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Gene-Environment Interaction in Nonfamilial Corticobasal Syndrome in Monozygotic Twins With Differential Occupational Exposure

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Abstract

Background and Objectives

Corticobasal syndrome (CBS) is a progressive neurodegenerative disorder often linked to 4-repeat tauopathies. Most CBS cases are nonfamilial and lack identified pathogenic variants, raising the possibility of environmental contributors, polygenic risk factors, and gene-environment interactions.

Methods

We describe a patient with clinically and neuroimaging-confirmed CBS who had prolonged occupational exposure to nitrobenzene and aniline in chemical manufacturing facilities. This case is contextualized by his reportedly monozygotic twin, who also worked in the chemical industry but without direct production-floor exposure and remains neurologically asymptomatic.

Results

The patient presented with 3 years of progressive left-sided motor and cortical sensory dysfunction with symptom onset approximately 20 years after cessation of chemical exposure. Neuroimaging demonstrated asymmetric right frontoparietal atrophy on MRI, corresponding hypometabolism on ¹⁸F-FDG PET, and reduced right basal ganglia dopaminergic uptake on DaTscan. Amyloid PET was negative. Genetic testing revealed *MAPT* H1/H1 homozygosity and a *CHMP2B* variant of uncertain significance.

Discussion

Phenotypic discordance in reportedly monozygotic twins for an uncommon disease supports the plausibility of gene-environment interactions in this patient's illness. This report underscores the importance of obtaining detailed exposure histories in patients with CBS and highlights the need for systematic investigation examining environmental determinants of disease penetrance in genetically susceptible individuals.

Introduction

Corticobasal syndrome (CBS) is a progressive neurodegenerative disorder characterized by asymmetric motor symptoms, including rigidity, dystonia, and myoclonus, alongside cortical sensory deficits and apraxia.¹ Neuropathologically, CBS is heterogeneous. Although most cases are associated with 4-repeat (4R) tauopathies, particularly corticobasal degeneration (CBD)

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and progressive supranuclear palsy (PSP), autopsy studies reveal Alzheimer disease (AD) pathology in up to 40% of clinically diagnosed CBS cases, and a smaller proportions demonstrate frontotemporal lobar degeneration (FTLD) with TAR DNA-binding protein 43 (TDP-43) inclusions.^{2,3} Lee and colleagues² suggest that in cases with CBD, atrophy/hypometabolism is usually frontally predominant and presents as behavioral variant frontotemporal dementia (bvFTD), progressive nonfluent aphasia, or as an executive motor syndrome, while AD is more likely when the atrophy/hypometabolism is parietally predominant. However, clinical features alone are often insufficient to distinguish between these etiologies. Advances in imaging and fluid biomarkers, such as amyloid PET and plasma phosphorylated tau, now enable more accurate differentiation between AD and non-AD CBS, underscoring the importance of biomarker-guided precision diagnosis as disease-modifying therapies emerge.⁴

Despite these diagnostic advances, the underlying causes of most 4R tauopathies remain poorly understood. While genetic variants can account for familial cases, most CBS cases are nonfamilial and lack identified pathogenic variants, raising the possibility of environmental contributors, polygenic risk factors, and gene-environment interactions. Experimental and epidemiologic studies suggest that exposure to industrial chemicals, such as nitrobenzene and aniline, which are widely used in synthetic dye manufacturing, increase vulnerability to tau protein modifications and aggregation.^{5,6} This has gained broader attention in the public discourse, where chemical exposure has been increasingly recognized as a modifiable risk factor for neurologic disorders. Whether similar exposures contribute to nonfamilial CBD remains unknown but represents an important frontier for research.

Monozygotic twin studies provide a powerful natural experiment for exploring gene-environment interactions in neurodegenerative disease. By controlling for genetic predisposition, phenotypic discordance between twins is uniquely informative for understanding how environmental exposures may influence disease expression. Here, we report a patient with CBS and prolonged occupational exposure to industrial chemicals, whose reportedly monozygotic twin without such exposure remains neurologically unaffected.

