CASE REPORT

Hypoxic ischemic brain injury with status myoclonus in a case with post-operative massive pulmonary thromboembolism: A diagnostic and therapeutic challenge

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ABSTRACT

Thromboembolic event is an important and widely regarded risk factor, influencing the outcome and overall survival in post-operative cases with second highest association with gynaecological surgeries. Here we report a 52 years old female who underwent total laparoscopic hysterectomy with bilateral salpingo-oophorectomy (TLH + BSO) presented to our emergency in unconscious and intubated state on her post-operative day-1 with cardiorespiratory failure. Based on the immediate investigations after successful resuscitation, an initial diagnosis of massive pulmonary thromboembolism was made following supportive and conservative management. Interestingly on subsequent days she started to display episodic non-rhythmic symmetric myoclonic jerks persisting for seconds to minutes; resembling 'post-hypoxic' or 'post-anoxic' status myoclonus due to hypoxic ischemic brain injury. Further neuro-electrophysiological examination revealed rhythmic well-formed delta activity on both sides symmetrically with a transformation into theta activity with forward displacement on subsequent days, bilaterally over the same areas. Later on, magnetic resonance imaging with magnetic resonance-spectroscopic findings also corroborated to hypoxic ischemic brain injury related changes over bilateral basal ganglia mostly in caudate nucleus. Post operative venous thromboembolism is a major clinical challenge and a subject of constant intensive care yet the neurological sequalae of such event is given less priority despite of its major contribution on overall prognostic and survival index.

KEYWORDS: TLH + BSO; Embolism; PTE; HIBI; HIE; Myoclonus; EEG; MRS

BACKGROUND

Laparoscopic procedures have been considered relatively safer with less post-operative complications in comparison to traditional laparotomy [1]. So far, a very few cases have been reported to be associated with post-operative massive pulmonary thromboembolism (PTE) with circulatory collapse and venous thromboembolism (VTE). Cardiogenic shock in setting of cardiorespiratory arrest or arrythmia in massive PTE is a challenging problem and the outcome mostly depends upon the timely resuscitation. The neurological sequelae of post anoxic or hypoxic episodes remain under-surfaced and unappreciated for a significant time afterwards; ranging from a spectrum of cognitive deficits due to damages in multiple cortical layers, hippocampus and watershed areas to a plethora of movement disorders, seizure, and autonomic dysfunction [2]. So higher metabolic brain areas which are mostly vulnerable to hypoxic insults heighten the challenges of a linear and prospective recovery in these patients [2]; especially more with disorder of consciousness (DOC) and arousal impairments [3]. As cerebral hypoxia remains an independent factor for unfavourable outcome, an intensive neurological monitoring with an optimally synchronised management strategy in critical care setting remains a diagnostic and therapeutic hurdle. Noteworthy to mention pure hypoxic injury may have a better prognosis and outcome in comparison to hypoxic ischemic brain injury (HIBI) in cardiorespiratory arrest which predominantly follows a 'two hit' pathological progression, limiting outcome and creating a contrast with other critical care diseases [4].

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CASE PRESENTATION

A 52 years old female who underwent TLH + BSO presented to emergency department in unconscious and intubated state with mechanical ventilation on her post operative day-1 after being referred from another centre. Following successful resuscitation of cardio-respiratory arrest, an initial diagnosis of massive PTE was made, based on emergency bedside 2D-Echocardiography & ECG findings. Vitals were deranged with hypotension (<90/60 mmHg), extreme tachycardia (140/min) and tachypnoea (30/min). On general survey there was anaemia with bilateral(B/L) pedal pitting edema. Physical examination revealed B/L vesicular breath sound on lung auscultation, S1 and S2 were audible in cardiovascular examination and sluggish peristaltic sound was noted on auscultation with soft abdomen on palpation. Pupillary dilatation with anisocoria and poor plantar response with glasgow coma scale (GCS) of E1V(T)M1 were also assessed. Initially PaO_2/FiO_2 ratio was 65.2 with Barthel index (BI) score of 20 points (very dependent) were recorded. Her revised coma recovery scale (CRS-R) score was 2/23. Within 5 hours following successful resuscitation from cardio-respiratory arrest, two episodes of brief myoclonic jerks occurred in an interval of five minutes along with subsequent four episodes, consecutively half an hour after the former incident.

On initial 4-days following admission there was no spontaneous eye opening and bilaterally symmetric with positive pupillary response of 3-mm was also recorded during PERRLA assessment. Extraocular movement showed intermittent conjugate downward gaze (ocular bobbing) with bilaterally positive corneal reflex. Oculocephalic response was also evident. GCS of E1V(T)M3 remained same during this period. On applying pain stimuli there was no response in upper limbs but flexor withdrawal was noted in lower limbs with poor plantar response. During the meantime, patient was kept on ventilator support with assisted volume control (VC-AC) mode.

