This *directly explains ME hypovolemia* and the dangerous reactions to exertion.

Conclusion

From Demitrack's early physiological markers, to Bayliss's autoantibodies, to the recent autopsies revealing structural destruction of CRH neurons, the evidence now tells a unified story:

ME/CFS involves profound neuroendocrine injury, is not deconditioning, or psychogenic (FND)

It is a disease rooted in damage to one of the most essential regulatory systems in the human body.

And the consequences of ignoring this - both medically and ethically - have been nothing short of devastating. The autopsy results reveal why Graded Exercise Therapy (GET) or one of its euphemisms, 'Activity Management'/'Pacing-UP', has had such disastrous consequences for so many.

SAFEGUARDING RISKS

Parents protecting their child from exertion-triggered deterioration are frequently mislabelled as "fabricating illness" while some adults are sectioned in the belief that they can be exercised to recovery, or that their hypovolaemic-driven thirst, typically observed in patients with ME, is polydipsia, a psychiatric condition for which some have been sectioned.

In the light of the present findings, **protecting a patient from harmful exertion is safeguarding, not abuse and accusations of** Fabricated or induced illness (FII) amounts to:

- professional misconduct
- breach of statutory safeguarding obligations
- potential defamation
- violation of parental rights
- unlawful interference with medical decision-making

Such Actions Will Result in Foreseeable Harm to the patient

Forcing "activity management" on a patient with HPA pathology risks:

- multi-system dysfunction leading to potential collapse
- medical-imposed psychological trauma
- long-term PEM, permanent reduction in baseline functioning and progression to severe or very severe ME
- need for feeding tubes or long-term care
- in an increasing number of cases, death

This meets criteria for **iatrogenic harm** and, in severe cases, **medical child abuse** (when enforced by professionals.)

CRH loss, furthermore, disrupts sleep and autonomic control, impairing glymphatic clearance and contributing to brain inflammation and metabolic waste buildup in ME/CFS.

HPA collapse is not a side feature of ME/CFS. It can generate almost all the entire clinical syndrome.

Potential Interventions

- **Supportive / compensatory strategies**:
  - Cortisol replacement therapy
  - Reducing physiological and cognitive stress
  - Pacing / energy conservation to avoid triggering PEM
  - Treating peripheral systems affected by HPA collapse (hypovolemia, autonomic dysfunction, sleep disturbance)
- **Experimental approaches:**
  - Neuroregenerative therapies are mostly in research stages (stem cell or growth factor approaches)

Caveats: The above is based on the 2025 conference report. It has not yet been published in a peer-reviewed paper, while further autopsies are required to validate the research.

It is not known yet whether this affects ALL ME patients or a severe subset. The mildest patients may experience the least CRH loss with the potential to progress, depending on the degree of neuroinflammation, and disease mismanagement.

THE HPA AXIS IN ME/CFS & LONG COVID: NEW FINDINGS FROM AUTOPSIES AND HISTORICAL RESEARCH COULD EXPLAIN THE CORE PATHOPHYSIOLOGY

By Jenny Wilson

Associate Member of Doctors With ME

ME is a serious, chronic, multisystemic, potentially fatal disease that usually follows a viral or bacterial infection, or toxic exposure. Reports also suggest that traumatic injury, especially to the neck, can result in an ME-like disease.

Some recover in the first year, if they rest and avoid post-exertional malaise (PEM), especially those under 18, but after two - five years, the recovery rate is only about 5%.

In the 20th century, ME was associated with Coxsackie B infection. The name was created for that subset of post-acute infectious syndromes (PAIS).

Research that compared the Quality of Life (QoL) of ME patients to 20 other major diseases (2015, Hvidberg et al), including cancers, heart disease, MS, and lung diseases, revealed that the QoL is the lowest in ME. When it is medically neglected or mismanaged, it can be fatal.

Some of the clinical findings in the 1990s raised concerns about low cortisol, autonomic dysfunction, and abnormal stress responses in ME patients.

Early autopsies dating back to 1956, although few, have previously revealed dorsal root ganglionitis, fibrosed hearts, and brain, liver and kidney involvement. **New autopsy evidence** involving seven cases was presented at the 2025 IACFS/ME Conference that revealed **near-complete loss** of corticotropin-releasing hormone **(CRH)-producing neurons** in the hypothalamus of ME/CFS patients.

EARLIER RESEARCH ALREADY POINTED TO HPA AXIS DAMAGE

For more than 35 years, the HPA axis (hypothalamic–pituitary–adrenal axis) has been recognised as abnormal in ME/CFS. Early work by **Demitrack et al. (1991–1992)** demonstrated a distinctive pattern: **blunted ACTH and cortisol responses** to physiological stress, a profile inconsistent with depression but indicative of central (hypothalamic) hypofunction.

