Review

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
50(3) 1–26

DOI: 10.1177/03000605221081429
journals.sagepub.com/home/imr
SAGE

Epileptic manifestations, pathophysiology, and imaging characteristics of non-ketotic hyperglycaemia: a review of the literature and a report of two cases with irreversible cortical vision loss

Dhanashree Peddawad

Abstract

The purpose of this review is to create more awareness regarding the epileptic manifestations of non-ketotic hyperglycaemia, which are not widely recognised, and to assist understanding of the pathophysiology involved. Given that type II diabetes is one of the common causes of morbidity worldwide, it is important to appreciate the various neurological manifestations of non-ketotic hyperglycaemia.

Here, I present two cases and review the existing literature. Both patients developed irreversible vision loss, which is a novel finding because only transient visual defects have previously been reported. The review includes a detailed discussion of the pathophysiology and characteristic magnetic resonance imaging (MRI) findings of patients with defects in cerebral lobar regions, which were associated with a variety of clinical manifestations. These manifestations can be ascribed to epileptic phenomena involving various parts of the cerebrum.

Hyperglycaemia can lead to the irreversible loss of vision. Early diagnosis and treatment on the basis of the clinical features and characteristic MRI findings are important to avoid an epilepsia partialis continua-like state and irreversible visual impairment.

Jupiter hospital, Pune, India

Corresponding author:
Dhanashree Peddawad, DM Neurology, Jupiter Hospital, Prathamesh Park, Baner, Pune 411045, India.
Email: dhanashree27j@gmail.com

Keywords
Non-ketotic hyperglycaemia, occipital seizure, vision loss, partial seizure, parieto-occipital region, electroencephalography, magnetic resonance imaging, T2 hypointensity

Date received: 11 November 2021; accepted: 1 February 2022

Introduction

Hyperglycaemia can cause encephalopathy, hemiparesis, hemisensory loss, focal seizures, and movement disorders, such as chorea, athetosis, and hemiballismus.[1–4] In this review, I shall discuss the lesser-known symptoms of non-ketotic hyperosmolar hyperglycaemia, which are referable to various cerebral regions, and have a variety of clinical presentations. In addition, I shall describe two cases of irreversible cortical vision loss owing to non-ketotic hyperglycaemia (NKH), a phenomenon that has not been described previously.

The reporting of these cases conforms to the CARE guidelines.[5]

Case 1

Patient information and clinical findings

A woman in her 60s was hospitalised because of transient visual symptoms in the form of flashes of colour lasting for few seconds several times a day for more than 2 weeks, followed by severe bilateral symmetrical loss of vision. Physical and neurological examinations revealed bilateral vision loss with no light perception. Her pupils were equal in size and reacted to light, and her optic discs were both normal.

Diagnostic assessment

The patient's fasting and postprandial blood glucose concentrations at the time of admission were 13.6 mmol/L and 22.2 mmol/L, respectively, but serum ketones were absent. Her serum creatinine, urea, sodium, and potassium concentrations were 0.380 mmol/L, 40.5 mmol/L, 138 mmol/L, and 3.40 mmol/L, respectively. Her creatinine and urea concentrations were reduced to 0.230 mmol/L and 20.1 mmol/L by three cycles of haemodialysis. Her cerebrospinal fluid (CSF) was normal, but electroencephalography (EEG) showed a loss of the posterior occipital alpha rhythm.

Therapeutic intervention

Consent for treatment was obtained from the patient and her hyperglycaemia was immediately corrected by means of an insulin infusion.

Follow-up and outcome

There had been no improvement in the patient's vision 6 months after the initial examination (Figure 1). This case has been described previously.[6]

Case 2

Patient information and clinical findings

A man in his 60s presented with frequent episodes of flickering bright colour in his right visual field that lasted for a few seconds to a few minutes and continued for more than 1 month, after which he experienced sudden-onset persistent loss of vision in his right hemi-field. He had also experienced a few partial motor seizures, involving transient gaze preference towards the right side and occasional episodes of right-sided facial spasm. Neurological

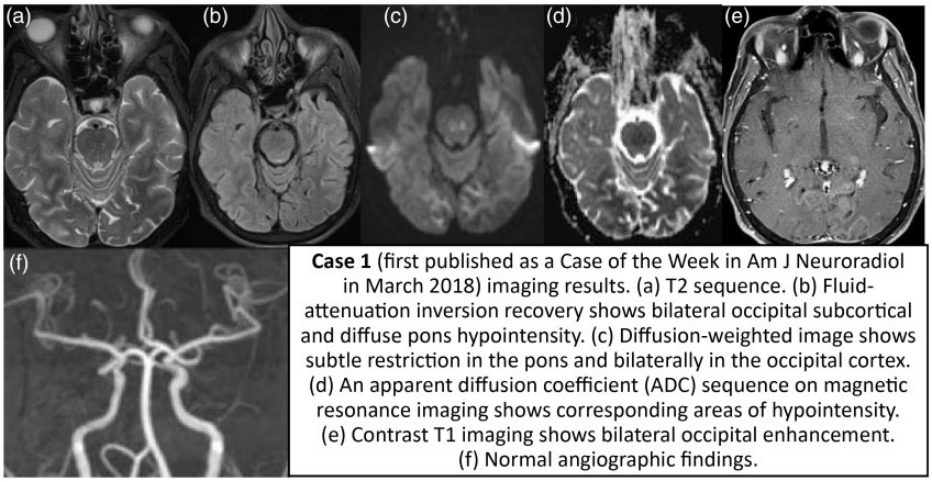

Figure 1. Case 1 (first published as a Case of the Week in Am J Neuroradiol in March 2018) imaging results. (a) T2 sequence. (b) Fluid-attenuation inversion recovery shows bilateral occipital subcortical and diffuse pons hypointensity. (c) Diffusion-weighted image shows subtle restriction in the pons and bilaterally in the occipital cortex. (d) An apparent diffusion coefficient (ADC) sequence on magnetic resonance imaging shows corresponding areas of hypointensity. (e) Contrast T1 imaging shows bilateral occipital enhancement. (f) Normal angiographic findings.

examination revealed right homonymous hemianopia, but no other focal deficits.

Diagnostic assessment

The patient's fasting and postprandial blood glucose concentrations were 14.4 mmol/L and 22.9 mmol/L, respectively, and his glycosylated haemoglobin (HbA1c) was 13%, but serum ketones were absent. His other biochemical and haematological parameters were normal. Interictal EEG showed intermittent slowing of the theta range in the left occipital region.

Therapeutic intervention

Consent for treatment was obtained from the patient, and his blood glucose concentration was brought under control by means of an insulin infusion and subsequent subcutaneous insulin injection. Perimetry revealed right homonymous hemianopia.

Follow-up and outcome

No improvement in the patient's vision occurred, and findings consistent with this were made by repeat perimetry (Figures 4A and B) and brain magnetic resonance imaging (MRI) 2 years after discharge (Figures 2 and 3).

Epileptic presentations of non-ketotic hyperglycaemia

Transient visual symptoms (Tables 1, 2, and 3)

In NKH that predominantly affects the occipital lobes, visual complaints of various types are the most common manifestations. Flickering light, transient flashes of colour (occipital seizures), nystagmoid eye movements, transient conjugate eye deviation, transient bilateral visual loss, transient hemianopia, field defects,[7–17] unformed or

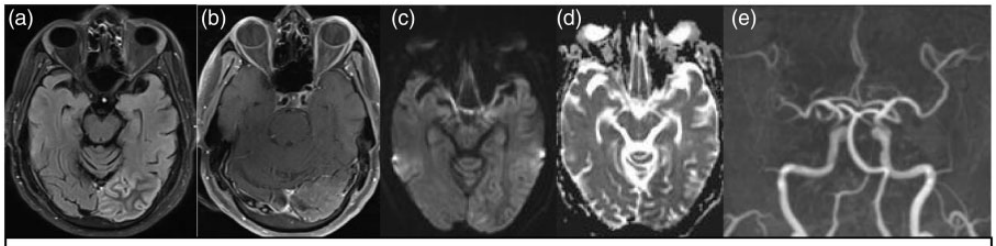

Figure 2. Case 2: initial imaging results. (a) Fluid-attenuation inversion recovery shows left occipital subcortical hypointensity and gyral hyperintensity. (b) After contrast enhancement. (c) Subtle streaks of diffusion restriction are apparent in the left medial lower occipital region. (d) The corresponding apparent diffusion coefficient (ADC) sequence on magnetic resonance imaging. (e) Normal angiographic findings.