On subsequent days from day-5th till day-9th following admission facial twitching with lip smacking and occasional spontaneous eye opening were noted with consistent ocular bobbing. GCS improvement was also evident. Nerve conduction study (NCS) of all four limbs was done on 7th day to assess limb weakness as well as to undertake possible preventive measures from any critical illness neuropathy. Subsequently patient was switched to pressure support ventilation (PSV) till day-10. On the 10th day tracheostomy was performed and facial grimacing was also observed on the same day. From 10th day onwards following admission, spontaneous eye movement was evident GCS-E4V(T)M4] with overall improvement. On day-11th, patient was successfully weaned off from PSV to Ventilator-assisted continuous positive airway pressure (V-CPAP) with continuation for the next subsequent 2 days with optimum maintenance on low FiO_2. T-piece trial has been performed with low oxygen support from next day & subsequently on atmospheric oxygen (Figure 1C). On day 15th she was stepped down to general ward for follow-up observation.

DIAGNOSTICS & ASSESSMENT

Transthoracic 2D-echocardiography (Figure 2a) showed hugely dilated right atrium (RA) and right ventricle (RV) with compensatory left ventricular (LV) dysfunction. RV systolic dysfunction sparing the apex part (McConnell's sign), dilated pulmonary artery (PA), low-pressure tricuspid regurgitation (TR) and IVC diameter of 26mm with <30% respiratory collapsibility was also noticed. 12-lead ECG showed sinus tachycardia, new onset right bundle branch block (RBBB), T-wave inversion in V1-V4 chest leads, P-pulmonale and S1Q3T3 pattern (McGinn White sign). Wells-score for PE classified the patient under high-risk group (9-points) along with simplified-pulmonary embolism severity index (s-PESI) score of 3-points (higher severity). Additionally, serum D-dimer with fibrinogen degradation product (FDP) were also done which came out to be significantly high i.e., 32.5 mg/L & 1600 ng/ml respectively. During subsequent 2 days right RV systolic function gradually improved with tricuspid annular plane systolic excursion (TAPSE) values of 13 & 21mm and pulmonary arteriolar pressure (PAP) of 40 & 27mmHg respectively with normalizing IVC diameter and respiratory collapsibility on follow-up echocardiography (Figure 1a). LV function improved gradually with increased systolic ejection fraction (EF) on the following day after admission with repeat ECG findings of T-wave inversion in chest leads from V1-V4 & S-wave dipping in lead-1(Figure 2b). Initial NCCT was done in order to rule out any underlying intra-cranial haemorrhage (ICH) and follow-up reports did not show any identifiable abnormalities (Figure 3a). Serum neuron specific enolase (NSE) on day 5th following admission was found significantly heightened (25.7 ng/ml). NCS revealed distal axonal & demyelinating type of motor variant polyradiculoneuropathy involving all four limbs, suggestive of 'critical illness neuropathy'. Following multiple brief episodes of bilaterally non-rhythmic myoclonic jerks, an initial EEG was performed using 10-20 international system which revealed rhythmic well-formed delta activity of 3-4 cycles/sec on both sides symmetrically. Follow-up EEG revealed rhythmic well-formed theta activity (5-7 cycles/sec) on both sides, symmetrically over parieto-occipital areas with forward displacement on subsequent days (Figure 3b). MRI was planned accordingly but could not be performed initially due to the criticality of the patient. Electrical activity started to normalize gradually from day 11th proportionately with overall neurocognitive improvement. On due course D-dimer level decreases gradually (Figure 1b). Arterial blood gas (ABG) was performed daily to maintain pO_2 level by optimizing external oxygen in a minimal range (Table-2). Upon significant improvement MRI with MR-spectroscopy was performed which revealed subtle FLAIR hyperintensity involving bilateral basal ganglia mostly in caudate nucleus & ill-defined areas in bilateral cerebral hemisphere without any significant diffusion restriction, suggesting progressive sequelae of hypoxic ischaemic encephalopathy (Figure 4b). On MR spectroscopy there was reduction of N-acetylaspartate (NAA)-peak with increased lactate peak in bilateral basal ganglia. Mild diffuse increase in lactate-peak was also seen in multiple cortical areas; evidentially corroborating with HIE related changes (Figure 4a).

Brain stem evoked response audiometry (BERA) test revealed normal hearing threshold level bilaterally with an impression of normal retro-cochlear region up-to the lateral lemniscus level & the firing of the neural impulses at the cochlea is reaching up-to the lateral lemniscus level. Oto acoustic emission (OAE) was pass/present in all three tested frequencies (2000, 3000 & 4000 Hz) bilaterally.

