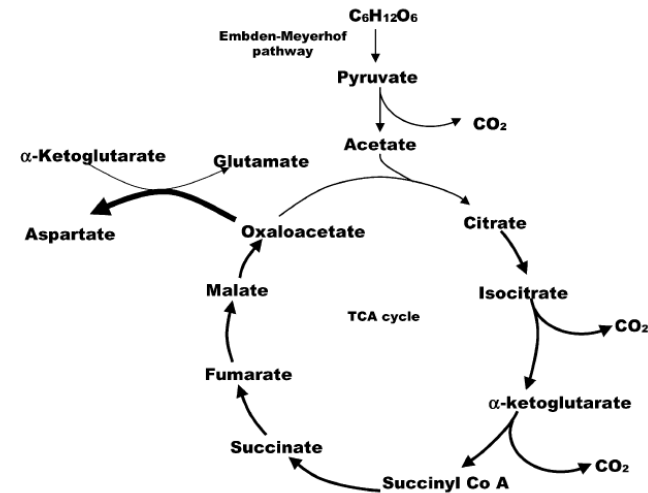
Selective neuronal damage

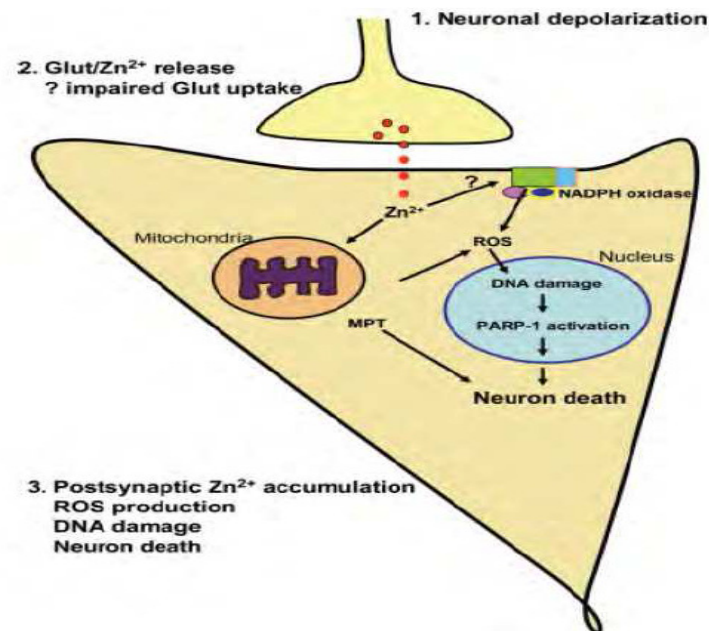
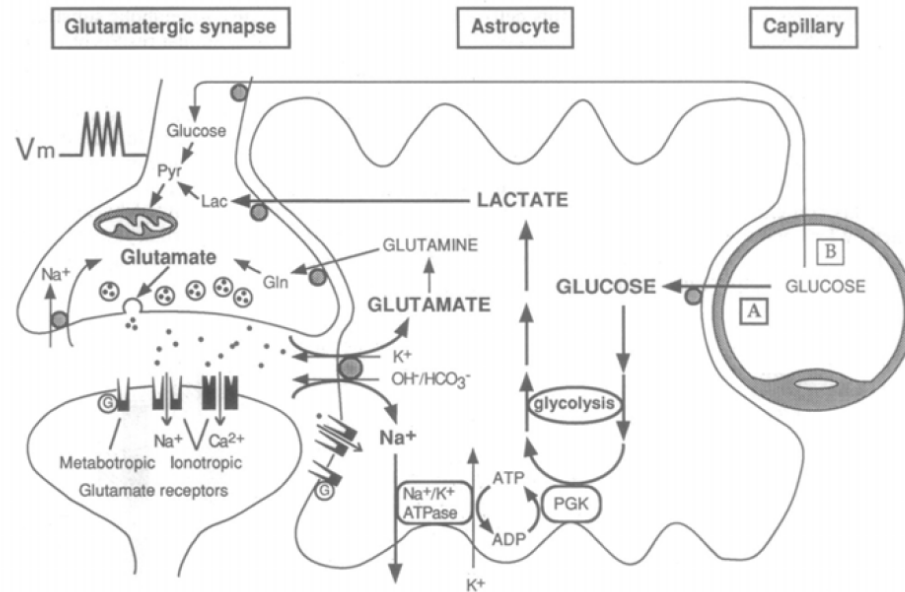
- Areas most vulnerable are subiculum, area CA1, dentate gyrus, (at hippocampus), small and medium size caudate neurons, superficial cortical layers, substantia nigra
- Cerebellum suffers a lesser insult, probably due to greater efficiency of the cerebellar glucose transporter
- Appears damage more severe to those neurons near the cerebrospinal fluid spaces



