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Reactive Oxygen Species Causing Gene Mutations Linking Heavy Metal Toxicity to Neurodegeneration

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ABSTRACT

Background: Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder characterized by combined upper and lower motor neuron loss. While most cases are sporadic, environmental and occupational exposures are increasingly recognized as important disease modifiers.
Case Presentation: A 57-year-old male presented with an insidious onset of asymmetric upper limb weakness, which gradually progressed to involve significant muscle wasting, fasciculations, and early bulbar symptoms. Electromyographic studies demonstrated fasciculations, fibrillations, and neurogenic recruitment patterns, findings consistent with motor neuron disease. The patient had a prolonged occupational history of manual labor at oil production sites, with chronic exposure to heavy metals, and was known to have chronic hepatitis B infection. Despite initiation of riluzole therapy and comprehensive multidisciplinary supportive management, the disease followed a progressive course, culminating in respiratory failure and end-stage disease.
Discussion: This case underscores the potential contribution of chronic heavy metal exposure as a molecular driver in the pathogenesis of amyotrophic lateral sclerosis (ALS). The underlying mechanisms may involve zinc displacement from DNA repair proteins, oxidative DNA damage, mitochondrial dysfunction, disrupted axonal transport, and neuroinflammatory cascades. Additionally, concomitant systemic comorbidities such as chronic hepatitis B infection and prolonged physical strain may have synergistically accelerated neurodegenerative processes, contributing to disease progression.
Conclusion: Environmental and occupational exposure to neurotoxicants may influence the clinical trajectory of amyotrophic lateral sclerosis (ALS) by exacerbating intrinsic neuronal vulnerabilities. Recognition of these pathogenic modifiers is crucial for comprehensive risk assessment, patient counseling, and the formulation of targeted therapeutic strategies, including antioxidant therapy, mitochondrial stabilization, and metal chelation approaches.

INTRODUCTION

Amyotrophic lateral sclerosis is a relentlessly progressive neurodegenerative disorder characterized by selective loss of upper and lower motor neurons, leading to weakness, disability, and premature mortality. While the majority of cases are sporadic, growing evidence implicates a convergence of genetic predisposition and acquired modifiers, including metabolic, immune, and toxicological factors, in disease pathogenesis. Environmental and occupational exposures, particularly to hydrocarbons, heavy metals, and volatile compounds have been implicated in the induction of oxidative stress, mitochondrial dysfunction, and glutamatergic excitotoxicity, all of which play central roles in motor neuron injury and degeneration.

The case of a 57-year-old male patient with ALS, whose clinical course was shaped by chronic occupational toxicant exposure, concomitant hepatitis B infection, and sustained physical strain from manual labor has been reported. This case highlights the complex interplay between systemic comorbidities and neurotoxic mechanisms, emphasizing how extrinsic modulators can accelerate the trajectory of ALS.

CASE PRESENTATION

A 57-year-old male with no prior history of diabetes mellitus, hypertension, coronary artery disease, or chronic kidney disease presented in 2022 with an insidious onset of left upper limb weakness. The weakness gradually progressed over several months to involve the right upper limb, with greater severity on the left side. This was followed by noticeable wasting of the hand and forearm muscles and difficulty sipping liquids, indicative of early bulbar involvement. Electromyography and nerve conduction studies revealed widespread denervation changes consistent with motor neuron disease (Figure 1), leading to a diagnosis of amyotrophic lateral sclerosis (ALS). The patient was initiated on riluzole 50 mg twice daily and supportive therapy including Mito Q7 and Orofer XT. Baseline serology was positive for Hepatitis B surface antigen (HBsAg), though liver function tests were within normal limits (Table 1). Given the need for ongoing pharmacotherapy, serial liver function monitoring was