Case History

A 61-year-old, left-handed man with no family history of neurodegenerative disease presented with 3 years of progressive left hand dysfunction beginning in late 2021. Neurologic examination revealed asymmetric rigidity, dystonic posturing, tremor, myoclonus, impaired rapid alternating movements, and cortical sensory deficits, most prominent in the left upper extremity. A 3-month trial of carbidopa-levodopa (up to 10 tablets daily, per patient report) yielded no clinical benefit. Cognition remained intact throughout the course.

Neuroimaging demonstrated asymmetric right-sided frontoparietal atrophy on MRI with corresponding hypometabolism on ¹⁸F-FDG PET and reduced uptake in the right basal ganglia on DaTscan. Amyloid PET was negative. Genetic testing ruled out known pathogenic variants associated with the disease (i.e., *GRN*, *MAPT*, and *C9orf72* repeat expansions) and identified a *MAPT* H1/H1 haplotype as well as a heterozygous *CHMP2B* missense variant (c.339C>G, p.Asn113Lys), which was classified as a variant of uncertain significance. Together, these findings supported a diagnosis of CBS likely due to an underlying 4R tauopathy, most consistent with CBD (Figure 1).

From 1986 to 2001, the patient worked directly in chemical plants, including a 4-year period early in his career at a nitrobenzene and aniline production facility. Symptom onset occurred approximately 20 years after cessation of chemical exposure. His reportedly monozygotic twin, who worked primarily as a consultant to the chemical industry without direct production floor exposure, remains neurologically asymptomatic, although future disease cannot be excluded.

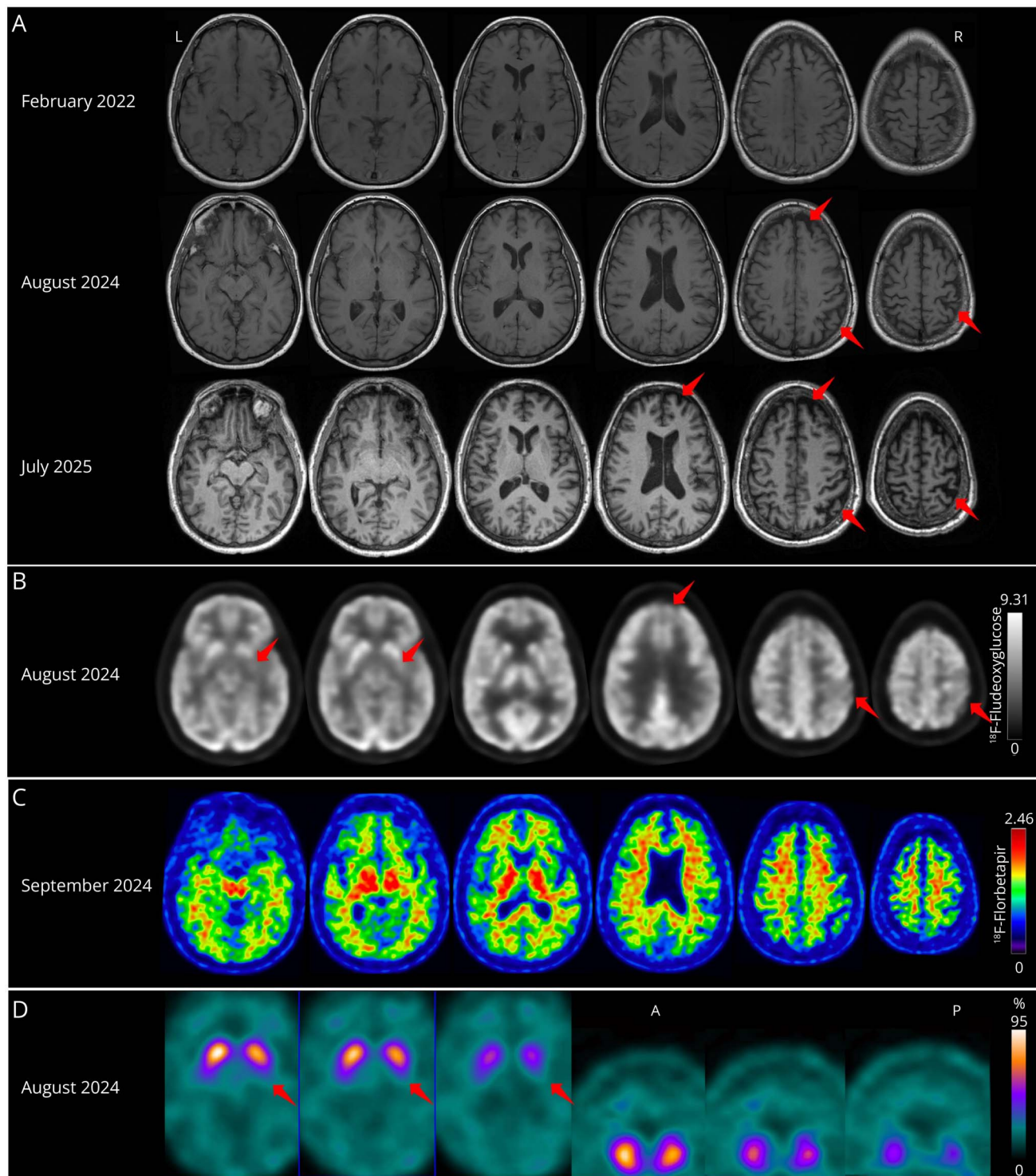
Standard Protocol Approvals, Registrations, and Patient Consents

