‘Cold and Locked in’: A Frozen Body and Frozen Eyes in End-Stage ALS

Sir,

Amyotrophic lateral sclerosis (ALS) was thought to lead to neurodegeneration of somatic motor neurons but spare the oculomotor, sphenetic, and sensory neuronal functions. However, as ALS patients survive longer with tracheostomy and invasive ventilation (TIV); impairment of these have also been noticed in long survivors.¹ The average life expectancy in nonventilated ALS is around 2 years and <10% of cases live longer than 10 years.² Increasingly, patients with ALS have started opting for TIV (up to 10% of ALS patients in western countries and 45% in Japan).³ TIV prolongs life expectancy in ALS by approximately 7 years.⁴ A totally locked in state (TLS), defined as total paralysis of all voluntary and ocular muscles, develops in about 13–19% of patients, within 3 years of TIV.⁵

Comparatively, only a small number of patients in India opt for TIV, and there is scant data on TLS from India. We report two cases of ALS with a near TLS and ICU associated hypothermia.

A 62-year man presented with weakness of the right hand 16 months earlier. Electromyography had shown extensive denervation and reinnervation in all four segments. He was diagnosed with ALS by the Gold coast criteria.⁶ One year after onset, he required a TIV. He was admitted for a tracheostomy tube change. Examination revealed an emaciated male (body weight 30 kg) with grade 0/5 MRC power in all muscles, bifacial wasting with inability to close the eyelids fully. He also had generalised wasting and areflexia. He was occasionally able to communicate through eye blinks [Hayashi stage IV].⁷ Oculomotor evaluation revealed slow horizontal saccades and downward saccades. Pursuit movements and vertical saccades were absent [Video 1]. Vertical and horizontal oculocephalic reflexes were preserved. He was hypothermic (34.4° C). Arterial blood gases and electrocardiogram were normal (no Osborn or J Waves). Routine blood tests including total WBC counts, serum lactate, blood cultures renal, liver, and thyroid function tests were normal. An extensive evaluation for causes of hypothermia was inconclusive. The ambient temperature in the ICU was noted to be 20° C.

He required continuous surface warming (bed warmer), multiple blankets, and warm IV fluids to maintain normothermia. Detailed history revealed the presence of cold intolerance (air conditioning) for the previous few months. He maintained normothermia only when the ICU ambient temperature rose to 31–32° C. 45 days later, he developed a lobar pneumonia, sepsis and succumbed.

The second case was a 55-year-old man with ALS of 4 years duration. After 6 months, his family opted for TIV. Four years later, he was in a TLS with total external ophthalmoplegia (Hayashi stage V) and no response to oculocephalic manoeuvres. During admission to ICU for repeated respiratory infections, he was noted to be emaciated and hypothermic (35° C). He also required similar warming measures to achieve normothermia. At home, in a non-air-conditioned room, he remained normothermic.

Human beings are endotherms that require generation of sufficient endogenous heat or dissipation of excess heat [‘waste heat’] to maintain normothermia within a limited range of environmental temperature [Figure 1]. Beyond a certain range of temperature, internal homeostatic mechanisms are inadequate to maintain body temperature. We then require external aids to maintain normothermia such as external heat or cooling (fans, air conditioning, heaters, warm clothing, or other temperature control devices).

The generation of internal heat is largely by two mechanisms. First, exothermic ‘metabolic heat’ is produced by various organs. Second, skeletal muscle constitute the largest proportion of body weight and contribute significantly to the whole-body metabolic rate (WBMR) [approximately ~40% of WBMR].⁸ Muscle primarily utilizes nonshivering thermogenesis (NST) to generate heat, either by the uncoupling of oxidative phosphorylation (mitochondrial proton leak; 8–16% of WBMR) or by a sarco/endoplasmic reticulum calcium-ATPase pump, which accounts for 24–58% of WBMR.⁹

If these mechanisms are inadequate to generate heat, then muscle shivering is initiated (shivering thermogenesis or ST) to generate additional body heat (24–32% of WBMR during cold exposure). The causes of hypothermia are many [Figure 2].¹⁰¹¹ We hypothesize that the loss of nearly all his skeletal muscle led to a drastic reduction in both his myogenic NST and ST. As a result, he was unable to maintain normothermia with exposure to the ICU air conditioning.

A corollary can be drawn from hypothermia in sepsis.¹² In the early phase of sepsis, patients develop fever as an adaptive strategy. However, in the late phase of sepsis or in decompensated individuals, hypothermia occurs. Hypothermia can occur beneficially if the body resorts to an energy saving adaptive hypothermia to reduce tissue metabolic requirements (van’t Hoff’s rule, tissue metabolic requirements reduce by >10% for every 1°C drop in body temperature). More often, hypothermia is an ominous sign of energy depletion, decompensation, and impending death.