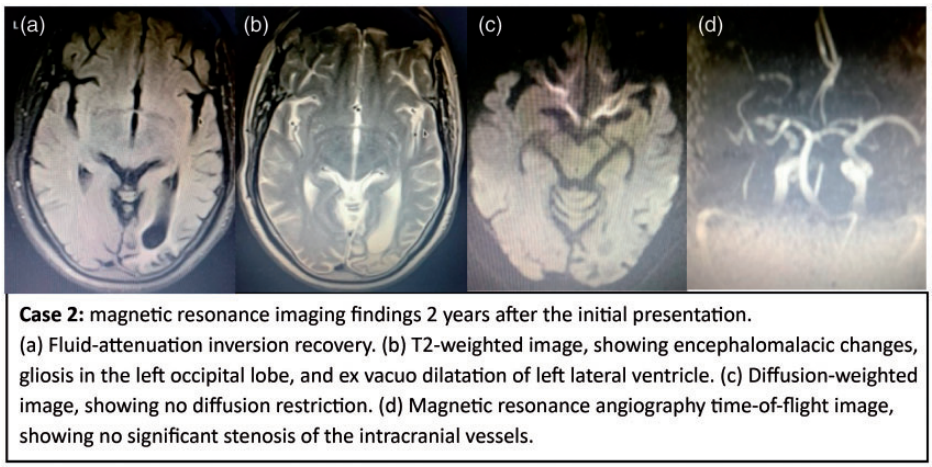

Figure 3. Case 2: magnetic resonance imaging findings 2 years after the initial presentation.
(a) Fluid-attenuation inversion recovery. (b) T2-weighted image, showing encephalomalacic changes, gliosis in the left occipital lobe, and *ex vacuo* dilatation of left lateral ventricle. (c) Diffusion-weighted image, showing no diffusion restriction. (d) Magnetic resonance angiography time-of-flight image, showing no significant stenosis of the intracranial vessels.

complex visual hallucinations,[16,18–23] oscillopsia, metamorphopsia, and pallinopsia[24–27] have been recorded.

Irreversible visual loss (Table 4)

Irreversible bilateral cortical blindness[6] (Case 1), irreversible hemianopia (Case 2), and permanent changes in colour perception[11] can also occur in patients with NKH.

Non-visual symptoms (Tables 5 to 10)

Focal motor seizures (automatism; clonic or tonic types) and non-motor focal seizures can occur, the latter causing

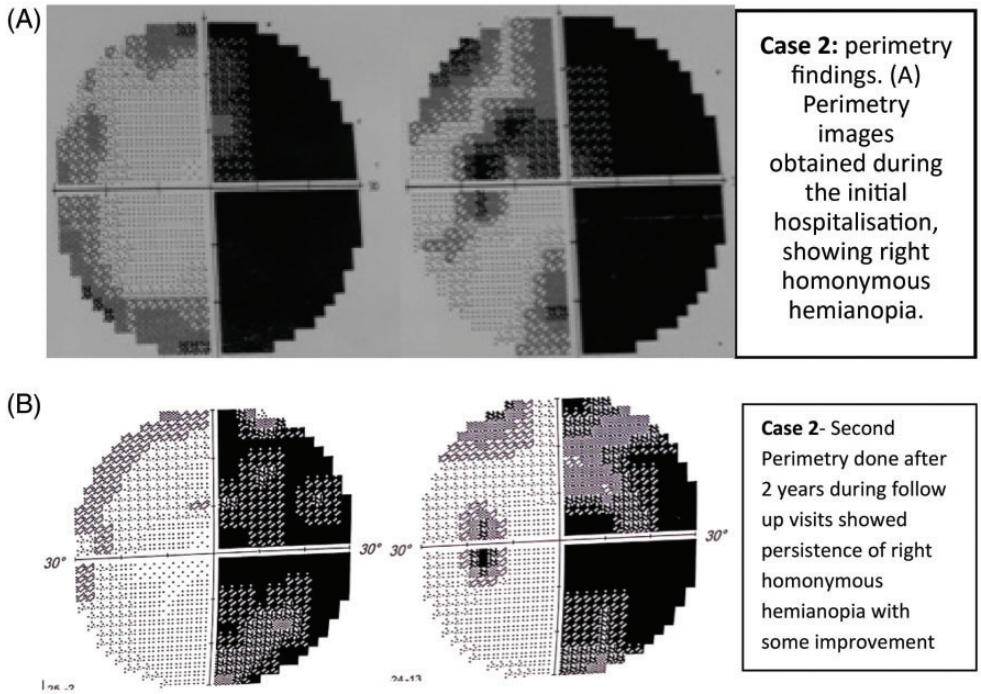

Figure 4. Case 2: perimetry findings. (A) Perimetry images obtained during the initial hospitalisation, showing right homonymous hemianopia. (B) Perimetry images obtained 2 years after the initial hospitalisation, showing persistence of the right homonymous hemianopia, but some improvement.

behavioural arrest or abnormalities such as psychosis or delirium.[28–30] Cognitive seizures, such as aphasia, aphasic status epilepticus, and alexia; somatosensory seizures;[16,31–37] and epilepsia partialis continua (EPC)[38–40] can also be observed. Thus, focal seizures that involve normal awareness or impaired awareness, and reflex seizures[41–50] can be caused by NKH.

Pathogenesis

A number of pathogenetic mechanisms have been postulated for the symptoms described above. Low concentrations of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) can cause seizures, and in NKH, low Krebs cycle activity and brain glucose utilisation leads to greater metabolism of GABA to succinic acid to yield energy (the GABA shunt), causing GABA deficiency. In contrast, in ketotic hyperglycaemia, GABA concentrations are maintained by the activity of glutamic acid decarboxylase.[51] In addition, the utility of a ketogenic diet for seizure control may indicate that ketones help prevent seizures.[3]

ATP-sensitive potassium channels are also thought to be responsible for neuronal hyperexcitability and the precipitation of seizures in hyperglycemia.[52] Astrocytes cultured in a high-glucose environment show low mRNA expression of the Kir4.1 potassium channel, but a restoration of the normal glucose concentration normalises the expression after a few days. In addition, glial glutamate uptake is low in a high-glucose environment. Thus, low glutamate uptake in combination with poor potassium clearance, because of low Kir4.1 expression,

Table 1. Vision loss and or occipital seizures documented.

Reference	Symptoms	Imaging findings	EEG	Blood glucose concentration (mmol/L)	Additional remarks
Harden *et al.*, 1991	Episodic blurring/flashes of red and green in the left visual field Left-sided homonymous hemianopia	Contrast brain CT normal in two cases Old lacunar infarcts in one case	Irregular rhythmic discharges in the right occipital region	20.6 25.1 26.9	1) One patient reported the television set becoming larger and moving towards him 2) Stereotypical contraversive head and eye movements towards the left side
Kenn *et al.*, 2004	Left-sided homonymous hemianopia and flashes of light	Brain MRI normal	Not done	17.9	Fragmentation and rolling of the vision, which may represent visual perseveration
Patrick *et al.*, 2005	Progressive homonymous hemianopia, hemi-field visual hallucinations, staring spells, unilateral neglect, partial seizures	Occipital region showed hypointensity on T2, FLAIR sequence; gyral enhancement on T1 contrast; diffusion restriction on DWI	Temporal and occipital slowing, spikes, irregular theta and delta, left occipital discharge spreading to the opposite side	27.9 23.6 23.7 27.0	1) Reflex seizures precipitated by visual stimuli 2) One patient had permanent difficulties distinguishing shades of the same colour
Raghavendra *et al.*, 2007	Complex partial or focal motor seizures, homonymous hemianopia, headache	Focal subcortical hypointensity and focal gyral hyperintensity on T2 FLAIR Contrast enhancement and DWI restriction in one patient	Left parieto-temporal spike wave Discharges, normal in one patient	17.4–18.0 312–317 mOsm/L	Of four patients, two had visual symptoms and the other two only partial seizures 1) Bilateral striatal hyperintensities in one patient (reversible) 2) Follow-up scans showed mild volume loss in one patient after 3 years and focal gliosis in another after 6 weeks
Gupta *et al.*, 2008	Generalised seizure followed by altered sensorium for 2 days; later transient cortical blindness	Normal MRI	Normal	33.3	1) VEP absent on admission; returned to normal after 8 weeks 2) Young patient

(continued)

Table 1. Continued.