Pathophysiology

- Postulated that not merely due to energy failure
- Less glucose as substrate for acetate
- Increased oxaloacetate → aspartate and glutamate production
 - Excitatory amino acids
 - Aspartate in tissue increases in 4-fold and CSF increase to 16 fold
 - Sustained glutamate receptor activation, particularly at the NMDA receptors causing excitotoxicity





Excitotoxicity

- Sodium and water influx
- Cerebral edema
- Followed by calcium influx and causes dysfunction of intracellular processes
- production of reactive oxygen species with damage to DNA and proteins
- The balance shifts toward excitation, which is why seizures (25– 30%) can be seen in profound hypoglycemia

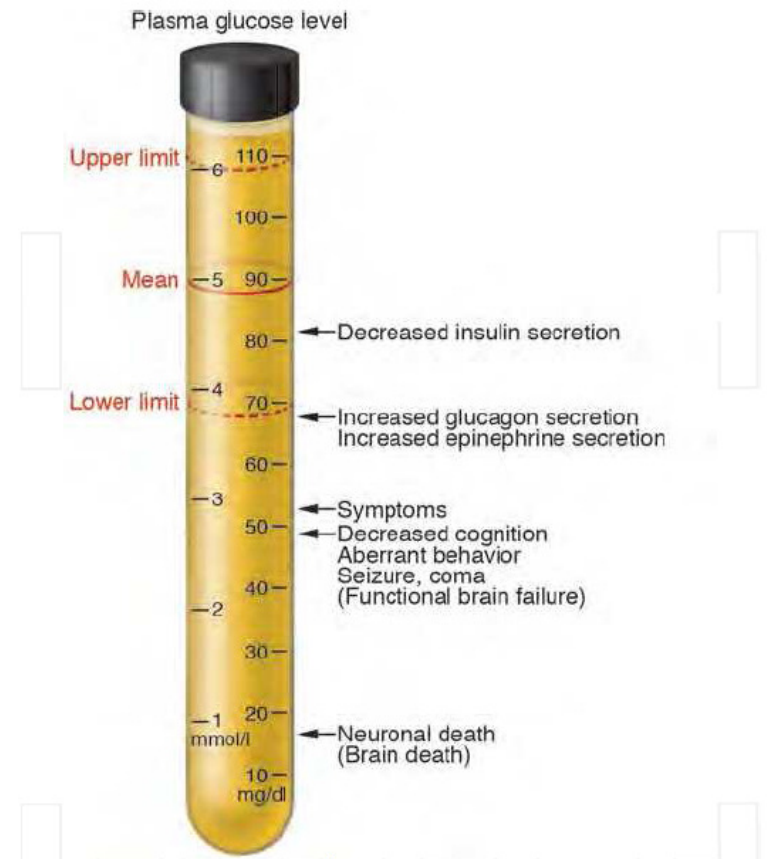
Tissue alkalosis

- Usage of protein as substrate causing ammonia accumulation in resulting in brain alkalosis
- Brain consume lactic acid and ketone bodies in profound hypoglycemia
- The above events conspire to increase cellular pH from 7.3 to ~ 7.5

	Hypoxic brain	Hypoglycemic encephalopathy
REDOX	reductive	oxidative
Acid-base	Acidic	Alkaline due to increase ammonia
	Ketone bodies/ lactate present due to anerobic metaboism	Ketone and lactic acid low as used as substrate

Clinical manifestation

- Insulin secretion ceases at 4.5 mmol/l
- Counterregulatory hormones (glucagon, adrenaline) secreted at 3.8 mmol/l
- Sympathetic nervous activation with Autonomic symptoms (sweating, irritability and tremor) at around 3.3 mmol/l
- Neuroglycopenic symptoms (seizure/ confusion) occur at 2.8 mmol/l
- Stupor and predominance of delta waves
- Coma/ flat EEG/ neuron death occurs below 1.36 mmol/l