The psychiatric lobby dismissed these findings as "emotional stress responses" or "maladaptive beliefs." But as the decades progressed, more evidence accumulated that something was organically malfunctioning in the core physiological stress-regulation system of people with ME.

Bayliss et al., 2012 identified autoantibodies against key HPA axis receptors in a subset of ME patients. This suggests the immune system may mistakenly attack the HPA axis, reducing its ability to regulate blood volume, metabolism, and physiological stress responses.

This meant:

- The immune system could directly interfere with HPA signalling
- The system, apart from the overactive branch of the dysfunctional immune system, could be pushed into chronic under-activation
- Cortisol output would be insufficient even under stress
- Blood-volume regulation and autonomic stability would deteriorate

New Evidence 2025 presented at the IACFS/ME Conference: Near-Total Loss of CRH Neurons

The development came from seven ME/CFS recent autopsies

CRH-producing neurons in the hypothalamus were virtually absent.

CRH is the master hormone that initiates the entire physiological stress response. Without CRH, the pituitary cannot release ACTH, and the adrenal glands cannot release cortisol. The result is a body locked into:

- Low blood volume (hypovolemia)
- Orthostatic intolerance and impaired vascular tone
- Inability to respond to metabolic stress
- Immune dysregulation
- Severe post-exertional crashes (PEM)

The discovery that these neurons were *missing* - not merely dysfunctional - confirms a level of structural neuroendocrine injury that aligns with the severity of clinical symptoms.

What does this mean?

When CRH neurons are severely depleted, the entire HPA axis collapses. This produces many core ME symptoms:

- **Hypovolemia** (low blood volume)
- **Orthostatic intolerance / POTS-like symptoms**
- **Severe fatigue and delayed energy crashes following exertion (PEM)**
- **Temperature dysregulation**
- **Low Adenosinetriphosphate (ATP) production**
- **Sleep disruption**
- **Cognitive dysfunction**
- **Exercise intolerance**
- **Chronic excitability from raised glutamate, which can kill hypothalamic neurons — including CRH cells.**

If autopsy findings show *almost no CRH-producing neurons*, that is **not mild HPA dysregulation** - it is a **structural HPA axis collapse.** (**N.B. Normal cortisol levels can mask CRH-receptor loss due to HPA-axis compensation.**)

It explains most ME/CFS symptoms; in addition, autoantibodies to adrenergic and muscarinic receptors drive vascular dysfunction (Scheibenbogen), while persistent and reactivated viruses (Behan, Mowbray, Chai; Klimas, Prusty) underpin immune abnormalities.

These findings confirm that ME/CFS is a **biological, multi-system disease and further validate the Bayliss findings (2012) that found ME to be an autoimmune disease of the HPA axis.**

Why do CRH Neurons Die?

Likely triggers include:

- Viral infections (EBV, enteroviruses, SARS-CoV-2)
  → Can directly infect or inflame the hypothalamus
  → Can trigger autoimmunity against HPA structures
- Toxicant exposure (organophosphates, organochlorines)
  → Both are known neurotoxins
  → Can damage hypothalamic nuclei and HPA feedback loops

- Chronic immune activation
- Excess glutamate destroys neurons
- → Sustained inflammation can induce neuronal apoptosis
- → Fits with the "Cell Danger Response" model.

Summary: The new autopsy evidence reveals: near-total absence of **CRH neurons**; structural degeneration of the hypothalamus; degeneration of the pituitary gland; failure of corticosteroid stress-response system. This is organ-level pathology.

Consequences of HPA Collapse

Patients cannot: mount a normal cortisol rise; stabilise heart rate or blood pressure under exertion; maintain glucose homeostasis; buffer inflammation triggered by physical stress; avoid delayed neuroimmune deterioration (PEM)

Therefore:

Exertion is a Medical Stressor

Under these conditions, enforced increases in activity predictably cause: orthostatic collapse; metabolic crash; inflammatory flare; long-lasting PEM; permanent deterioration; tube-feeding or catheter dependence; severe autonomic crises; fatal in very severe cases

Therefore, graded increases in activity constitute a foreseeable medical hazard resulting in serious harm

How CRH Receptor Loss Causes Hypovolaemia

CRH → ACTH → Cortisol pathway regulates blood volume

CRH neurons in the hypothalamus trigger ACTH release, which triggers cortisol production. Cortisol is essential for: **maintaining plasma volume** and vascular tone; keeping **aldosterone** signalling normal; supporting **renal sodium retention**; regulating the **renin–angiotensin–aldosterone (RAAS) system**; preventing **inappropriate vasodilation**; Maintaining **blood pressure**, especially on standing

Without adequate CRH: ACTH falls; cortisol falls; aldosterone signalling becomes abnormal; plasma volume drops; patients develop **orthostatic intolerance** and **hypovolemia**

This pattern is documented repeatedly in ME/CFS research: **Low blood volume + low or volatile blood pressure + high renin + impaired vasoconstriction = classic HPA insufficiency.**