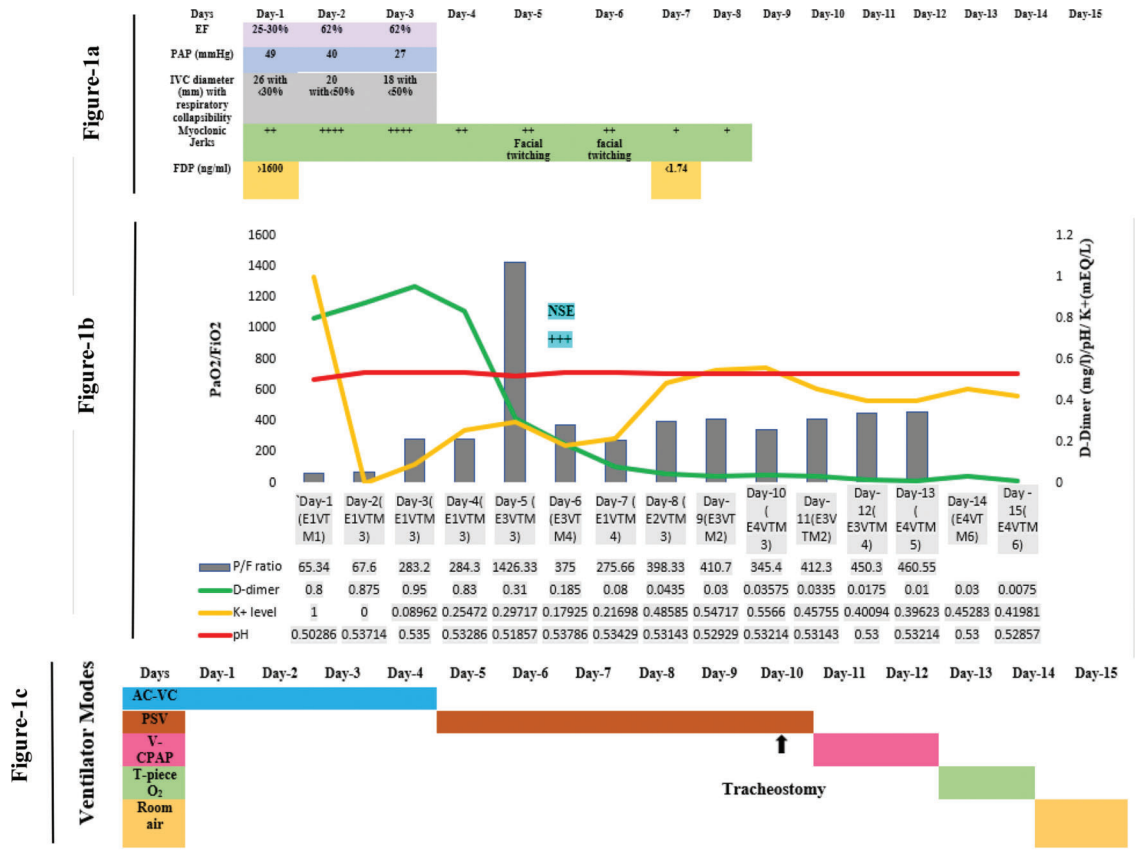

Fig. 1. Overall patient's time line with GCS status: (a)- Initial and follow-up 2D-Echocardiographic paramters, FDP(ng/ml), and frequncy of myoclonic jerks. (b)- Variabilites in bio-physical(PaO2/FiO2 ratio) and bio-chemical parameters[D-dimer(mg/l), K+(mEq/L), pH(Log-H+)] with patient's progressing timeline. Mean and maximun values of D-dimer (mg/l), K+(mEq/l), and pH have been scaled between **0**(as mean) and **1**(as maximum). In case of K+, identified serum level of 2.67 has been considered minimum and 4.79 has been considered as maximum. (c)- Alterations in ventialtor support modes throughout the ICU admission phase.

TREATMENT & INTERVENTION

On suspecting massive PTE with circulatory collapse, patient was put on vasopressor support and injectable unfractioned heparin (UFH)-5000 units intra-venous (I/V) was given immediately following continuous infusion at the rate of 2500 units/hr. Thrombolysis was done with off-label dose of injectable Alteplase-50mg I/V (Given over 1-hour) [5]. Injectable Fondaparinux was started subcutaneously (s/c) as a prophylactic measure from 3rd-7th day following administration of injectable Enoxaparin(s/c) on 2nd day after admission. Severe metabolic acidosis was corrected with injectable $NaHCO_3$(I/V) loading dose & by giving infusion. Injectable Levetiracetam was started immediately after myoclonic jerks following administration of injectable Lorazepam & injectable Midazolam. Broad spectrum antibiotics started eventually and was changed accordingly upon considering seizure threshold and culture-sensitivity reports. Injectable Piracetam was given prophylactically from 3rd day following infusion along with injectable Mannitol. Mannitol was continued for the following 7 days.

Injectable Fosphenytoin I/V was started & continued for 5 days following a loading dose on day-7th. Therapeutic drug monitoring (TDM) in serum for phenytoin was done on 11th day which came out 12.6 mcg/ml and the patient was switched to tablet form of phenytoin & syrup form of Levetiracetam. The anticoagulants were withheld from day 9^{th} following sequential compression devices (SCD) of lower limbs with a single administration of injectable Enoxaparin s/c on day 8^{th}. Tracheostomy was performed on day 10th with switching to syrup form of piracetam [Table-1]. Following day-12^{th} patient was switched to oral anti-coagulant, Tab. Apixaban-5mg (BD), as a prophylactic measure with a closed-up monitoring of target coagulation range.