EEG in hypoglycemia

Stages of Hypoglycemia

Clinical	EEG	Blood glucose (mM)
Normal	Normal	>3.5
Anxiety (adrenergic discharge)	↑ amplitude, ↓ frequency (θ, δ waves)	2–3.5
Stupor	δ waves	1–2
Coma, cushioning response (↑BP)	Flat	<1.36

- Glucose 2–3.5mmol/l, increased theta wave
- Glucose 1–2mmol/l, delta waves predominant, accompanied with stupor or drowsiness
- EEG isoelectricity, coma supervenes when the threshold of energy failure is reached
- A flat EEG is the harbinger of neuronal necrosis
- In experiment the blood glucose level threshold for neuronal necrosis varies from 0.12mmol/l to 1.36 mmol/l

Hypoglycemic coma

- First recognised by Dr. M Sakel who was nominated for Nobel prize 1950 for insulin shock therapy in schizophrenia (insulin induced hypoglycemic coma)
- Later noticed duration <30 mins allowed patients to recover from coma, but coma would be irreversible if treatment is longer

Drug-Induced Hypoglycemic Coma in 102 Diabetic Patients

Haim Ben-Ami, MD; Pradeep Nagachandran, MD; Ayelet Mendelson, MD; Yeouda Edoute, MD, PhD

Background: Hypoglycemic coma is a continuous threat for diabetic patients treated with insulin and/or oral hypoglycemic agents; it may be associated with substantial morbidity and mortality.

Methods: We retrospectively reviewed our clinical experience with drug-induced hypoglycemic coma during a 7-year period.

Results: The study consisted of 102 patients and included 61 females and 41 males. The median age was 72 years. Ninety-two patients suffered from type 2 diabetes mellitus; 10 patients had type 1 diabetes mellitus. The median lowest blood glucose level was 1.77 mmol/L (32 mg/dL). Drug-induced hypoglycemic coma occurred in 99 patients out of the hospital, while 3 patients developed it during hospitalization. Drug-induced hypoglycemic coma occurred in patients undergoing treatment with insulin, glyburide, and combined therapy with insulin and glyburide, insulin and metformin, or glyburide and metformin. Ninety-three patients had at least

1 of the following risk factors: age older than 60 years, renal dysfunction, decreased intake of energy, and infection. Fourteen patients concomitantly received drugs that potentiated hypoglycemia. Forty patients responded to treatment within the first 12 hours, while 62 patients had protracted hypoglycemia of 12 to 72 hours duration. Morbidity included physical injuries in 7 patients, myocardial ischemia in 2 patients, and stroke in 1 patient. Death occurred in 5 patients.

Conclusions: Hypoglycemic coma is a serious and not an uncommon problem among elderly patients with diabetes mellitus and treated with insulin and/or oral hypoglycemic drugs. Risk factors contribute substantially to the morbidity and mortality of patients with drug-induced hypoglycemic coma. Enhanced therapeutic monitoring may be warranted when hypoglycemic drugs are administered to an elderly patient with the above predisposing factors and potentiating drugs for hypoglycemia.

Arch Intern Med. 1999;159:281-284

- A retrospective analysis over a 7 year period evaluated 102 patients admitted with coma and blood glucose of below 49 mg/dL (2.72mmol/L) and improvement with glucose administration.
- Most patients were type 2 diabetics (92/102) taking glycemic agents.
- 93/102 had one or more risk factors included age over 60, renal dysfunction, decreased energy intake or infection.
- Sixty two patients responded within 12 hours of treatment, 40% (40) took 12-72 hours to improve
- Morbidity:
 - 7 physical injury
 - 8 seizures
 - 1 ischemic heart attack
 - 1 stroke
 - Death occur in 5 patients(4.9%), but causality with hypoglycemia not established and all 5 patients who died had other serious medical conditions

[Ann Neurol.](#) 1985 May;17(5):421-30.

Hypoglycemia: causes, neurological manifestations, and outcome.