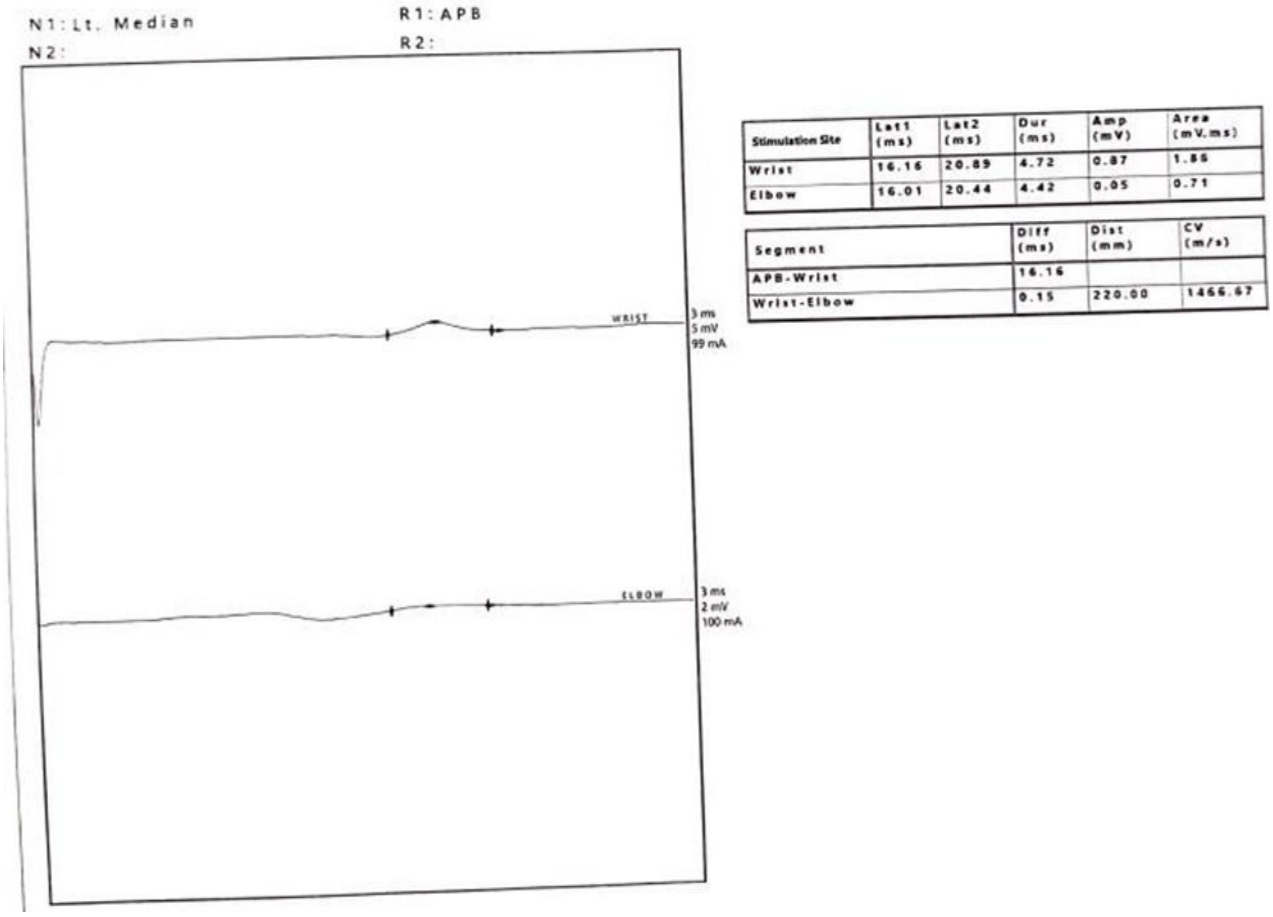
instituted, and tenofovir was commenced under gastroenterology supervision for HBV management.