Written informed consent for publication of this information was obtained from the patient.

Discussion

We present the case of a patient with CBS confirmed by characteristic clinical features and multimodal imaging, occurring in the context of *MAPT* H1/H1 homozygosity and prolonged occupational exposure to nitrobenzene and aniline. The discordance between this patient and his genetically identical monozygotic twin provides a unique opportunity to examine gene-environment interactions in the pathogenesis of nonfamilial CBD.

Our patient was occupationally exposed to multiple chemicals, including nitrobenzene and aniline, during his 15-year career in manufacturing. Among these exposures, nitrobenzene and aniline have been mechanistically linked to tau pathology through oxidative and nitrative stress pathways. Experimental models demonstrate that aniline induces dose-dependent lipid peroxidation and protein oxidation through reactive oxygen species generation and iron-mediated catalytic mechanisms.⁷ In addition, *in vitro* models show that aniline triggers mitochondrial dysfunction, oxidative DNA damage, and apoptotic cell death.⁵ Crucially, nitrative stress directly modifies tau protein leading to tau nitration and aggregation. Nitrated tau has been detected in neurofibrillary tangles across multiple neurodegenerative tauopathies, including AD, CBD, and Pick disease, with experimental peroxynitrite treatment sufficient to generate nitrated tau aggregates in cultured cells models.⁸ These findings establish plausible mechanisms whereby chronic industrial exposure to

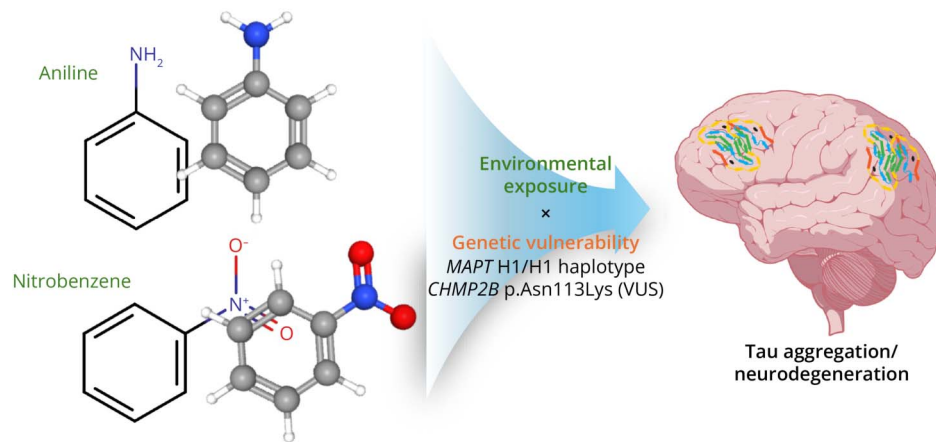
Figure 1 Structural and Functional Neuroimaging Findings