[Malouf R.](#) [Brust JC.](#)

Abstract

During a 12-month prospective study there were 125 visits to the Harlem Hospital Emergency Room for symptomatic hypoglycemia. Sixty-five patients had obtundation, stupor, or coma; 38 had confusion or bizarre behavior; 10 were dizzy or tremulous; 9 had had seizures; and 3 had suffered sudden hemiparesis. Diabetes mellitus, alcoholism, and sepsis, alone or in combination, accounted for 90% of predisposing conditions; others included fasting, terminal cancer, gastroenteritis, insulin abuse, and myxedema. Average blood glucose levels were lower among comatose than among obtunded patients, but overlap was considerable, and overall there was little correlation among cause, blood glucose levels, and symptoms. Although mortality was 11%, only one death was attributable to hypoglycemia per se, and only four survivors had focal neurological residua.

- A prospective study on 125 patients for symptomatic hypoglycemia in 1 year
- 65 (52%) with obtundation/ stupor or coma
- 11 patients determined to be comatose for 12 hours or more
 - And among them, 10 remained comatosed
 - One death associated with hypoglycemia with coma > 20 hours

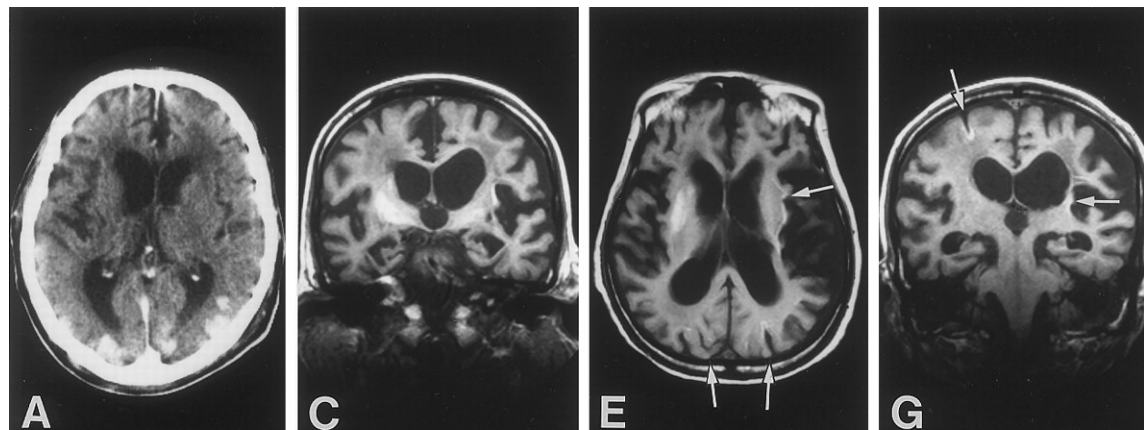
MRI finding

- Limited data for hypoglycemic encephalopathy as not all hypoglycemic patients underwent MRI
- DWI (diffuse weight imaging) has been reported as more sensitive and definite compared with other modality
 - Detect alteration in water diffusion resulting from cellular dysfunction, identifying early neuronal damage
 - Represent selective neuronal loss, proliferative astrocytes, paramagnetic substance deposition

Distribution

- MRI images of those in persistent vegetative state from hypoglycemia revealed lesions in bilateral basal ganglia, cerebral cortex, substantia nigra and hippocampus (vulnerable area)
- A study in Korea investigation MRI image in 11 hypoglycemic encephalopathy with coma [diffusion MR imaging of hypoglycemic encephalopathy. Kang EC. AJNR 2010; 31:559-64]
 - Posterior limb of Internal capsule (54%)
 - Hippocampus 36%
 - Central semiovale 82%
 - cortex 73%
 - Corona radiata 64%

Case	Initial MRI	
	T1WI	T2WI
1		
	Day 8	



Reversibility?

Serial Magnetic Resonance Imaging Changes in Hypoglycemic Encephalopathy

Chuo-Yu Lee, Kuang-Chung Liou, Lu-An Chen

Abstract-

Purpose: Reports of serial magnetic resonance imaging (MRI) in hypoglycemic encephalopathy were limited because MRI is not routinely performed in these patients. Here we present one patient with a history of hypoglycemic encephalopathy and discuss sequential neuroimaging findings.

Case Report: A 53-year-old male mistakenly took oral hypoglycemic agents developed hypoglycemic encephalopathy. Immediate brain diffusion-weighted image (DWI) demonstrated extensive symmetrical hyperintensive lesions over bilateral subcortical white matter. 14 days later, new hyperintensive lesions involving bilateral cerebral cortex were found on DWI, while previous subcortical white matter lesions disappeared. On day 86, diffusion-weighted images abnormalities vanished and diffuse brain atrophy was noted.