Reference	Symptoms	Imaging findings	EEG	Blood glucose concentration (mmol/L)	Additional remarks
Del Felice *et al.*, 2009	Right hemianopia, red flashes, left-sided headache Transient conjugate deviation of the head and eyes to the right	Normal MRI	Sharp spike waves arising from the left posterior region	26.0 Glycosuria >1 g/24 hours HbA1c 10.5% Serum osmolality 333 mmol/kg	Left Brodmann's area 18 (the visual association area) showed BOLD activation on continuous EEG-fMRI
Moien-Afshari *et al.*, 2009	Blue and green flashes in the left visual field; occasional myoclonic seizure affecting the arm and confusion	Brain CT normal MRI not done	Seizures arising from the left occipital region Ictal activity was fast beta f/b Post-ictal activity was theta and delta	35.5 316 mOsm/L	Rapid seizure activity during seizure episodes Early recovery
Goto *et al.*, 2011	Visual hallucinations in the left visual field, left-sided hemianopia	Cortical hyperintensity with subcortical hypointensity in the right temporo-occipital region on T2 FLAIR	Spikes in the right temporo-occipital region	37.6 310 mOsm/L	
Putta *et al.*, 2014	Visual hallucinations of mathematical figures in peripheral vision, right-sided homonymous hemianopia	Subcortical T2 hypointensity in the left occipital lobe and leptomeningeal enhancement along the left parieto-occipital region	Ictal: left occipital polyspikes spreading to the right occipital region, and later becoming diffuse	19.9 HbA1c 13.4%	1) Impairment in attention and calculation 2) Apraxia: difficulty getting dressed and brushing teeth
Sasaki *et al.*, 2016	Flashes of pastel-coloured light in the right lower visual field, right-sided quadrantanopia	Subcortical hypointensity, gradient echo, and mild diffusion restriction on T2	Few alpha waves in the left occipital lobe	20.5 HbA1c 11.4% 326 mOsm/L	1) Gradient echo suggests iron accumulation as a possible mechanism for the T2 hypointensity 2) SPECT using 1123-N-isopropyl-iodoamphetamine showed hyperperfusion in the dominant occipital lobe

(continued)

Table 1. Continued.

Reference	Symptoms	Imaging findings	EEG	Blood glucose concentration (mmol/L)	Additional remarks
Seo *et al*., 2003	Episodic flashes in the left visual field	T2 and FLAIR showed hypointensity in the right medial occipital region	Slowing in the right posterior head region	20.3 18.8 30.5	1) One patient showed fluctuating aphasia with left frontotemporal involvement, and temporal encephalomalacia 6 months later 2) One patient had complex visual hallucinations (details given in Table 2)

CT, computed tomography; fMRI, (functional) magnetic resonance imaging; SPECT, single-photon emission computerised tomography; EEG, electroencephalography; FLAIR, fluid-attenuation inversion recovery; HbA1c, glycosylated haemoglobin; BOLD, blood oxygen level-dependent imaging, DWI, diffusion-weighted imaging.

Table 2. Complex hallucinations and delusions documented.

Reference	Symptoms	Imaging findings	EEG	Blood glucose concentration (mmol/L)	Additional remarks
Seo *et al*., 2003	Visual hallucinations, described as people walking towards the patient Focal, right-sided clonic seizures	Hypointensity in the left parieto-occipital area and hyperintensity along the adjacent cortex on T2 T1 contrast showed leptomeningeal enhancement	Epileptiform activity originating from the left occipital region Interictal periodic epileptiform discharges in the posterior temporal region	30.5 HbA1c 11.9% 309.7 mOsm/L	Mild residual atrophy in the left parieto-occipital region on MRI 6 months after presentation
Sowa *et al*., 1989	Complex visual hallucinations: environment shaking, images appearing in the left visual field, from right to left	CT, MRI, and CSF normal	Rhythmic activity occurring over the right temporal area only during CVHs	33.9	Nineteen different types of hallucinations and illusions noted by the patient CVHs lasted 7 weeks

(continued)

Table 2. Continued.

Reference	Symptoms	Imaging findings	EEG	Blood glucose concentration (mmol/L)	Additional remarks
Duncan *et al.*, 1991	Headache, flashes of light in the left visual field, left hemianopia, small luminous ball in the left visual field, which expanded like a "bright sun", and later developed into objects, such as articles of furniture and unfamiliar human faces	Brain CT and MRI normal	Right temporo-occipital discharges at the same time as visual images appeared	27.7 308 mOsm/L	Reflex seizures: stereotyped visual symptoms when looking to the left
Wang *et al.*, 2005	Flickering red objects in the right visual field, abrupt blurring of vision, ictal nystagmus complex, visual hallucinations, illusions, and distortions, and right hemianopsia	Gyral hyperintensity in the left occipital lobe, along with FLAIR and T2 subcortical hypointensity	Continuous spike from the left occipital region	29.7	1) HMPAO SPECT: left occipital perfusion higher during status epilepticus, but less pronounced 6 months later 2) Smaller NAA peak in the left occipital lobe on MRS 3) P100 amplitude 50% larger on the right side during visual seizures, but slightly higher on the left side 6 months later 4) Visual seizures recurred due to poorly controlled blood glucose, but responded to glucose reduction
Hung *et al.*, 2010	Green flashes in the left visual field, left gaze deviation, illusion and distortion of images on the left, left-sided hemianopia	Subcortical hypointensity, cortical hyperintensity in the right occipital and mesial temporal lobes	Seizures originating from the left occipital region Interictal beta paroxysms	17.3–20.6 295–304 mOsm/kg	SPECT showed hyperperfusion of the right occipital region

(continued)

Table 2. Continued.

Reference	Symptoms	Imaging findings	EEG	Blood glucose concentration (mmol/L)	Additional remarks
	Episodic complex visual hallucinations				
Fletcher *et al.*, 2011	Confusion, visual hallucinations (brightly coloured numbers) in the right visual field, right homonymous hemianopia	Brain MRI normal	Left occipital seizure activity	37.0	Confusion: patient not able to recognise their relatives
Richardson *et al.*, 2018	Left hemianopsia, complex hallucinations (seeing dogs, men, and children)	Brain MRI normal	Recurrent episodes of seizures, starting from the right occipital region	13.4 HbA1c 14.8%	CT angiography showed prolongation of the mean transit time, and low cerebral blood volume and flow in both posterior cerebral arteries, suggesting post ictal state

NAA, n-acetylaspartate; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; CT, computed tomography; CSF, cerebrospinal fluid; HMPAO, D,L-hexamethylene-propyleneamine oxime; SPECT, single-photon emission computerised tomography; EEG, electroencephalography; FLAIR, fluid-attenuation inversion recovery; HbA1c, glycosylated haemoglobin; CVHs, complex visual hallucinations.

Table 3. Unusual visual phenomena documented.