FOLLOW-UP EVALUATION

After 2days upon transferring the patient to general ward, 3-4 episodes of spike in temperature were recorded. Multiplex-PCR was performed on the sample, collected from tracheostomy suctioning, revealing Klebsiella Pneumoniae (10^7 copies/ml). Automated blood culture came out negative upon 5 days of incubation. Infection drastically improved with antibiotics therapy with gradual improvement in biomarker. Patient was further evaluated by the department of physical medicine and rehabilitation (PMR) with prospective planning towards her neurological and cognitive rehabilitation.

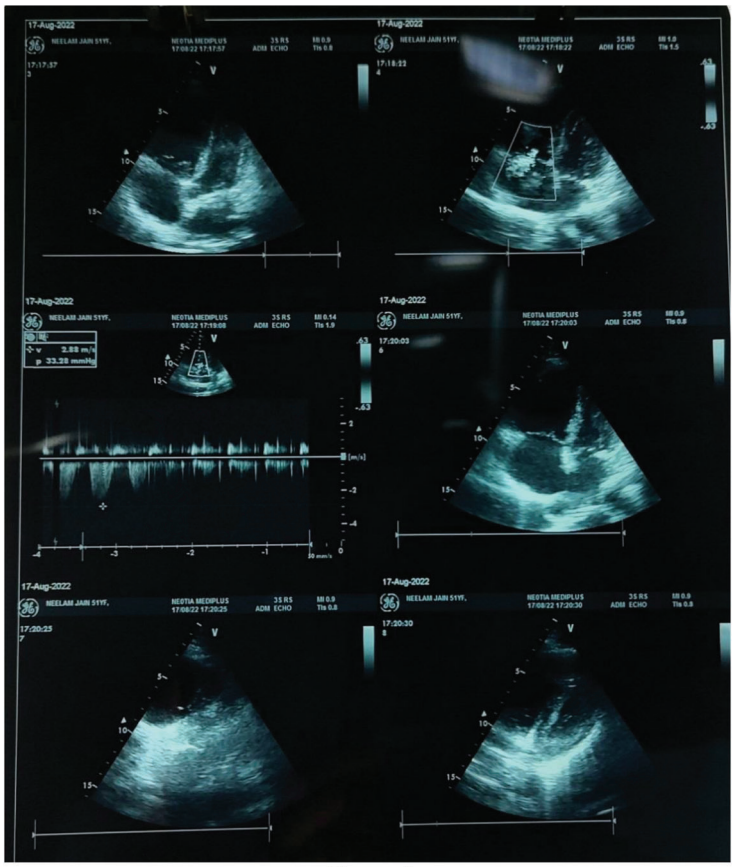

Figure 2a

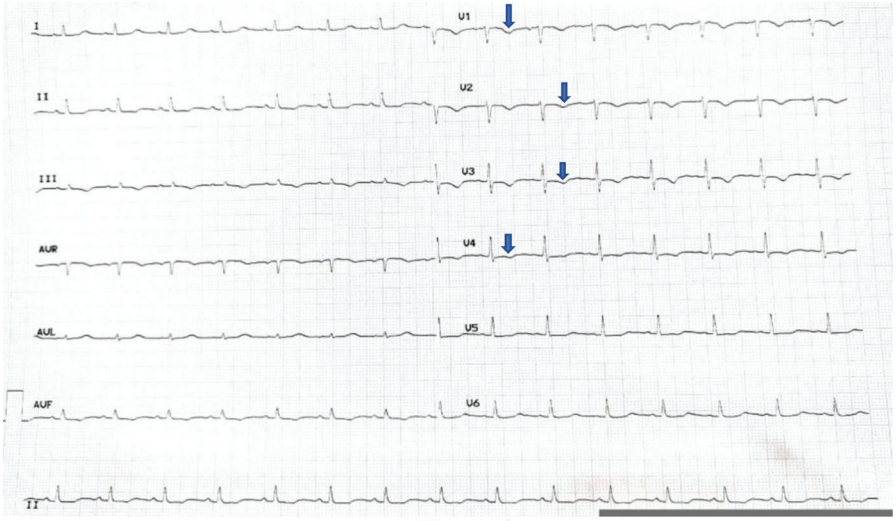

Figure 2b

Fig. 2. Initial 2D-Echocardiography and Electrocardiography findings: (a)- Tranthorasic 2D-Echo with hugely dialated RA and RV(*) with compensated LV dysfunction. RV systolic dusfunction with apical sparing (McConnel's sign), dilated Pulmonary artery(PA), Low pressure TR(←), IVC diameter of 26mm with <30% respiratory collapsibility were also recorded. (b)- Repeat ECG on Day-2 showed T-wave inversion ( ) in chest leads (V1-V4) and significant S1 deepening.