Conclusion: Although subcortical white matter involvement in hypoglycemic encephalopathy was occasionally reported in the literature, few report revealed similar serial MRI changes as our case. Although its mechanism is still unknown, it is important to follow sequential images in hypoglycemic encephalopathy. The brain tissue which was normal in early DWI may not necessarily guarantee undamaged.

Diffusion-weighted MRI predicts prognosis in severe hypoglycemic encephalopathy[☆]

Yoshiichi Yanagawa^{a,*}, Naoaki Itoi^a, Aya M. Tokumaru^b,
Toshihisa Sakamoto^a, Yoshiaki Okada^a

^a Department of Traumatology and Critical Care Medicine, National Defense Medical College, 3-1 Tokorozawa, Saitama, 359-8513 Japan

^b Department of Radiology, National Defense Medical College, Saitama, Japan

Received 24 February 2004; accepted 18 February 2005

Abstract

A 20-year-old woman presented unconscious due to hypoglycemia after a self-administered insulin injection. Diffusion-weighted MRI (DWI), performed 5 days after admission, demonstrated heterogeneous high-intensity signal areas in both the cortex and subcortex but sparing the motor and sensory centers. On the 11th day after admission, she began making incomprehensible verbal sounds, eye opening spontaneously and moving her extremities with pyramidal tract signs. Three months later, she had aphasia, agnosia and apraxia but a normal gait without pyramidal tract signs or ataxia. DWI is thus considered useful to predict the functional outcome of patients with severe hypoglycemia.

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Keywords: Hypoglycemia; MRI; Outcome; Diffusion weighted image

- Case reports showed DWI hyperintensity disappear with time ~ 14 days to 50 days in patient with hypoglycemic encephalopathy with neurological sequelae

Case report

Time related changes in reversible MRI findings
after prolonged hypoglycemiaSoichi Maekawa, Mayuki Aibiki*, Keiichi Kikuchi,
Satoshi Kikuchi, Kensuke Umakoshi*Department of Emergency Medicine and Radiology, Ehime University, School of Medicine,
454 Shitsukawa, Tohon, Ehime 791-0295, Japan*

Received 5 December 2004; received in revised form 29 January 2005; accepted 12 February 2005

Abstract

Diffusion weighted magnetic resonance images (DWI) in hypoglycemic coma show more definite and earlier findings than do T1-weighted images, or even fluid-attenuated inversion recovery (FLAIR). However, there has been limited information on the time related changes of such MRI images. We report here the time related changes of MRI findings after prolonged hypoglycemia in a diabetic 62-year-old man without hypoxia. We found in the patient that hyperintensities in DWI, T2-weighted and FLAIR images disappeared on the 14th day along with normalization of the apparent diffusion coefficient (ADC). Single photon emission computed tomography (SPECT) showed no low perfusion findings throughout the course. Since the day when the hyperintensities disappeared, the patient became to open his eyes in response to verbal command. This paper demonstrates serial alterations in reversible DWI findings after prolonged hypoglycemia and we need to define its mechanisms in the future.

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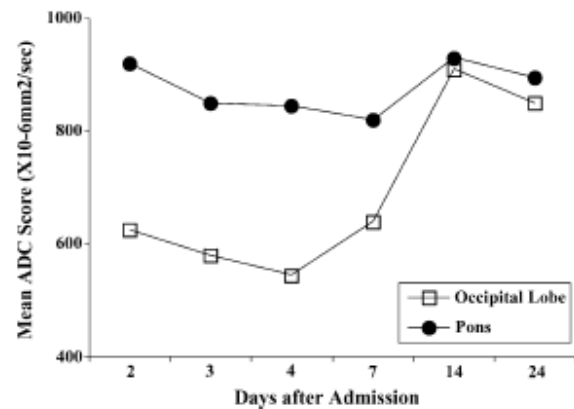


Fig. 2. Mean ADC scores at each site are depicted. The scores at the occipital lobes are lower than the levels at the pons in the early phase, but from the 7th day ADC scores at the lobes increase toward those of the pons.