Depression, cognitive impairment, frontotemporal dementia, oculomotor dysfunction, and progressive loss of ability to communicate develop with time in ALS patients. Cranial motor impairment in ALS usually ascends from the bulbar muscles and occurs in the reverse order of the developmental sequence of the cranial motor nuclei, reflecting the older ontogenesis of

References:

[1] Sir, Annals of Indian Academy of Neurology, Volume 25, Issue 4, July-August 2022

[2] Letters to the Editor, ‘Cold and Locked in’: A Frozen Body and Frozen Eyes in End-Stage ALS

Figures:

Figure 1

Figure 2

Video 1

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oculomotor nuclei. Oculomotor abnormalities (OMA) are seen in around 10% of ALS patients as the disease progresses. The most common early OMA are smooth pursuit and saccadic abnormalities followed by supranuclear ophthalmoplegia and finally total external ophthalmoplegia. Initially, frontal oculomotor areas are involved in ALS, followed in the end stages by ocular motor neuron degeneration.[13]

Hayashi et al.[7] have proposed a five-stage classification system that describes the communication abilities of patients with advanced ALS. In stage I, patients can communicate through sentences. By stage II, communication is limited to one-word answers. By stage III, communication is limited to nonverbal yes/no responses. By stage IV, communication is difficult due to uncertain yes/no responses. By stage V, the patient reaches TLS and cannot communicate by any means. Our patients with ALS were in stages IV and V with TLS. Severe muscle loss precluded endothermic muscular heat generation necessary to maintain normothermia in a cold environment. Progressive degeneration of supranuclear followed by infranuclear oculomotor motor neurons must have produced the total external ophthalmoplegia.

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**Conflicts of interest**
There are no conflicts of interest.

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Dear Editor,

Takayasu arteritis (TA) is a systemic vasculitis causing inflammation of the large and medium-sized arteries. It is characterized by aneurysm formation and stenosis of the affected vessels with a predilection for the aorta and its major branches. Various atypical presentations of TA have been described in the literature.

Posterior reversible encephalopathy syndrome (PRES) is a rare clinico-radiologic syndrome that usually manifests as an acute to subacute headache, confusion, visual disturbances, seizure, and encephalopathy with typical neuroimaging findings on neuroimaging. PRES is often associated with reduced, hypothermia with increased mortality in septic patients with congestive heart failure. Am Heart J 2005;149:927‑33.

The computed tomography angiography of the aorta and renal arteries showed low attenuation concentric mural thickening of the proximal left common carotid artery [Figure 2a‑b], resulting in significant stenosis. There was also mild involvement of the infrarenal aorta [Figure 3d] with discrete generalized tonic-clonic convulsions and blurred vision with no reoccurrence of seizure. On further evaluation, the magnetic resonance imaging (MRI) of the brain was done initially which showed hypodense areas in the bilateral occipital lobes. He was managed with intravenous glucocorticoids and methotrexate with a resolution of posterior reversible encephalopathy syndrome (PRES) at 1 month after discharge.

The child fulfilled the European Society Against Rheumatism (EULAR) and Pediatric Rheumatology European Society (PReS) criteria for diagnosis. Following a 3-month follow-up period, there was no disease activity and the child was asymptomatic. He was restarted on amlodipine and labetalol, and the blood pressure was controlled with improvement in headache and visual acuity was reduced bilaterally with pupils equal and reactive to light. The fundus examination showed features of grade 4 hypertensive retinopathy bilaterally.

The laboratory studies revealed normal blood counts, serum electrolytes, liver, and renal function tests. The erythrocyte sedimentation rate (ESR) was raised (59 mg/L). A non-contrast computed tomography (NCCT) of the brain showed a patchy hyperintense signal in bilateral frontal and parietal white matter in watershed zone (A, blue arrow) and bilateral occipital region (C and D, yellow arrow). The ultrasonographic (FLAIR) sequences [Figure 1a‑d]. The echocardiography and peripheral pulse was asymmetrically reduced in the left radial, in the right upper arm and 110/70 in the left upper arm. His pulse rate of 106/min and blood pressure of 180/110 mmHg were no meningeal signs or focal neurological deficit. His visual pressure was controlled with improvement in headache and visual acuity was reduced bilaterally with pupils equal and reactive to light. The fundus examination showed features of grade 4 hypertensive retinopathy bilaterally. The laboratory studies revealed normal blood counts, serum electrolytes, liver, and renal function tests. The erythrocyte sedimentation rate (ESR) was raised (59 mg/L). A non-contrast computed tomography (NCCT) of the brain showed a patchy hyperintense signal in bilateral frontal and parietal white matter in watershed zone (A, blue arrow) and bilateral occipital region (C and D, yellow arrow).

On admission, he was conscious and oriented. He was afebrile with a regular pulse rate of 106/min and blood pressure of 180/110 mmHg. His birth and development history were normal with unremarkable past and family history. He reported in the literature.

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Letters to the Editor