Reference	Symptoms	Imaging findings	EEG	Blood glucose concentration (mmol/L)	Additional remarks
Lavin *et al.*, 1986	Seizures started with unresponsiveness and staring, later head and eye deviation to the left and left-sided nystagmus with pupillary oscillations	Plain brain CT normal	Loss of posterior rhythm in the right occipital region	34.1	Pupils dilated as they moved laterally and constricted as they returned to the central position Both the ocular deviation and pupillary oscillations were clonic
Johnson *et al.*, 1988	Palinopsia, complex visual hallucinations, right homonymous hemianopia, motor seizures	Brain CT normal	Seizures originating from the left occipital region	33.8	Palinopsia considered to be an ictal phenomenon
Guez *et al.*, 2010	Sudden-onset homonymous hemianopia Autoscopic phenomenon	T2 FLAIR showed hypointensity in the medial part of the occipital lobe, mild diffusion restriction	Mild slowing in the right hemisphere	52.3 341 mOsm/L	1) when the patient watched television, they saw themselves being projected into the hemianopic field 2) MRS: high choline, creatine, and myoinositol peaks, but normal lipid, lactate, glucose, and ketone peaks suggestive of hyperosmolality
Conduit *et al.*, 2016	Episodic coloured images in the left hemi-field f/b homonymous hemianopia, complex visual hallucinations including palinopsia, oscillopsia, and metamorphopsia	DWI showed restriction in the right occipital lobe Subtle hyperintensity of the right occipital cortex on T2	No epileptiform activity	>25.0	Micro-haemorrhages on SWI that were still present 3 months later

SWI, susceptibility-weighted imaging; DWI, diffusion-weighted imaging; CT, computed tomography; MRS, magnetic resonance spectroscopy; FLAIR, fluid-attenuation inversion recovery.

Table 4. Irreversible vision loss documented.

Reference	Symptoms	Imaging findings	EEG	Blood glucose concentration (mmol/L)	Recovery	Additional remarks
New case (Figures 2 and 3)	Flashes of coloured light in the right visual field for more than 4 weeks, followed by sudden loss of vision in same hemifield	Left occipital T2 hypointensity and gyral enhancement Repeat MRI after 2 years showed left occipital gliosis	Mild background slowing	Fasting: 14.4 Postprandial: 22.9 HbA1c 13%	Minimal improvement in vision loss after the correction of the blood glucose concentration	Persistent homonymous hemianopia on perimetry after 2 years
Peddawad et al., 2018 (Figure 1)	Transient flashes of colour lasting for a few seconds several times a day, bilateral symmetric irreversible cortical visual loss	Bilateral occipital subcortical and central pontine hypointensity T1 contrast showed occipital gyral enhancement	Generalised theta range slowing	Fasting: 13.6 Postprandial: 22.2 HbA1c 12%	No Improvement in vision Light perception 2 months after the onset of symptoms	Patient also had acute renal failure and mild hyponatremia, which were corrected within first 72 hours of hospitalisation
Patrick et al., 2005	Progressive homonymous hemianopia, hemi-field visual hallucinations	Occipital region showed hypointensity on T2, FLAIR sequence; gyral enhancement on T1 contrast sequence; diffusion restriction on DWI image	Right occipital slowing	27.9	One patient had a permanent deficit in colour perception	

HbA1c, glycosylated haemoglobin; MRI, magnetic resonance imaging; FLAIR, fluid-attenuation inversion recovery, DWI, diffusion-weighted imaging.

Table 5. Aphasic status epilepticus documented.

Reference	Symptoms	Area involved	Imaging findings	EEG	CSF	Blood glucose concentration (mmol/L)	Recovery	Additional remarks
Manford *et al.*, 1995	Progressive difficulty speaking, leading to global aphasia Executive dysfunction	Left frontal and temporal regions	Brain CT showed generalised cerebral atrophy	Seizure discharge of 12 Hz over the left temporal region	Acellular, high protein and sugar content	38.7	6 weeks	SPECT showed lower uptake in the left superior temporal and inferior frontal gyri Repeat SPECT showed resolution of the abnormality
Pro *et al.*, 2011	Predominantly motor aphasia	Frontotemporal	Brain CT and MRI normal	Frequent electrical seizures lasting 60 to 90 seconds		19.4 HbA1c 12.8%	1–2 days	EEG findings and clinical features were suggestive of non-convulsive status
Huang *et al.*, 2014	Mixed aphasia	Frontotemporal	MRI showed mild cerebral atrophy	Left frontotemporal continuous theta to delta mixed with epileptiform discharges	Normal	21.1 HbA1c: 13.5 g%	2 weeks	Impaired fluency, repetition in naming and comprehension
Syuichi *et al.*, 2016	Isolated persistent mixed aphasia Occasional spontaneous speech, able to follow commands	Left frontotemporal	MRI showed mild cerebral atrophy	Diffuse continuous theta to waves mixed with epileptiform discharges	Normal	30.8 15.2 g%	6 days	EEG became completely normal, with restoration of the alpha background after the resolution of aphasia
Lee *et al.*, 2016	Motor dominant aphasia and intermittent headache		MRI showed no abnormalities	Diffuse slowing with intermittent irregular delta		26.1 HbA1c 15.8%	6 days	Serum ketones 1+ Serum osmolality 312 mOsm/L
Melek *et al.*, 2017	Inability to identify relatives and difficulty in understanding	Left temporo-occipital	Left temporo-occipital hyperintensity on FLAIR T2 DWI Leptomeningeal enhancement on contrast T1	Continuous spike and wave activity in left temporo-occipital region	Normal	19.9 HbA1c 14%	1 week	

HbA1c, glycosylated haemoglobin; MRI, magnetic resonance imaging; FLAIR, fluid-attenuation inversion recovery, DWI, diffusion-weighted imaging; EEG, electroencephalography; SPECT, single-photon emission computerised tomography; CT, computed tomography.

Table 6. Non-convulsive status epilepticus/frontal lobe dysfunction documented.

Reference	Symptoms	Area involved	Imaging findings	EEG	Blood glucose status	Recovery	Additional remarks
Thomas et al., 1999	Frontal NCSE	Frontal region	Brain MRI normal	Frontopolar, anterior temporal discharges Left frontal recurrent fast activity Normal background	Non-ketotic hyperglycaemia	Complete	Alert, oriented, continuous euphoria and disinhibition, attention deficit, anosognosia, perseveration

EEG, electroencephalography; NCSE, non-convulsive status epilepticus.

Table 7. Non-convulsive status epilepticus/psychosis delirium documented.

Reference	Symptoms	Blood glucose concentration (mmol/L)	Recovery	Additional remarks
Maharajh *et al.*, 2006	42-year-old man who set his house on fire after seeing a number of big rats	27.5	2 days	Normal higher mental status and neurological examination on admission No past history of psychiatric disorders
Lopes *et al.*, 2018	History of behavioural abnormality Stopped treatment for diabetes 6 months prior to symptoms developing	20.4 HbA1c 10.1%	2 weeks	One-month history of behavioural changes, agitation, disorganisation, confusion, impulsivity and irritability, social isolation, and illogical thinking, with delusional ideas of persecution and insomnia Patient started living in poor conditions and neglected their hygiene

HbA1c, glycosylated haemoglobin.

Table 8. Non-convulsive status epilepticus/alexia without agraphia documented.

Reference	Symptoms	Imaging findings	EEG	Blood glucose concentration	Recovery	Additional remarks
Kutluay et al., 2007	Right homonymous hemianopia Unable to read written words, despite recognising individual letters and writing normally No other neurological deficits	Cortical swelling and hyperintensity over the left temporo-occipital region, involving the middle occipital and middle temporal gyri on FLAIR sequences	Electrographic seizures arising from the left temporo-occipital region, lasting 150–220 seconds	37.6 mmol/L	3–4 days	Hemianopia and alexia completely resolved, including the EEG and MRI abnormalities

EEG, electroencephalography; FLAIR, fluid-attenuation inversion recovery; MRI, magnetic resonance imaging.

might lead to excitotoxic damage to neurons.[53]

Previous studies have also suggested that disruption of the blood-brain barrier plays a role in the pathogenesis of the neurological signs described above. Gyral and leptomeningeal contrast enhancement has been observed, and may result from a disruption of the blood–brain barrier and extravasation of contrast medium, because of the greater metabolic activity during seizures. A delay in the gadolinium enhancement of the CSF space overlying the cortical region has also been observed using fluid-attenuation inversion recovery (FLAIR), and is suggestive of blood–brain barrier disruption.[54] This could be related to a delay in gadolinium enhancement on FLAIR imaging, which also occurs in patients who experience post-thrombolysis stroke. In this situation, early blood–brain barrier disruption occurs, which is also referred to as hyperintense acute reperfusion marker, and this is associated with haemorrhagic transformation and a poor clinical outcome. Iwata *et al*. demonstrated contrast enhancement of the globus pallidus prior to the development of homogenous hyperintensity on T1-weighted imaging, which is suggestive of blood–brain barrier destruction.[55,56]

The hypoxic ischemic state that is caused by hyperglycaemia could lead to excitotoxic axonal damage and the accumulation of free radicals or iron, causing a hypointense signal on T2-weighted images,[16] which could also be caused by intracellular osmotic dehydration.