- A case report show MRI changes were sustained for 7 days but on the 14th day the findings lessened and even disappeared
- These changes were found not only in DWI but also in T2- weighted and FLAIR findings

Prognostic factors in hypoglycemic encephalopathy

Prognostic value in MRI

- Good prognosis
 - Hyperintensity in white matter such as corona radiata/ internal capsule
 - hyperintensity regress on follow imaging
- Poor prognosis
 - Lesions detected in the cerebral cortex, basal ganglia, hippocampus, and not regress on follow up MRI
 - Grey matter damage, or selective neuronal necrosis

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[Diabetes Metab Res Rev.](#) 1999 Jan-Feb;15(1):5-12.

Evaluation of serum markers of neuronal damage following severe hypoglycaemia in adults with insulin-treated diabetes mellitus.

[Strachan MW¹](#), [Abraha HD](#), [Sherwood RA](#), [Lammie GA](#), [Deary IJ](#), [Ewing FM](#), [Perros P](#), [Frier BM](#).

Author information

Abstract

BACKGROUND: Neurone-specific enolase (NSE) and protein S-100 (S-100) may be used as markers of acute neuronal damage in humans with neurological disorders.

METHOD: To evaluate their use following a single episode of severe hypoglycaemia (defined as an episode requiring external assistance to aid recovery), serum concentrations of NSE and S-100 were measured following hypoglycaemia which had not caused persistent neurological impairment in 16 patients with insulin-treated diabetes (the 'hypo' subjects), and in three diabetic patients who died following severe hypoglycaemia. The serum proteins were also measured in 10 subjects with insulin-treated diabetes who had not experienced an episode of severe hypoglycaemia within the preceding year (the 'control' subjects).

RESULTS: No differences in serum concentrations of NSE and S-100 were observed between the 'control' and the 'hypo' subjects at either 36 hours or seven days after the episode of severe hypoglycaemia ($p > 0.05$). However, in two of the three subjects who died following hypoglycaemia, serum concentrations of the markers were markedly elevated.

CONCLUSIONS: Any neuronal injury occurring during severe hypoglycaemia that is not associated with persistent neurological deficit is insufficient to provoke elevation of these serum markers. However, the measurement of serum concentrations of NSE and S-100 may have a prognostic role in evaluating clinical outcome following severe hypoglycaemia which is associated with neurological damage.

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- Neuron specific enolase
 - dominant enolase-isoenzyme found in neuronal and neuroendocrine tissues
 - Organ-specific: neurons and small amount in erythrocytes
 - The biological half-life of approximately 24 hours.
 - Elevated in neuronal destruction, also frequently overexpressed by neural crest-derived tumors. Up to 70% of patients with small cell lung carcinoma (SCLC)
- S 100 protein
 - S100 proteins are homodimeric polypeptides
 - normally present in cells derived from the neural crest, chondrocytes, adipocytes, macrophages, and keratinocytes

Predictors of neuronal damage

- Neural specific enolase (NSE)
- S-100
- markedly elevated in 3 patients who died from hypoglycemic brain injury compared with 16 patients with hypoglycemia with good recovery
- But not elevated in patients with hypoglycemia without neurological sequelae
- Any neuronal injury without persistent neurological deficit is insufficient to provoke elevation of these serum markers
- May predict death or otherwise poor outcome in profound hypoglycemic coma

hypothermia



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& Diabetes
Metabolism

Short report

Hypothermia is a frequent sign of severe hypoglycaemia in patients with diabetes

C. Tran^{a,*}, K. Gariani^a, F.R. Herrmann^c, L. Juan^a, J. Philippe^a, O.T. Rutschmann^b, U.M. Vischer^c

^a Division of Endocrinology, Diabetes and Nutrition, Geneva University Hospital, 1206 Geneva, Switzerland

^b Department of Community, Primary Care and Emergency Medicine, Geneva University Hospital, Geneva, Switzerland

^c Department of Internal Medicine, Rehabilitation and Geriatrics, Geneva University Hospital, Geneva, Switzerland

Received 24 February 2012; accepted 4 March 2012

Abstract

Aim. – Hypothermia is a recognized complication of severe hypoglycaemia, but its prevalence and characteristics are poorly studied. For this reason, this study aimed to evaluate hypothermia in severely hypoglycaemic patients.

Methods. – A retrospective chart review was performed including all patients discharged between 2007 and 2010 from the Emergency Department of the Geneva University Hospital with a diagnosis of severe hypoglycaemia.

Results. – Hypothermia was identified in 30 (23.4%) out of 128 patients with severe hypoglycaemia. Its incidence was not affected by age, sex, or duration of diabetes.