DISCUSSION

Despite of the overall low risk profile of laparoscopic surgical procedures, an accelerated number of cases are being notified with PTE and DVT, mostly following laparoscopic cholecystectomy [6]; attracting attention due to its potentially fatal outcome. Though the predictive etio-pathological parameters of VTE in laparoscopic gynaecological surgeries remain a grey area; still intra-anaesthesia hypercarbia mostly in general anaesthesia, reverse trendelenburg posture,

increased intrabdominal pressure causing pneumo-peritoneum and ventilatory pressure have been found to be augmentative factors [7]. Here, in our case of post-TLH + BSO massive PTE with sudden circulatory collapse; HIBI with subsequent encephalopathic changes followed, instead of timely resuscitation and utmost intensive management focused towards better neurological outcome. Pre-operative thromboprophylaxis is crucial in averting such complications in known prothrombotic patients and can be adopted in laparoscopic gynaecological procedures with rigorous investigations and parametric standardization [8].

In this case, patient's neuro-cognitive status declined subsequently with early onset episodic non rhythmic status myoclonus. Initial changes in EEGs reflected towards acquisition of hypoxic brain injury mediated parieto-occipital encephalopathic changes with a differential of acute lance-adams syndrome (LAS). HIBI mostly happens in a 'two hit' propagation; with a primary post cardiac arrest (CA) mediated cerebral oxygen delivery (CDO_2) derangement phase and a secondary post-resuscitation phase. Within minutes from circulatory collapse, neuroglycopenia sets in the cortical and sub-cortical areas with debilitating neuro-glial metabolic alterations, cytotoxic edema, and neurological loss of function [4]. Yet significant neuronal death and cerebral ischemia follows immediately after return of spontaneous circulation (ROSC) induced cerebral reperfusion injury despite of CDO_2 restoration [9]. Several studies have implicated $PaCO_2$ fluctuations due to post Cardiac arrest hypo-hypercapnic changes, as a predictor towards adverse neurological outcome in HIBI; affecting ICP, tissue oxygenation and cerebral blood flow (CBF) auto-regulation [10]. Additionally, the role of anaemia behind secondary injury in HIBI remains debatable; with a few studies corroborating haemoglobin as an independent predictor of neurologic outcome [11]. Subsequently all these factors may trigger the development of cerebral edema during secondary phase by deranging cerebral perfusion, turning the entire sequalae into a vicious cycle.

Thrombolysis in acute massive PTE, as in our case, with circulatory collapse; imparts the need of an optimal maintenance of mean arteriolar pressure (MAP), particularly in patients with LV failure. Yet it is utterly important to monitor the downsides of maintaining higher MAP in post circulatory shock patients as with increasing afterload in decompensated ventricular failure the stroke volume decreases, further aggravating an already injured brain with ischemia [12]. Hence setting MAP targets should be taken very seriously, especially where patient is already on ionotropic support with post-CA HIBI, as in our case. On note, recent development of near-spectroscopic (rSO_2) monitoring and arterial spin labelling MR imaging (ASL-MRI) have generated a promising non-invasive procedure towards optimal MAP identification in anoxic/hypoxic brain injury [13,14]. Further in depth understanding of dynamic cross-talks between MAP and CBF from larger cohort studies, will delineate individual perfusion target in cerebral hypoxia which may widen up possibilities of better neurological outcome in these patients.

CONCLUSION

Post operative PTE with circulatory shock is a clinical emergency that requires prompt response and extensive interdisciplinary collaboration between specialities with smooth mobility. Extent of intuitive and timebound management with mutual decision points is an important conglomeration to address the wide range of variabilities behind clinical and sub-clinical scenarios, especially whenever neurological impairment emerges into the picture. HIBI is qa complex pathophysiological process with a significant clinical attribution mostly due to Secondary injury. Therefore, dissociation in multiple systemic-neurologic homeostatic domains create several important decisive variables