The presence of diffusion restriction in many cases of NKH suggests that cytotoxic oedema may be an underlying pathogenetic mechanism. Classic posterior reversible encephalopathy syndrome (PRES), which also involves the parietooccipital region, has vasogenic oedema as an underlying mechanism, but this is associated with a

Table 9. Epilepsia partialis continua documented.

Reference	Symptoms	Imaging findings	EEG	CSF	Blood glucose concentration (mmol/L)	Recovery	Additional remarks
Singh et al., 1980	Repetitive, non-spreading clonic movements of parts of the body that persisted for several hours to several days Total of 21 patients	Brain CT normal in the majority of cases Abnormal radionuclide scan in two patients	Seizures not always associated with discharges, PLEDs, temporal discharges, sharp and slow wave discharges Normal in a few patients	Normal, except for slightly high protein concentration in a few patients	17.8–83.8 Serum osmolality 278–372 mOsm/L	Hours to days	Higher blood glucose concentrations and serum osmolalities were associated with poorer levels of consciousness and the cessation of seizures Severity of hyponatremia correlated with the duration of EPC
Wang et al., 2017		No significant lesions	Spikes, slow waves, and sharp waves		24.7–34.6 290–332 mOsm/L	76 hours	Six of 13 patients showed persistent partial seizures
Cokar et al., 2004	Clonic movement of the right arm for 10 days, with progressive involvement of the right leg and face	CT and MRI normal	Ictal discharges in the ipsilateral hemisphere		85.5 391 mOsm/L	1 week	Paradoxical lateralisation of electrical activity, because of oblique projection of epileptic activity from the left mesial temporal lobe to the right temporal region

EEG, electroencephalography; CSF, cerebrospinal fluid; CT, computed tomography; MRI, magnetic resonance imaging; EPC, epilepsia partialis continua; PLEDs, periodic lateralised epileptiform discharges.

Table 10. Reflex epilepsy documented.

Reference	Symptoms	Imaging findings	EEG	Blood glucose concentration (mmol/L)	Recovery	Additional remarks
Gabor *et al.*, 1974	Frequent episodes of left carpopedal spasm and facial dystonia, lasting a few seconds, produced by repeated grasping	Brain CT normal	Interictal and ictal epileptiform discharges from the right centroparietal region	29.1 CSF normal	Few days	Brachial plexus anaesthesia block was administered When attempting left hand movement, EEG showed electrical activity, which was similar to that produced by clinical seizures, suggesting a central mechanism
Venna *et al.*, 1981	Use of the patient's right arm consistently induced seizures	Contrast brain CT normal	Sharp, slow-wave paroxysms over the left frontal region	30.4	3 days	Pain, light touch, other stimuli, and passive movement of the limb did not precipitate seizure activity
Neufeld *et al.*, 1988	Stereotypic clonic movements of tongue, lasting a few seconds to minutes, which were triggered the patient raising their left arm and rubbing their scalp	Plain and contrast CT normal	Sharp waves in right frontocentral region, with semirhythmic 3–5 Hz activity	26.6	6 days	Few episodes comprised turning the head to the left, clonic contraction of the left corner of the mouth, and aversion of the eyes
Hennis *et al.*, 1992	Walking or movement-induced focal seizures	One patient showed perisylvian atrophy on the opposite side		17.8–37.7 mmol/L	Few days	Termed kinesigenic seizures

(continued)

Table 10. Continued.

Reference	Symptoms	Imaging findings	EEG	Blood glucose concentration (mmol/L)	Recovery	Additional remarks
Tedrus *et al.*, 1995	Movement-induced visual seizures	Normal CT	Right hemispheric discharges	38.6	~2 weeks	Repeated focal visual seizures
Moro *et al.*, 1999	Any voluntary movement of the patient's left hand triggered seizures that were recorded on video EEG	Brain MRI showed multiple infarcts in both hemispheres and the pons	Ictal EEG recorded several seizures induced by voluntary movement of the left hand Interictal EEG was normal	30.0	6 days	Ictal SPECT showed high activity in the contralateral striatum, and frontal and parietal lobes
Siddiqi *et al.*, 2002	Posturing of the right hand, with short alteration in sensorium in feedback to a specific movement or position of the right hand	Subacute infarct in the left frontal region, anterior aspect of the prefrontal gyrus, on MRI	Left temporal rhythmic discharges	20.3	~1 week	Stereotypic seizures reproduced continuously whenever the patient tried to write or was given a handset or mobile phone
Ozer *et al.*, 2003	Seizures occurred whenever the patient's right hand was extended and pronated, and their forearm was flexed at the elbow	CT and MRI normal	Ictal: left fronto-central region showed spikes and slow waves, spreading to the temporal occipital region and right hemisphere	22.2	9 days	Focal seizures, becoming generalised in association with particular positions of the right hand
Tiras *et al.*, 2009	Left partial seizures induced by forced voluntary closure of the eyes	MRI normal	Right temporoparietal electrodes showed spike and wave activity	30.5	5 days	No photoparoxysmal response No seizure, but spontaneous blinking or eye movements

(continued)

Table 10. Continued.

Reference	Symptoms	Imaging findings	EEG	Blood glucose concentration (mmol/L)	Recovery	Additional remarks
Wu *et al.*, 2010	Seizures induced by playing Mah-Jong	MRI normal in three cases, cortical atrophy in one, and an old middle cerebral artery infarct in one	Temporal sharp waves in three cases, normal in two cases	16.7–30.0	Few days	Mah Jong (a traditional Chinese game) involves cognitive processes, including thinking, memory, and decision-making

hyperintense signal on T2-weighted images and diffusion restriction is not typical.[57]

Central pontine myelinosis (CPM) has been documented in a patient during the treatment of hyperosmolar hyperglycaemia, which implies that osmotic demyelination may be involved in the pathogenesis. Oedema could lead to the compression of fibre tracts, leading to demyelination. The pons may become involved because of its tightly packed grey and white fibres, which are susceptible to osmotic demyelination.[58] However, the basal ganglia, thalamus, and cortico-white matter junction also have tightly packed grey and white fibres.[59,60] Disruption of blood-brain barrier and endothelial injury leads to oedema, which may cause compression of nerve fibres, and therefore demyelination, and it can also can cause damage to myelin by releasing excitotoxins, such as glutamate.[61]

In most previous studies, HbA1c has been assessed, but Maccario *et al.* found that serum osmolality has a more important role than hyperglycaemia or hyponatremia, because the neurological manifestations of NKH do not develop in patients with normal serum osmolality. In addition, a rapid increase in blood glucose concentration, rather than prolonged hyperglycaemia, is considered to be more important in the pathogenesis of the condition. Rapid hyperglycaemia-induced diuresis creates a sudden steep gradient between the extracellular and intracellular compartments.[3] The two cases described herein were characterised by long-term symptoms, which suggests that a longer duration of symptoms may result in more severe neurological deficits.

Homonymous hemianopsia, aphasia, hemisensory defects, hemiparesis, hyperreflexia, and the Babinski sign, along with both simple and complex visual hallucinations, all suggest the presence of diffuse cortical or subcortical damage.[1]

Diagnostic investigations

Laboratory parameters

Patients with NKH have moderate-to-severe hyperglycaemia and high HbA1c levels, implying poor long-term glucose control, although an acute increase in blood glucose can be responsible for similar symptoms. In many cases, diabetes is diagnosed after the onset of these symptoms, and patient 1 was diagnosed as having diabetes mellitus after admission because of neurological symptoms. She showed a slight-to-moderate increase in serum osmolality, in the absence of circulating ketones. A mild-to-moderate electrolyte imbalance is also common, but other routinely measured biochemical and haematological parameters are usually normal, and CSF analysis does not reveal abnormalities[17,62].