- Retrospective study on 128 patients with severe hypoglycemia
- Hypothermia ($< 35\text{ C}$) was identified in 30 out of 128 patients in severe hypoglycemia, not affected by age, type of DM, season or time of day
- Using linear regression, the lowest recorded temperature was associated with initial Glasgow coma scale (GCS) score ($r^2 = 13.8\%$, $P < 0.0001$) and inversely associated with the leukocyte count ($r^2 = 13.1\%$, $P = 0.001$)
- Hypothermia may be a marker for hypoglycemia severity or duration
- May also represent an important compensatory mechanism in severe hypoglycemia, reflecting a decrease in energy demand during glucose deprivation



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Predictors of outcome in hypoglycemic encephalopathy

Tetsuhiko Ikeda^a, Tetsuya Takahashi^a, Aki Sato^b, Hajime Tanaka^c,
Shuichi Igarashi^b, Nobuya Fujita^d, Takeo Kuwabara^e, Masato Kanazawa^a,
Masatoyo Nishizawa^a, Takayoshi Shimohata^{a,*}

^a Department of Neurology, Brain Research Institute, Niigata University, Japan

^b Division of Neurology, Niigata City General Hospital, Japan

^c Department of Neurology, Shinrakuen Hospital, Japan

^d Department of Neurology, Nagaoka Red Cross Hospital, Japan

^e Department of Neurology, Niigata Prefectural Shibata Hospital, Japan

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ABSTRACT

Aims: The aim of this study was to investigate factors predicting poor prognosis in patients with hypoglycemic encephalopathy.

Methods: We retrospectively analyzed data on 165 consecutive patients with hypoglycemic encephalopathy. We evaluated their outcome 1 week after hypoglycemia onset using the Glasgow outcome scale (GOS) and compared the clinical features of patients with good outcomes (GOS = 5) and poor outcomes (GOS ≤ 4).

Results: The poor-outcome group included 38 patients (23%). The initial blood glucose level in the poor-outcome group was lower than that in the good-outcome group ($p = 0.002$). The duration of hypoglycemia in the poor-outcome group was longer than that in the good-outcome group ($p < 0.001$). Body temperature during hypoglycemia in the poor-outcome group was higher than that in the good-outcome group ($p < 0.001$). Furthermore, lactic acid level in the poor-outcome group was lower than in the good-outcome group ($p = 0.032$). There was no significant difference in the frequency of posttreatment hyperglycemia between the good-outcome and poor-outcome groups ($p = 0.984$).

Conclusion: Profound and prolonged hypoglycemia, normal or higher body temperature, and a low lactic acid level during hypoglycemia may be predictors of a poor outcome in patients with hypoglycemic encephalopathy.

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- Recruit 165 patients with hypoglycemic encephalopathy with coma or stupor with blood glucose < 50 mg/dl (2.78mmol/l)
 - 127 good outcome (Glasgow outcome scale (GOS) =5)
 - 38 poor outcome (11 patients GOS= 1, 12 GOS=2, 6 GOS=3, 9 GOS=4)

	Glasgow outcome scale	
1	Death	No life
2	Vegetative state	Unaware of self and environment
3	Severe disability	Unable to live independently
4	Moderate disability	Able to live independently
5	Mild disability or good recovery	Able to return to work/ school

poor outcome

- Lower Initial glucose (18.0 (1); 9.0–27.0 mg/dL vs 24.0 (1.3); 20.0–31.0 mg/dL; $p = 0.002$)
- Longer Duration of hypoglycemia (16.0; 12.0–24.8 h vs 9.0; 3.5–18.0 h; $p < 0.001$)
- Higher body temperature (37.0 $\pm$ 1.4 $^{\circ}$ C and 35.5 $\pm$ 1.2 $^{\circ}$ C, respectively; $p < 0.001$)
 - May be accounted by compensatory mechanism of hypothermia to decrease energy demand during hypoglycemia
- Lower Whole blood lactic level (1.0; 0.8–1.9 mmol/L vs 2.2; 1.7–2.5 mmol/L; $p = 0.032$)
 - Postulated lactic acid may be protective as brain utilise in energy metabolism

Animal experiments

Prevention of hypoglycemia-induced neuronal death by hypothermia

Byung Seop Shin^{1,2,3,6}, Seok Joon Won^{1,6}, Byung Hoon Yoo^{1,4}, Tiina M Kauppinen¹ and Sang Won Suh^{1,5}