PARAMETER	VALUES	
	May 2023	**May 2024**
Hemoglobin	-	14.6 g/dl
Total WBC Count	-	4,500 /cu.mm
Neutrophils	-	52%
Lymphocytes	-	40%
Eosinophils	-	8%
Monocytes	-	0%
Basophils	-	0%
Platelet Count	-	1.10 lakhs/cu.mm
Urea	20 mg/dl	-
Creatinine	0.88 mg/dl	0.78 mg/dl
eGFR	-	165
Random Glucose	-	165 mg/dl
Triiodothyronine (T3)	-	1.24 nmol/L
Thyroxine (T4)	-	118 nmol/L
Thyroid Stimulating Hormone (TSH)	-	1.43 mIU/L
Total Bilirubin	0.41 mg/dl	0.64 mg/dl
Direct Bilirubin	0.10 mg/dl	-
Indirect Bilirubin	0.31 mg/dl	-
Alkaline Phosphatase (ALP)	75 IU/L	-
SGPT (ALT)	21 IU/ L	246 IU/L
SGOT (AST)	31 IU/ L	185 IU/L
HCV	-	Negative
HBsAg	-	Positive(7920)
HIV (Retroviral Screening Test)	-	Negative

Table 1: Laboratory Investigation

Further occupational history revealed over three decades of manual labor at oil production sites, involving repetitive heavy lifting and chronic exposure to heavy metals and chemical agents. In September 2024, the patient developed acute worsening of breathlessness over nine days. On admission, his respiratory rate was 42 breaths/min, pulse rate 109 beats/min, blood pressure 110/60 mmHg, and oxygen saturation 94% on room air. The use of accessory respiratory muscles was evident, suggesting diaphragmatic weakness.

Neurological examination revealed marked wasting of the left abductor pollicis brevis, first dorsal interosseous, triceps, and forearm muscles, with relatively lesser involvement on the right. Fasciculations were noted in the left flexor digitorum profundus and right deltoid. Muscle tone was normal, and no spasticity was observed. Power testing showed weakness of the shoulder abductors, external rotators, triceps, and mild neck flexion weakness. Triceps reflexes were absent bilaterally, while biceps reflexes preserved. Sensory examination was normal.



Stimulation Site	Lat1 (ms)	Lat2 (ms)	Dur (ms)	Amp (mV)	Area (mV.ms)
Wrist	16.16	20.89	4.72	0.87	1.88
Elbow	16.01	20.44	4.42	0.05	0.71

Segment	Diff (ms)	Dist (mm)	CV (m/s)
APB-Wrist	16.16		
Wrist-Elbow	0.15	220.00	1466.67

Figure 1: Electromyography of Abductor pollicis brevis – Left median nerve showing severe median neuropathy at the wrist (carpal tunnel), with both demyelinating (marked latency) and axonal features (low amplitude).

Chest auscultation was clear despite dyspnea at rest. Abdominal examination revealed a small (8 mm) supraumbilical hernia with omental herniation, and per rectal examination showed grade I prostatomegaly. Despite ongoing multidisciplinary supportive care, his respiratory function progressively deteriorated, and the disease culminated in end-stage respiratory failure.

DISCUSSION

Nuclear Vulnerabilities

Exposure to heavy metals serves as a considerable environmental stressor, intensifying the innate molecular weaknesses in motor neurons and hastening the development of amyotrophic lateral sclerosis (ALS). Metals like lead (Pb^{2+}), cadmium (Cd^{2+}), mercury (Hg^{2+}), and manganese (Mn^{2+}) can replace zinc in essential zinc finger proteins, causing the destabilization of DNA repair enzymes such as PARP1, XPA, and XPC, along with crucial transcription factors. This displacement interrupts genome stability and hinders both base excision repair (BER) and nucleotide excision repair (NER) pathways. At the same time, the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) induced by heavy metals promotes oxidative base modifications and DNA strand breaks. In ALS, the misfolded or mutant form of superoxide dismutase 1 (SOD1) shows impaired nuclear translocation, which scavenging disability ROS and further compromising genomic integrity within motor neurons.