Electroencephalography

In contrast to the generalised seizures that categorise hypoglycemia,[63] hyperglycaemia in general causes focal seizures,[64] which may be related to the presence of K-ATP channels in certain parts of neocortex.[65] EEG generally reveals focal epileptiform activity,[11,13,22,39] with sharp or spike wave activity apparent on the posterior cortical leads. Unilateral or bilateral, asynchronous or synchronous focal epileptiform discharges are most common in the occipital region, followed by the temporal and parietal regions. Patients can also develop EPC,[38,39] which is often characterised by continuous focal epileptic activity on EEG, and generalised or focal slowing is common. However, patients can also display normal electroencephalograms.

Visual evoked potential

Pattern-reversal visual evoked potential has been performed in a patient with visual seizures, and this shows a large unilateral P100 amplitude.[22,66]

Imaging findings

Brain computed tomography

Computed tomography (CT) typically does not show any changes; therefore, a diagnosis of NKH cannot be made using CT. Indeed, corroborative CT changes have not been identified in any of the reported cases, including when contrast-enhanced CT was used[7].

MRI

T1-weighted images do not show changes, but contrast-enhanced images often show a gyral or leptomeningeal enhancement pattern. T2 hypointensity in the subcortical posterior cerebral region is the most characteristic finding on MRI, and FLAIR images show similar hypointensity. In addition, contrast FLAIR has been shown to demonstrate enhancement patterns better than contrast T1. Diffusion-weighted images may or may not show restriction.[67] MR angiography does not show any stenosis or paucity of intracranial vessels. Most published cases have shown resolution of the T2 hypointensity on follow-up scans after few weeks or months, but a few have shown focal atrophy in the same region on follow-up scans.[16] A susceptibility-weighted imaging (SWI) sequence can show small hypointense foci that represent microhaemorrhages or the presence of gemistocytes.[24] In one of the present cases, there was diffusion restriction and a hypointense signal on FLAIR in the central pontine region in addition. Central pontine hyperintensity has also been reported in a patient with NKH, a hyperosmolar state, and EPC.[59] Because the present case featured hypointensity, as opposed to the pontine hyperintensity reported by Mao *et al.*[58],

osmosis and secondary demyelination likely played a role in the pathogenesis.

A comparison with the imaging findings that typify hyperglycaemic chorea may also be instructive. In patients with chorea, unenhanced T1-weighted images show hyperintensity in the basal ganglia region,[2] and most commonly in the putamen, followed by the caudate and globus pallidus, whereas T2-weighted images may feature hyper-,hypo-, or isointense signals.[68]

Shan *et al*. linked a hyperintense T1 signal to a layer of hydrated proteins inside the cytoplasm, which typifies gemistocytes. Stereotactic biopsy reveals abundant gemistocytes, which are swollen reactive astrocytes with a high protein content that are typically seen after an acute injury, and subsequently shrink.[69] According to Chu *et al*., patients with chorea and ballismus resulting from hyperglycaemia show normal gradient echo (GRE) images, whereas diffusion-weighted imaging (DWI) shows restricted diffusion, consistent with hyperviscosity, rather than petechial haemorrhages as the cause of the cytotoxic oedema and imaging findings.[70] Nevertheless, a few authors have suggested that greater paramagnetic deposition may be the cause of putaminal hypointensity on SWI images.[71]

Magnetic resonance spectroscopy (MRS)

It is advisable to perform MRS alongside routine sequences. In some previous studies, MRS showed large peaks corresponding to metabolites such as choline, myoinositol, and particularly creatine, but normal lipid, lactate, glucose, and ketone peaks,[25] which is indicative of hyperosmolality.[72] In a few previously reported cases, the N-acetylaspartate (NAA) peak was small,[22,66] which is suggestive of cortical laminar necrosis and neuronal loss. A small NAA peak may also suggest that cortical laminar necrosis is the cause of the gyral enhancement on T1 contrast and also implies irreversible damage.

Functional MRI

Alessandra *et al*. showed a positive blood oxygen-dependent (BOLD) signal in Brodmann area 18 (the visual association area) during continuous EEG[8] using blood oxygen level-dependent contrast imaging, which utilises the magnetic properties of haemoglobin. This method is sensitive to blood flow changes induced by metabolic or neuronal activity.

Fluorodeoxyglucose-positron emission tomography

Hypermetabolism in the right occipital cortex has previously been documented in a patient with hyperglycaemia-induced hemianopia and T2 hypointensity,[72] and this had resolved 3 months later.

Single-photon emission computerised tomography

Tc99m-D,L-hexamethylene-propyleneamine oxime or I123-N-isopropyl-iodoamphetamine-single-photon emission computerised tomography shows hyperperfusion during ictal activity, as confirmed using simultaneous EEG, but hypoperfusion during the interictal phase or after the symptoms resolve.[15,22,23]

Differential diagnosis and management

In patients with diabetes and visual defects or partial seizures, it is important to consider NKH. Many patients with NKH who present with cortical symptoms are diagnosed as being diabetic upon admission.[73,74] Thus, a diagnosis could be missed if a CT examination alone is performed, and this fails to show any

abnormalities. The most characteristic MRI feature is T2 hypointensity, predominantly in the posterior cerebrum. Other causes of T2 hypointensity are early stroke, metastasis, meningitis, encephalitis, multiple sclerosis, and moyamoya disease, but these causes can be ruled out on the basis of clinical presentation, physical examination, blood glucose and HbA1c, CSF examination, and the EEG and MRI findings.[75] Early detection is the key to the resolution of symptoms and the prevention of vision loss. In addition, the immediate initiation of insulin infusion, fluid and rehydration therapy, and the correction of electrolyte abnormalities are important.

Discussion

It can be inferred from the literature that abnormal circulating glucose concentrations, whether hypoglycaemia or hyperglycaemia, tend to have effects on the posterior cerebral region, and especially on the parieto-occipital region.[76] Metabolic derangement leading to a GABA shunt or the activation of kATP channels in the posterior neocortex might also be responsible for focal or occipital seizures.

Diffusion restriction can be caused by hyperviscosity, because it also characterises hyperglycaemia-induced hemichorea hemiballismus.[69] Nevertheless, plain T1-weighted images do not show changes in the posterior cerebral region resulting from hyperglycaemia, in contrast to the hyperintense signal in the basal ganglia that typifies hemichorea hemiballismus. In addition, the findings of T2 and FLAIR are dissimilar in these two conditions, which suggests differing pathophysiology, even though the aetiology of both conditions is NKH.

Although previous case reports have described only transient symptoms associated with posterior cerebral defects, both of the present cases featured irreversible vision loss, which can be explained by the identification of cortical laminar necrosis on the initial scan and focal gliosis on follow-up imaging. The presence of cortical laminar necrosis is consistent with the low NAA concentration identified using spectroscopy and the gyral enhancement pattern on contrast MRI. One of the most important reasons for irreversible visual loss is likely to have been late presentation, implying long-term metabolic derangement and neuronal hyperexcitability. The only predictor of seizure control in patients with NKH identified to date is the frequency of seizures.[77] The patients reported herein had been experiencing occipital seizures over a long period of time, which is likely to explain the irreversible loss of vision.

A diagnosis of cortical lesions secondary to NKH may be delayed because of a lack of awareness of the various manifestations, and may lead to inadequate management and a lack of full recovery. Therefore, it is important to perform a detailed clinical evaluation and brain MRI in patients with an abnormal blood glucose concentration and visual or other cortical symptoms.

It is possible that many of the cases reported previously might have had some irreversible cortical vision loss or field defects. However, because visual field testing was not performed during the monitoring of these patients, it is quite likely that mild-to-moderate unilateral field defects were missed.