¹Department of Neurology, University of California, San Francisco Anesthesiology, Samsung Medical Center, Sungkyunkwan Univ

³Department of Pain Medicine, Samsung Medical Center, Sungk Seoul, Korea; ⁴Departments of Anesthesiology, Sanggye Paik Ho Seoul, Korea; ⁵Department of Physiology, College of Medicine, I

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Hypothermia reduces neuronal damage after cerebral ischemia. Hyperthermia exacerbates damage from these insults. Previous studies have shown that temperature-dependent modulation of excitotoxic neuronal death is mediated by changes in the synaptic release/translocation of Zn²⁺. In this study, we found that hypoglycemia-induced neuronal death is also temperature-dependent. To test our hypothesis, we investigated the mechanism of temperature-dependent neuronal death by brain temperature, that is, hypothermia inhibited while hyperthermia exacerbated damage from these insults. To investigate the mechanism of temperature-dependent neuronal death, we measured zinc release/translocation, reactive oxygen species production, and microglia activation. Here we found that hypoglycemia-induced Zn²⁺ release, superoxide production, and microglia activation were inhibited by hypothermia but exacerbated by hyperthermia. Zinc chelation during hyperthermia reduced neuronal death. We conclude that neuronal death after hypoglycemia is mediated by increased Zn²⁺ release, superoxide product

Journal of Cerebral Blood Flow & Metabolism (2010) 30, 390–402; 28 October 2009

Prevention of acute/severe hypoglycemia-induced neuron death by lactate administration

Seok Joon Won^{1,6}, Bong Geom Jang^{2,6}, Byung Hoon Yoo^{1,3}, Min Sohn⁴, Min Woo Lee², Bo Young Choi², Jin Hee Kim², Hong Ki Song⁵ and Sang Won Suh^{1,2}

¹Department of Neurology, University of California at San Francisco and Veterans Affairs Medical Center, San Francisco, California, USA; ²Department of Physiology, Hallym University, College of Medicine, Chuncheon, Korea; ³Department of Anesthesiology, Inje Paik Hospital, Inje University, School of Medicine, Seoul, Korea; ⁴Department of Nursing, Inha University, Incheon, Korea; ⁵Department of Neurology, College of Medicine, Hallym University, Chuncheon, Korea

Hypoglycemia-induced cerebral neuropathy can occur in patients with diabetes who attempt tight control of blood glucose and may lead to cognitive dysfunction. Accumulating evidence from animal models suggests that hypoglycemia-induced neuronal death is not a simple result of glucose deprivation, but is instead the end result of a multifactorial process. In particular, the excessive activation of poly (ADP-ribose) polymerase-1 (PARP-1) consumes cytosolic nicotinamide adenine dinucleotide (NAD⁺), resulting in energy failure. In this study, we investigate whether lactate administration in the absence of cytosolic NAD⁺ affords neuroprotection against hypoglycemia-induced neuronal death. Intraperitoneal injection of sodium L-lactate corrected arterial blood pH and blood lactate concentration after hypoglycemia. Lactate administered without glucose was not sufficient to promote electroencephalogram recovery from an isoelectric state during hypoglycemia. However, supplementation of glucose with lactate reduced neuronal death by ~80% in the hippocampus. Hypoglycemia-induced superoxide production and microglia activation was also substantially reduced by administration of lactate. Taken together, these results suggest an intriguing possibility: that increasing brain lactate following hypoglycemia offsets the decrease in NAD⁺ due to overactivation of PARP-1 by acting as an alternative energy substrate that can effectively bypass glycolysis and be fed directly to the citric acid cycle to maintain cellular ATP levels.

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Does our patient suffer from hypoglycemia induced vegetative state?

- For

- Documented hypoglycemia in ambulance (undetectable)
- Possible long duration of hypoglycemia (last seen 19 hours)
- Other metabolic/ seizure/ structural causes excluded

- Against

- No MRI lesions typical of hypoglycemia
 - The MRI lesions can be reversible even in patient with neurological sequelae

- Our patient consciousness remains static E4VtM2
- Tracheostomy done and later wean off from ventilator
- Suspected to have “hypoglycemia-induced vegetative state”
- Transfer to general ward and later to Tai Po Hospital for convalescence

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