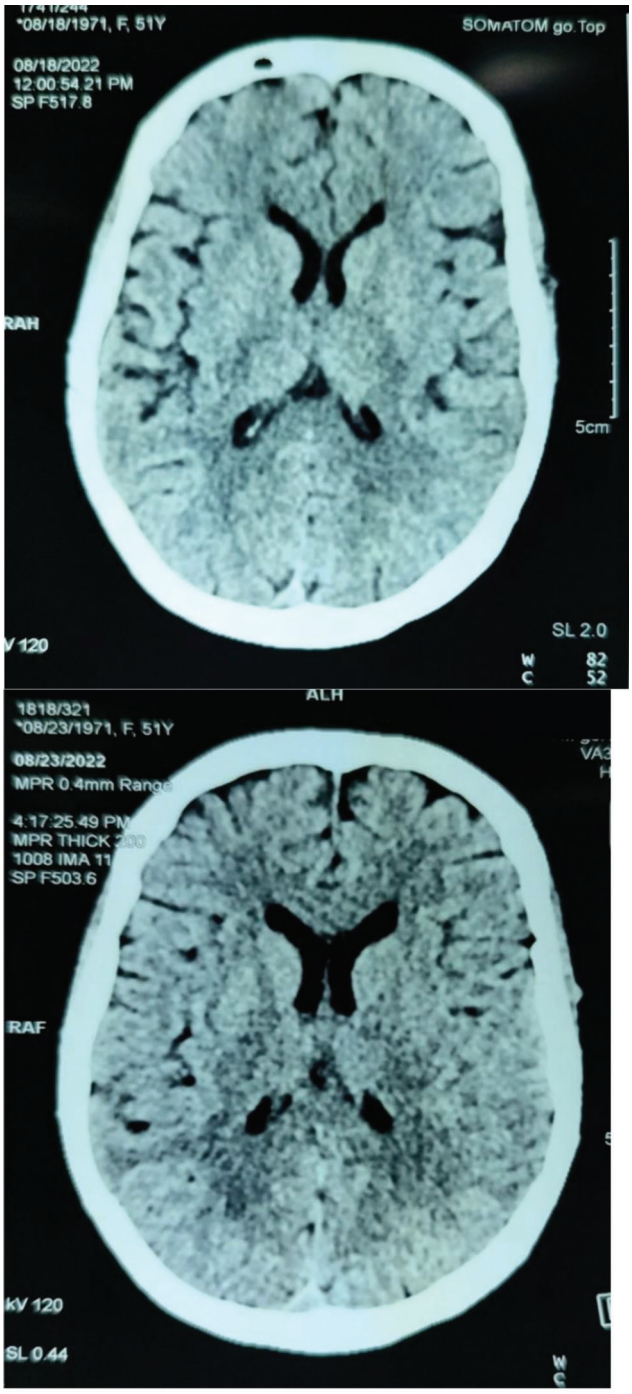

Fig. 3a

Fig. 3. Continued to next page.

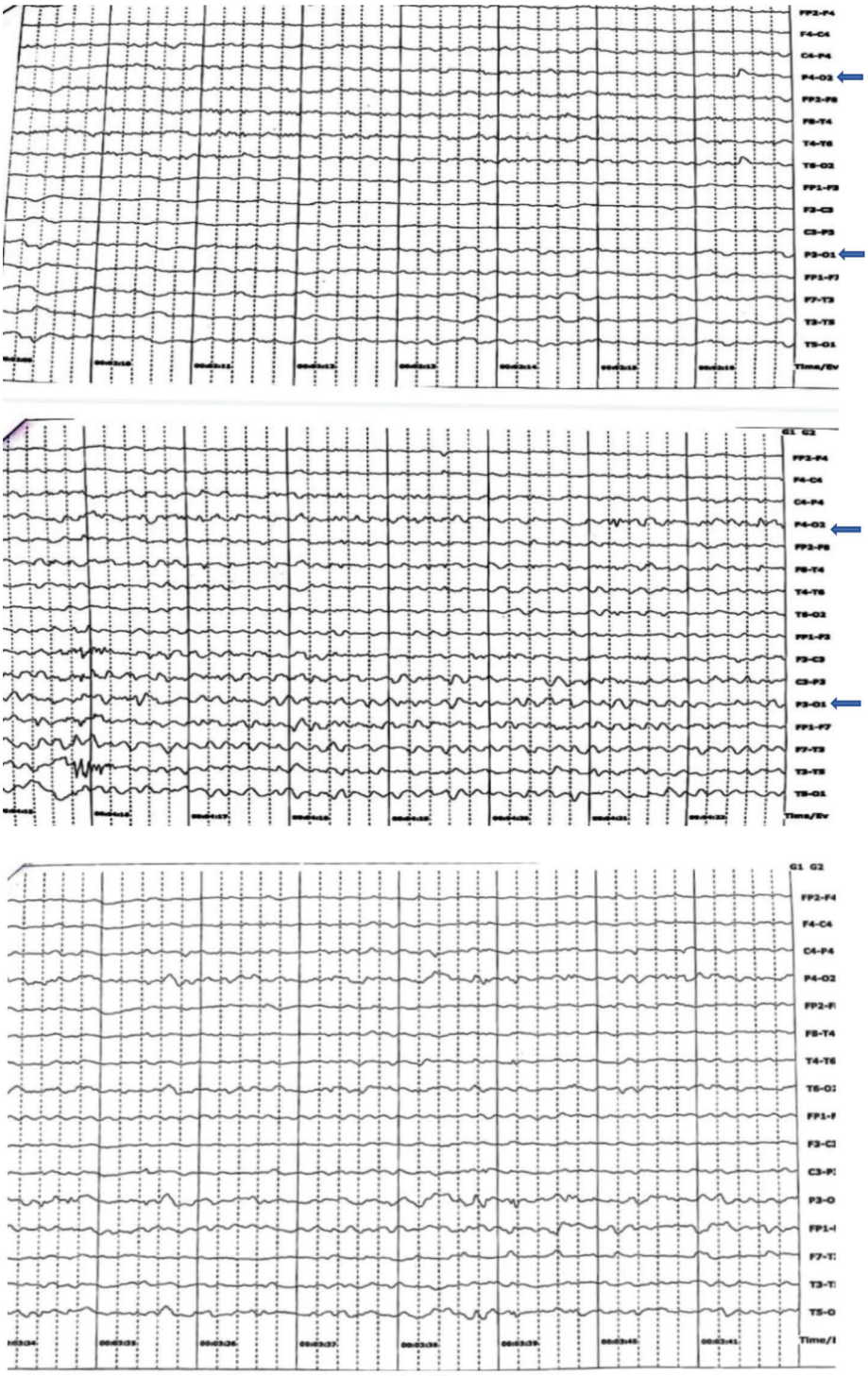

Fig. 3b

Fig. 3. NCCT-Brain and EEGs: (a)- Initial and repeat NCCT brain showed no significant changes. (b)- EEG showed initial Delta activity of 3-5 cycles/sec with followup findings of Theta activity of 5-7 cycles/sec, on both sides symmetrically and predominantly over P4-O2 (←) and P3-O1(→**)**. Normalisation of electrical activity was recorded subsequently with wellformed alpha activity on both sides symmetrically.