In summary, the symptoms of NKH are referable to the posterior cerebral cortex. Various types of focal seizures can be seen clinically, and occipital seizures and various visual defects are the most common symptoms, with irreversible vision loss being possible. The disease is characterised by specific MRI findings, and the differences in the MRI findings in the basal ganglia *versus* the posterior cerebral region suggest that the pathophysiology of the epileptic

manifestations of NKH and hemichorea hemiballismus differs.

Declaration of conflicting interest

The author declares that there is no conflict of interest.

Ethics statement

The present study was approved by the institutional ethics committee of Sir Jamshedjee Jeejeebhoy Hospital Mumbai, Jupiter Hospital. Written informed consent was obtained from the patients for their participation in the study, and for publication of the case reports and the accompanying images.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sector.

ORCID iD

Dhanashree Peddawad https://orcid.org/0000-0003-3764-2974

References

1. Guisado R and Arieff AI. Neurologic Manifestations of Diabetic Comas: Correlation with Biochemical Alterations in the Brain. *Metabolism* 1975: 24: 665–679.
2. Lai PH, Tien RD, Chang MH, et al. Chorea-Ballismus with Nonketotic Hyperglycemia in Primary Diabetes Mellitus. *AJNR Am J Neuroradiol* 1996; 17: 1057–1064.
3. Maccario M. Neurological Dysfunction Associated with Nonketotic Hyperglycemia. *Arch Neurol* 1968; 19: 525–534.
4. Tiamkao S, Pratipanawatr T, Nitinavakarn B, et al. Seizures in nonketotic hyperglycaemia. *Seizure* 2003; 12: 409–410.
5. Gagnier JJ, Kienle G, Altman DG, et al; CARE Group. The CARE guidelines: consensus-based clinical case reporting guideline development. *Headache* 2013; 53: 1541–1547.
6. Peddawad D and Nagendra S. Irreversible cortical blindness in nonketotic hyperglycemia. Case of the week. *Am J Neuroradiol* 2018; 29 March.
7. Harden CL, Rosenbaum DH and Daras M. Hyperglycemia Presenting with Occipital Seizures. *Epilepsia* 1991; 32: 215–220.
8. Del Felice A, Zanoni T, Avesani M, et al. EEG f-MRI coregistration in nonketotic hyperglycemic occipital seizures. *Epilepsy Res* 2009; 85: 321–324.
9. Gupta A, Rao VA, Pandian DG, et al. Cortical blindness with absent visually evoked potential in non-ketotic hyperglycemia. *Indian J Ophthalmol* 2008; 56: 88–89.
10. Goto H, Kumagai T and Momozaki N. MRI Findings of Occipital Seizures in Non-Ketotic Hyperglycemia. *Intern. Med* 2011; 50: 367–368.
11. Lavin PJ. Hyperglycemic hemianopia: a reversible complication of non-ketotic hyperglycemia. *Neurology* 2005; 66: 616–619.
12. Freedman KA and Polepalle S, et al. Transient Homonymous Hemianopia and Positive Visual Phenomena in Nonketotic Hyperglycemic Patients. *Am J Ophthalmol* 2004; 137: 1122–1124.
13. Moien-Afshari F and Téllez-Zenteno JF. Occipital seizures induced by hyperglycemia: A case report and review of literature. *Seizure* 2009; 18: 382–385.
14. Putta SL, Weisholtz D and Milligan TA. Occipital seizures and subcortical T2 hypointensity in the setting of hyperglycemia. *Epilepsy Behav Case Rep* 2014; 2: 96–99.
15. Sasaki F, Kawajiri S, Nakajima S, et al. Occipital lobe seizures and subcortical T2 and T2* hypointensity associated with nonketotic hyperglycemia: a case report *J Med Case Rep* 2016; 10: 228.
16. Seo DW, Na DG, Na DL, et al. Subcortical hypointensity in partial status epilepticus associated with nonketotic hyperglycemia. *J Neuroimaging* 2003; 13: 259–263.
17. Raghavendra S, Ashalatha R, Thomas SV, et al. Focal neuronal loss, reversible subcortical focal T2 hypointensity in seizures with a nonketotic hyperglycemic hyperosmolar state. *Neuroradiology* 2007; 49: 299–305.
18. Duncan MB, Jabbari B and Rosenberg ML. Gaze-Evoked Visual Seizures in Nonketotic Hyperglycemia. *Epilepsia* 1991; 32: 221–224.

19. Fletcher P and Pereira A. Visual hallucination of coloured numbers secondary to hyperglycaemia. *BMJ Case Rep* 2011; 2011: bcr0820103268.
20. Richardson S and Shah SK. Nonketotic Hyperglycemia Induced Occipital Lobe Seizures: a case report. *Marshall J Med* 2018; 4: article 8.
21. Sowa MV and Pituck S. Prolonged Spontaneous Complex Visual Hallucinations and Illusions as Ictal Phenomena. *Epilepsia* 1989; 30: 524–526.
22. Wang CP, Hsieh PF, Chen CC, et al. Hyperglycemia with occipital seizures: images and visual evoked potentials. *Epilepsia* 2005; 46: 1140–1144.
23. Hung WL, Hsieh PF, Lee YC, et al. Occipital lobe seizures related to marked elevation of hemoglobin A1C: Report of two cases. *Seizure* 2010; 19: 359–362.
24. Conduit C, Harle R and Jones DL. Nonketotic hyperglycaemia causing occipital seizures and persistent microhaemorrhages: mechanisms of focal deficits in hyperglycaemia. *Intern Med J* 2016; 46: 634–635.
25. Guez A, Obadia M, Lafitte F, et al. Magnetic resonance spectroscopy findings in a case of hyperglycaemic hemianopia. *Rev Neurol (Paris)* 2010; 166: 737–740.
26. Johnson SF and Loge RV. Palinopsia due to nonketotic hyperglycemia. *West J Med* 1988; 148: 331–332.
27. Lavin PJM. Pupillary oscillations synchronous with ictal nystagmus. *Neuro-ophthalmology* 1986; 6: 113–116.
28. Lopes R and Pereira BD, et al. Delirium and Psychotic Symptoms Associated with Hyperglycemia in a Patient with Poorly controlled Type 2 Diabetes Mellitus. *Innov Clin Neurosci* 2018; 15: 30–33.
29. Maharajh HD and Konings M. Fire Setting in a Patient with Hyperglycaemic Delirium. *J Forensic Sci* 2006; 51: 940.
30. Thomas P, Zifkin B, Migneco O, et al. Nonconvulsive status epilepticus of frontal origin. *Neurology* 1999; 52: 1174–1183.
31. Huang LC, Ruge D, Tsai CL, et al. Isolated Aphasic Status Epilepticus as Initial Presentation of Nonketotic Hyperglycemia. *Clinical EEG and Neuroscience* 2014; 45: 126–128.
32. Lee JH, Kim YA, Moon JH, et al. Expressive aphasia as the manifestation of hyperglycemic crisis in type 2 diabetes. *Korean J Intern Med* 2016; 31: 1187–1190.
33. Manfordg M, Fuller GN and Wade JP. "Silent diabetes": non-ketotic hyperglycaemia presenting as aphasic status epilepticus. *J Neurol Neurosurg Psychiatry* 1995; 59: 99–104.
34. Melek ÇA and Mert MA. Hyperglycemia-induced Nonconvulsive Status Epilepticus (NCSE) and Cranial Magnetic Resonance Imaging Results: A Case Presentation. *Epilepsia* 2017; 23: 84–90.
35. Pro S, Randi F, Pulitano P, et al. Non-convulsive status epilepticus characterized exclusively by a language disorder induced by non-ketotic hyperglycemia. *Epileptic Disord* 2011; 13: 193–193.
36. Tetsukaa S, Yasukawa N, Tagawa A, et al. Isolated Aphasic Status Epilepticus as a Manifestation Induced by Hyperglycemia without Ketosis. *J Neurol Res* 2016; 6: 85–88.
37. Kutluay E, Pakoz B, Yuksel A, et al. Nonconvulsive status epilepticus manifesting as pure alexia (alexia without agraphia). *Epilepsy Behav* 2007; 10: 626–628.
38. Cokar O, Aydin B and Ozer F. Non-ketotic hyperglycaemia presenting as epilepsia partialis continua. *Seizure* 2004; 13: 264–269.
39. Singh BM and Strobos RJ. Epilepsia Partialis Continua Associated with Nonketotic Hyperglycemia: Clinical and Biochemical Profile of 21 Patients. *Ann Neurol* 1980; 8: 155–160.
40. Wang X. Nonketotic hyperglycemia-related epileptic seizures. *Chin Neurosurg J* 2017; 3: 16.
41. Gabor AJ. Focal seizures induced by movement without sensory feedback mechanisms. *Electroencephalogr Clin Neurophysiol* 1974; 36: 403–408.
42. Hennis A, Corbin D and Fraser H, Focal seizures and non-ketotic hyperglycaemia. *J Neurol Neurosurg Psychiatry* 1992; 55: 195–197.
43. Suárez-Moro R, Salas-Puig J, Amorín M, et al. SPECT findings in reflex seizures

