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

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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.

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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 visual 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
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
complex visual hallucinations, oscillopsia, metamorphopsia, and pallinopsia have been recorded.

Irreversible visual loss (Table 4)

Irreversible bilateral cortical blindness (Case 1), irreversible hemianopia (Case 2), and permanent changes in colour perception 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 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.
behavioural arrest or abnormalities such as psychosis or delirium. Cognitive seizures, such as aphasia, aphasic status epilepticus, and alexia; somatosensory seizures; and epilepsy partialis continua (EPC) can also be observed. Thus, focal seizures that involve normal awareness or impaired awareness, and reflex seizures 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 $\gamma$-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. In addition, the utility of a ketogenic diet for seizure control may indicate that ketones help prevent seizures.

ATP-sensitive potassium channels are also thought to be responsible for neuronal hyperexcitability and the precipitation of seizures in hyperglycemia. Astrocytes cultured in a high-glucose environment show low mRNA expression of the Kir4.1 potassium channel, but a restoration of the normal glucose expression 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       | Contrast brain CT normal in two cases                                              | 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  |
|                    | Left-sided homonymous hemianopia                                           | Old lacunar infarcts in one case                                                  |                                                   |                                      | 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                                |
| Raghavendra et al., 2007 | Complex partial or focal motor seizures, homonymous hemianopia, headache | Focal subcortical hypointensity and focal gyral hyperintensity on T2 FLAIR        | Left parieto-temporal spike wave                  | 17.4–18.0, 312–317 mOsm/L            | 2) One patient had permanent difficulties distinguishing shades of the same colour |
|                    |                                                                         | Contrast enhancement and DWI restriction in one patient                            | Discharges, normal in one patient                 |                                      | Of four patients, two had visual symptoms and the other two only partial seizures |
| 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-MRI |
| 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 I123-N-isopropyl-iodoamphetamine showed hyperperfusion in the dominant occipital lobe |

(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.

**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 Intercital 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 |
| 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)
| Reference          | Symptoms                                                                 | Imaging findings | EEG                               | Blood glucose concentration (mmol/L) | Additional remarks                                                                                                                                                                                                 |
|--------------------|---------------------------------------------------------------------------|------------------|----------------------------------|--------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Fletcher et al., 2011 | Episodic complex visual hallucinations                                    | Brain MRI normal | Left occipital seizure activity   | 37.0                                 | Confusion: patient not able to recognise their relatives                                                                                                                                                               |
|                     | Confusion, visual hallucinations (brightly coloured numbers) in the right visual field, right homonymous hemianopia |                  |                                  |                                      |                                                                                                                                                                                                                  |
| 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.
| 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                                  | 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, oscillosia, 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  | 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 | 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; TI 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 hyponatraemia, 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 TI 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.
| 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   | 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% | EEG findings and clinical features were suggestive of non-convulsive status | Impaired fluency, repetition in naming and comprehension |
| 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% |                                                                                                             |
| Syuichi et al., 2016 | Isolated persistent mixed aphasia                           | Left frontotemporal         | MRI showed mild cerebral atrophy       | Diffuse continuous theta to waves mixed with epileptiform discharges | Normal                     | 30.8 | 15.2 g% | 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% | 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% |                                                                                                             |

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        | Non-ketotic         | Complete | Alert, oriented, continuous euphoria and disinhibition, attention deficit, anosognosia, perseveration |
|                            |                     |                 |                          | temporal discharges          | hyperglycaemia        |          |                                                                                  |
|                            |                     |                 |                          | Left frontal recurrent      |                      |          |                                                                                  |
|                            |                     |                 |                          | fast activity               |                      |          |                                                                                  |
|                            |                     |                 |                          | Normal background           |                      |          |                                                                                  |

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 |
|                            | History of behavioural abnormality                 |                                      |          |                                                                                  |
|                            | Stopped treatment for diabetes 6 months prior to symptoms developing |                                      |          |                                                                                  |
| Lopes et al., 2018         | History of behavioural abnormality                 | 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.
might lead to excitotoxic damage to neurons.\textsuperscript{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.\textsuperscript{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 \textit{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.\textsuperscript{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,\textsuperscript{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 8. Non-convulsive status epilepticus/alexia without agraphia documented. |
|---|---|---|---|---|---|
| Reference | Symptoms | Imaging findings | EEG | Blood glucose concentration | Recovery |
| Kutluay et al., 2007 | Right homonymous hemianopia despite recognising individual letters and writing normally | Cortical swelling and hyperintensity over the left temporoparietal region, involving the middle occipital and middle temporal gyri on FLAIR sequences | Electrographic seizures arising from the left temporoparietal region, lasting 150–220 seconds | 37.6 mmol/L | 3–4 days |
| Kutluay et al., 2007 | Unable to read written words, | | | | |
| Kutluay et al., 2007 | No other neurological defects | | | | |

EEG, electroencephalography; FLAIR, fluid-attenuation inversion recovery; MRI, magnetic resonance imaging.
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 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 CSF normal               | Few 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 semi-rhythmic 3–5 Hz activity | 26.6 6 days CSF normal               | Few 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 17.8–37.7 mmol/L   | Few days | Termed kinesigenic seizures |

(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 | 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 senso-rum 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)
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 be involved because of its tightly packed grey and white fibres. However, the basal ganglia, thalamus, and cortico-white matter junction also have tightly packed grey and white fibres. Oedema would lead to the compression of nerve fibres, which may cause demyelination.

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 |

In most previous studies, HbA1c has been assessed, but Maccario et al. found that serum osmolality has a more important role than hyperglycaemia or hyponatraemia. 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. This may result in more severe neurological deficits. Homonymous hemianopia, aphasia, and the Babinski sign, along with both simple and complex visual hallucinations, all suggest the presence of diffuse cortical or subcortical damage.
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\textsuperscript{17,62}.

Electroencephalography

In contrast to the generalised seizures that categorise hypoglycemia,\textsuperscript{63} hyperglycaemia in general causes focal seizures,\textsuperscript{64} which may be related to the presence of K-ATP channels in certain parts of neocortex.\textsuperscript{65} EEG generally reveals focal epileptiform activity,\textsuperscript{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,\textsuperscript{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.\textsuperscript{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\textsuperscript{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.\textsuperscript{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 a few weeks or months, but a few have shown focal atrophy in the same region on follow-up scans.\textsuperscript{16} A susceptibility-weighted imaging (SWI) sequence can show small hypointense foci that represent microhaemorrhages or the presence of gemistocytes.\textsuperscript{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.\textsuperscript{59} Because the present case featured hypointensity, as opposed to the pontine hyperintensity reported by Mao et al.\textsuperscript{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. 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. 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. 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.

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.

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