in therapeutic strategies to charter out the overall outcome. Hence after a twenty years of rigorous investigation outcome and prognosis of HIBI have changed a little. From the diagnostic viewpoint HIBI needs multiple modalities, most importantly neuroimaging as the injury patterns is highly variable. So NCCT, MRI and ultrasonography require vivid understanding of multiple images at different points of the timeline with specific emphasis on regions towards higher vulnerability of hypoxic injuries and clinical correlation.

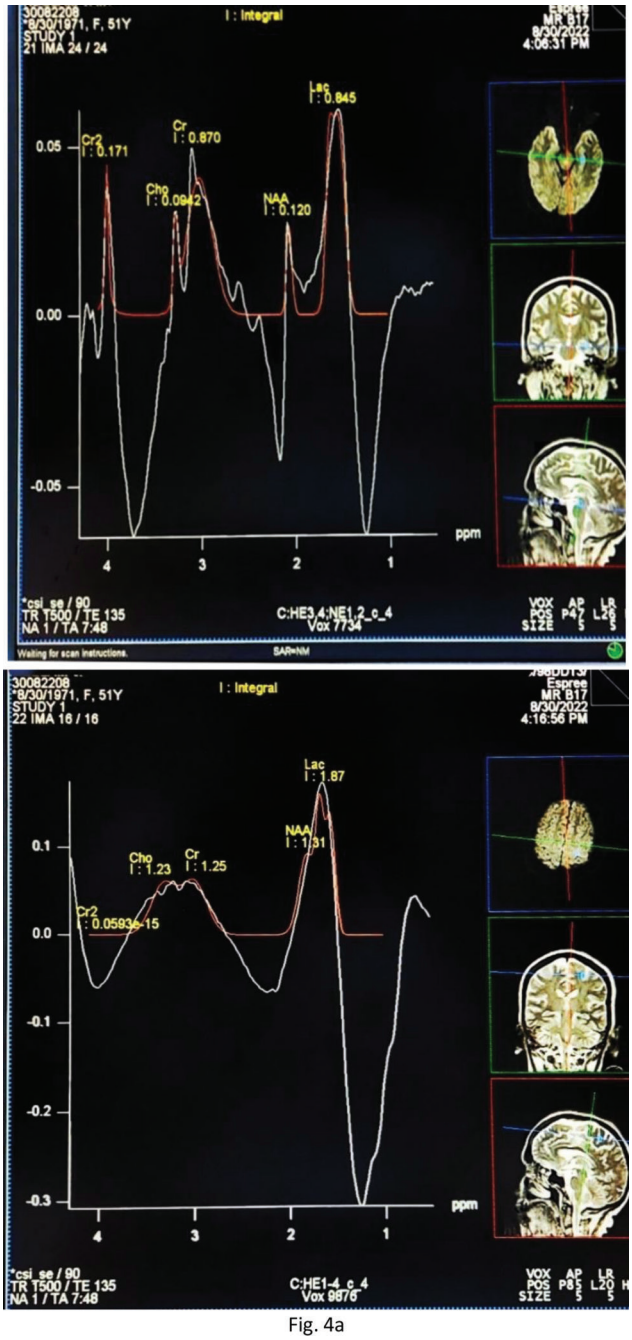

Fig. 4a

Fig. 4. Continued to next column.