induced by movement in non-ketotic hyperglycemia. *Epileptic Disord* 1999; 1: 199–201.
44. Neufeld MY, Blumen SC and Nisipeanu P. Lingual Seizures. *Epilepsia* 1988; 29: 30–33.
45. Ozer F, Mutlu A and Ozkayran T. Reflflflex epilepsy and non-ketotic hyperglycemia. *Epileptic Disord* 2003; 5: 165–168.
46. Siddiqi ZA, Vanlandingham KE and Husain AM. Reflflflex seizures and non-ketotic hyperglycemia: an unresolved issue. *Seizure* 2002; 11: 63–66.
47. Tedrus Gloria MA and Fonseca LC. Movement-induced visual seizures in non-ketotic hyperglycemia. *Arq Neuropsiquiatr* 1995; 53: 281–283.
48. Tiras R, Mutlu A, Ozben S, et al. Forced eye closure-induced reflex seizure and non-ketotic hyperglycemia. *Ann Saudi Med* 2009; 29: 313–315.
49. Venna N and Sabin TD. Tonic Focal Seizures in Nonketotic Hyperglycemia of Diabetes Mellitus. *Arch Neurol Aug* 1981; 38: 512–514.
50. Wu YJ, Tsai JJ and Huang CW. Nonketotic hyperglycemia-related reflex epileptic seizures induced by Mah-Jong playing. *Epilepsy Behav* 2010; 19: 533–535.
51. Treiman DM. GABAergic mechanisms in epilepsy. *Epilepsia* 2001; 42: 8–12.
52. Yamada K, Ji JJ, Yuan H, et al. Protective role of ATP-sensitive potassium channels in hypoxia-induced generalized seizure. *Science* 2001; 292: 1543–1546.
53. Rivera-Aponte DE, Méndez-González MP, Rivera-Pagán AF, et al. Hyperglycemia Reduces Functional Expression of Astrocytic Kir4.1 Channels and Glial Glutamate Uptake. *Neuroscience* 2015; 310: 216–223.
54. Kim DW, Moon Y, Gee Noh H, et al. Blood-brain Barrier Disruption is Involved in Seizure and Hemianopsia in Nonketotic Hyperglycemia. *Neurologist* 2011; 17: 164–166.
55. Iwata A, Koike F, Arasaki K, et al. Blood brain barrier destruction in hyperglycemic chorea in a patient with poorly controlled diabetes. *J Neurol Sci* 1999; 163: 90–93.
56. Warach S and Latour LL. Evidence of Reperfusion Injury, Exacerbated by Thrombolytic Therapy, in Human Focal Brain Ischemia Using a Novel Imaging Marker of Early Blood–Brain Barrier Disruption. *Stroke* 2004; 35: 2659–2661.
57. Stevens CJ and Heran MK. The many faces of posterior reversible encephalopathy syndrome. *Br J Radiol* 2012; 85: 1566–1575.
58. O'Malley G, Moran C, Draman MS, et al. Central pontine myelinolysis complicating treatment of the hyperglycaemic hyperosmolar state. *Ann Clin Biochem* 2008; 45: 440–443.
59. Mao S, Liu Z and Ding M. Central pontine myelinolysis in a patient with epilepsia partialis continua and hyperglycaemic hyperosmolar state. *Ann Clin Biochem* 2011; 48: 79–82.
60. Uchino A, Yuzuriha T, Murakami M, et al. Magnetic resonance imaging of sequelae of central pontine myelinolysis in chronic alcohol abusers. *Neuroradiology* 2003; 45: 877–880.
61. Ashrafian H and Davey P. A review of the causes of central pontine myelinosis: yet another apoptotic illness? *Eur J Neurol* 2001; 8: 103–109.
62. Stayman A, Abou-Khalil BW, Lavin P, et al. Homonymous hemianopia in nonketotic hyperglycemia is an ictal phenomenon. *Neurol Clin Pract* 2013; 3: 392–397.
63. Monami M, Mannucci E, Breschi A, et al. Seizures as the only clinical manifestation of reactive hypoglycemia: a case report. *J Endocrinol Invest* 2005; 28: 940–941.
64. Stahlman GC, Auerbach PS and Strickland WG. Neurologic manifestations of nonketotic hyperglycemia. *J Tenn Med Assoc* 1988; 81: 77–80.
65. Miki T and Seino S. Roles of KATP channels as metabolic sensors in acute metabolic changes. *J Mol Cell Cardiol* 2005; 38: 917–925.
66. Donat A, Guilloton L, Bonnet C, et al. Partial visual seizures induced by non-ketotic hyperglycemia: magnetic resonance imaging and visual evoked potential descriptions. A study of two cases reports with radiologic and electrophysiologic abnormalities. *Rev Neurol (Paris)* 2013; 169: 154–161.
67. Lee EJ, Kim KK, Lee EK, et al. Characteristic MRI findings in hyperglycaemia induced seizures: diagnostic value of

contrast-enhanced fluid-attenuated inversion recovery imaging. *Clin Radiol* 2016; 71: 1240–1247.
68. Oh SH, Lee KY, Im JH, et al. Chorea associated with non-ketotic hyperglycemia and hyperintensity basal ganglia lesion on T1-weighted brain MRI study: a meta-analysis of 53 cases including four present cases. *J Neurol Sci* 2002; 200: 57–62.
69. Shan DE, Ho DM, Chang C, et al. Hemichorea hemiballism: an explanation for MR signal changes. *Am J Neuroradiol* 1998; 19: 863–870.
70. Chu K, Kang DW, Kim DE, et al. Diffusion-weighted and gradient echo magnetic resonance findings of hemichorea hemiballismus associated with diabetic hyperglycemia. *Arch Neurol* 2002; 59: 448–452.
71. Cherian A, Thomas B, Baheti NN, et al. Concepts and Controversies in Nonketotic Hyperglycemia-Induced Hemichorea: Further Evidence from Susceptibility-Weighted MR Imaging. *J Magn Reson Imaging* 2009; 29: 699–703.
72. Brandao LA and Domingues RC. *MR Spectroscopy of the brain*. Philadelphia: Lippincott Williams and Wilkins; 2004.
73. Omar HR, El-Khabiry E and Vaughan S. Seizure as the first presentation of diabetes mellitus. *Ther Adv Endocrinol Metab* 2012; 3: 175–177.
74. Martínez MD and Megías SM. Occipital seizures with electroencephalographic alterations as the initial manifestation of diabetes mellitus. *Endocrinol Nutr* 2009; 56: 458–460.
75. Lee JH, Na DG, Choi KH, et al. Subcortical low intensity on MR images of meningitis, viral encephalitis, & leptomeningeal metastasis. *AJNR Am J Neuroradiol* 2002; 23: 535–542.
76. Efron D, South M, Volpe JJ, et al. Cerebral injury in association with profound iatrogenic hyperglycemia in a neonate. *Eur J Paediatr Neurol* 2003; 7: 167–171.
77. Tiamkao S, Janon C, Sawanyawisuth K, et al. Prediction of seizure control in non-ketotic hyperglycemic induced seizures. *BMC Neurology* 2009; 9: 61.