Mitochondrial Dysfunction

Within mitochondria, heavy metal exposure and SOD1 misfolding disrupt the function of electron transport chain complexes I and III, leading to electron leakage and excessive superoxide generation. The resulting accumulation of reactive oxygen species (ROS) damages cardiolipin within the inner mitochondrial membrane, reduces the mitochondrial membrane potential ($\Delta\psi m$), and induces opening of the mitochondrial permeability transition pore (mPTP), culminating in cytochrome c release and activation of apoptotic pathways. Furthermore, mitochondrial DNA (mtDNA), which lacks histone-mediated protection, becomes highly susceptible to oxidative lesions such as 8-oxo-7,8-dihydroguanine (8-oxoG) and deletions, thereby impairing the synthesis of essential respiratory chain proteins and exacerbating mitochondrial dysfunction.

Cytoplasmic and Cytoskeletal Effects

Oxidative stress reaches the cytoplasmic compartment, where heavy metals and reactive oxygen species (ROS) cause post-translational modifications of cytoskeletal proteins. When neurofilaments and microtubules suffer oxidative damage, it interrupts axonal transport processes. This results in a reduction of mitochondria and trophic factors at distal synapses. Metals like lead (Pb^{2+}) and manganese (Mn^{2+}) exacerbate transport dysfunction by further disrupting tubulin polymerization and impairing the function of motor proteins. Moreover, the improper regulation of vesicle docking and fusion proteins at presynaptic terminals undermines synaptic transmission, which contributes to the progressive degeneration of motor neurons.

Plasma Membrane and Extracellular Contributions

Reactive oxygen species (ROS) induce lipid peroxidation of polyunsaturated fatty acids at the plasma membrane, leading to the formation of reactive aldehydes like malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE). These products of lipid peroxidation create covalent crosslinks with membrane proteins, raise membrane permeability, and disturb ionic homeostasis. Damage to axonal membranes and proteins of the SNARE complex compromises further the efficiency of neurotransmission and fusion of synaptic vesicles. In addition to neuronal intrinsic mechanisms, the intracellular calcium influx and ATP demand are increased by sustained manual labor and chronic physical strain, which worsens mitochondrial stress and enhances ROS production. Microglia and the NLRP3 inflammasome become activated due to repetitive microtrauma and metabolic overload, which maintains a pro-inflammatory environment via the secretion of interleukins IL-1β and IL-18. Simultaneously, glutamate clearance is compromised because of a diminished expression or malfunction of the EAAT2 transporter enhances extracellular glutamate accumulation.

These converging mechanisms collectively promote excitotoxicity, dismantling of the neuromuscular junction, and ultimately, progressive motor neuron degeneration.

CONCLUSION

This study highlights chronic heavy metal exposure as a key molecular driver in the pathogenesis of amyotrophic lateral sclerosis (ALS). By displacing zinc, heavy metals destabilize zinc finger–dependent DNA repair enzymes and transcription factors, undermining nuclear genome integrity. Concurrently, mitochondrial dysfunction characterized by excessive reactive oxygen species (ROS) production, cardiolipin oxidation, mitochondrial permeability transition pore (mPTP) opening, and mitochondrial DNA (mtDNA) damage impairs ATP generation and primes apoptotic pathways. Cytoplasmic oxidative stress disrupts axonal transport, while lipid peroxidation and SNARE protein oxidation at the plasma membrane compromise ion homeostasis and synaptic transmission. Sustained physical strain further amplifies these processes by promoting calcium overload and chronic neuroinflammation, consistent with epidemiological links between heavy metal exposure, physically demanding occupations, and elevated ALS risk. Therapeutic strategies aimed at these converging mechanisms including metal chelation, antioxidant interventions such as NRF2 activation and epigallocatechin gallate (EGCG) supplementation, mitochondrial stabilization, and enhancement of DNA repair capacity represent a rational approach to slowing or preventing motor neuron degeneration.

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