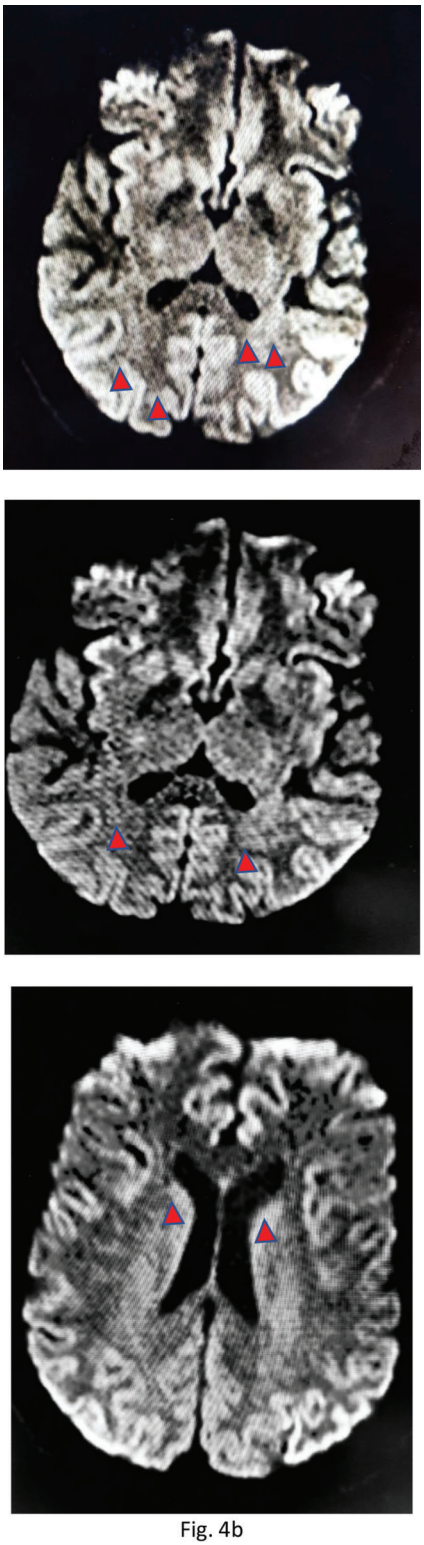

Fig. 4b

Fig. 4. MRI and MR-Spectroscopic findings: (a)- MR-spectroscopy reveals reduction of NAA level with Lactate peaks in bi-lateral basal ganglia. Mild diffuse increase in Lactate peaks were also noted in multiple cortical areas. (b) -MRI reveals hyperintesity involving bi-lateral basal ganglia predominantly in caudate nucleus and ill-defined areas in bi-lateral cerebral hemispheres on FLAIR sequences( ) without any significant diffusion restriction.

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Table 1. Therapeutic regime with overall treatment timeline.

Drugs	Day-1	Day-2	Day-3	Day-4	Day-5	Day-6	Day-7	Day-8	Day-9	Day-10	Day-11	Day-12	Day-13	Day-14	Day-15
Dobutamine (infusion)															
Noradrenaline (infusion)															
Heparin infusion															
Alteplase	*														
Fondaparinux (s/c)			‡	‡	‡	‡	‡								
Enoxaparin		‡						‡							
SCD															
Levetiracetam	‡‡‡	‡‡‡	‡‡‡	‡‡‡	‡‡‡	‡‡‡	‡‡‡	‡‡‡	‡‡‡	‡‡‡	‡‡ (syr.)	‡‡ (syr.)	‡‡ (syr.)	‡‡ (syr.)	‡‡ (syr.)
Piracepam		infusion	‡‡	‡‡	‡‡	‡‡	‡‡	‡‡	‡‡	‡‡ (syr.)	‡‡ (syr.)	‡‡ (syr.)	‡‡ (syr.)	‡‡ (syr.)	‡‡ (syr.)
Fosphenytoin							‡‡‡	‡‡‡	‡‡‡	‡‡‡					
Phenytoin											‡‡‡ (tab)	‡‡‡ (tab)	‡‡‡ (tab)	‡‡‡ (tab)	‡‡‡ (tab)
Mannitol				‡‡‡	‡‡‡	‡‡‡	‡‡‡	‡‡‡	‡‡‡	‡‡‡					
Piperacillin and tazobactam	‡‡‡														
Metronidazole		‡‡‡	‡‡‡												
Meropenem		‡‡‡	‡‡‡	‡‡‡	‡‡‡	‡‡‡									
Ceftazidime and Avibactam							‡‡‡	‡‡‡	‡‡‡	‡‡‡	‡‡‡	‡‡‡	‡‡‡	‡‡‡	
Aztreonam							‡‡	‡‡	‡‡	‡‡	‡‡	‡‡	‡‡	‡‡	
Teicoplanin							‡	‡	‡	‡	‡	‡	‡	‡	

‡-OD ‡‡-BD ‡‡‡-TD
*-Thrombolysis

Table 2. Dynamic changes in ABG parameters.

ABG parameters	Day-1	Day-2	Day-3	Day-4	Day-5	Day-6	Day-7	Day-8	Day-9	Day-10	Day-11	Day-12	Day-13	Day-14
pH	7.04	7.525	7.493	7.463	7.466	7.532	7.482	7.482	7.446	7.413	7.440	7.447	7.423	7.45
pCO_2	–	34.7	34	34.1	34.8	30.7	34.6	37.2	40.4	37.5	36.7	42.3	–	–
pO_2	250	37.2	113.3	99.5	427.8	112.5	82.7	119.1	123.2	109.5	144.3	110	120	–
HCO^{3-}	–	28.1	25.5	23.8	24.5	25.2	25.3	25.1	25.2	24.8	24.8	27.1	24.3	–
BE	5.3	2.4	0.2	1.0	2.7	2.1	1.1	0.6	0.8	0.9	3.0	–	–	–

– Not Recorded

Conflict of Interest
The authors declare that they have no conflict of interest.

Human/Animal Rights
All procedures followed were in accordance with ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008(5).

Informed Consent
Informed Consent was obtained from the patient to be included in the study.

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