(A) T1-weighted MRI scans from 3 time points (February 2022, August 2024, and July 2025) showing progressive, asymmetric cortical atrophy predominantly affecting the right frontal and parietal lobes (red arrows). (B) ^{18}F -Fluorodeoxyglucose PET (FDG-PET) scan obtained in August 2024 demonstrating right > left frontoparietal hypometabolism and right basal ganglia and thalamic hypometabolism (red arrows). (C) ^{18}F -Florbetapir amyloid PET scan from September 2024 revealing a negative result for amyloid deposition. (D) Dopamine transporter (DaT) SPECT scan from August 2024 shows reduced radiotracer uptake in the right basal ganglia (red arrows).

nitrobenzene and aniline could promote pathologic tau aggregation. Paradoxically, certain purified aniline derivatives, most notably methylene blue, have also been investigated for

therapeutic potential in tauopathies.^{9,10} Therapeutic formulations deliver controlled doses of specific purified derivatives, whereas occupational exposure involves complex

Figure 2 Conceptual Model Illustrating the Hypothesized Interaction Between Environmental Exposure and Genetic Susceptibility, Which May Promote Tau Aggregation and Neurodegeneration in Vulnerable Individuals



mixtures of parent compounds and metabolites at unpredictable concentrations over prolonged periods. The neurotoxicity of industrial aniline exposure should therefore not be conflated with pharmaceutical investigation of purified derivatives. This apparent contradiction likely reflects critical dose-dependent and compound-specific differences, highlighting the need for compound-specific and dose-specific investigation.

Epidemiologic observations reinforce the plausibility of environmental contributions to 4R tauopathies. Notably, a geographical cluster of PSP in northern France revealed an incidence 12-fold higher than expected among residents of an area with decades of industrial chromate and phosphate ore processing, textile dyeing, and tanning operations, resulting in persistent soil contamination by arsenic and hexavalent chromium.⁶ Critically, genetic analysis of autopsied cases from this cluster revealed that 95.8% carried the *MAPT* H1/H1 haplotype, which is strongly overrepresented in PSP and CBD and is associated with increased tau expression and enhanced 4R tau aggregation propensity.¹¹ Although causality remains unproven, the clustering of a rare tauopathy within a defined industrial region raises important questions about the role of environmental toxicants as potential triggers or amplifiers of tau aggregation in biologically vulnerable individuals.

The genetic architecture of this case warrants detailed consideration. As monozygotic twins, both siblings are expected to share *MAPT* H1/H1 homozygous, yet only the twin with 15 years of direct occupational exposure in chemical manufacturing facilities developed CBS. The temporal relationship is particularly instructive. Symptom onset occurred approximately 20 years after cessation of chemical exposure, more than 30 years after the specific nitrobenzene and aniline exposure, consistent with a long latency period between environmental insult and clinical manifestation that has been observed in other toxin-associated neurodegenerative

diseases. The genetic landscape is further nuanced by a heterozygous *CHMP2B* missense variant (c.339C > G, p.Asn113Lys) identified in the affected twin. Pathogenic *CHMP2B* variants have previously been linked to familial FTD and amyotrophic lateral sclerosis (ALS), most often through truncating mutations in exon 6 that disrupt the C-terminus of the protein.¹²⁻¹⁴ By contrast, the p.Asn113Lys variant is located in exon 4, immediately upstream of the second coiled-coil domain.¹⁵ This variant is extremely rare in population databases (allele frequency 0.00000401 in gnomAD, with no homozygotes reported) and appears in ClinVar as a single submission associated with FTD/ALS (ClinVar accession: VCV001392585.7). Genetic testing of the unaffected twin has not been performed, precluding confirmation of *CHMP2B* variant carrier status. Although definite functional evidence is lacking, this raises the possibility of oligogenic susceptibility wherein multiple genetic risk factors interact with environmental exposures to determine disease penetrance and phenotype (Figure 2).

While establishing conclusive causality from a single case report is not possible and stochastic factors cannot be excluded, this observation fulfills several key epidemiologic criteria for assessing potential causal relationships, with important clinical and research implications: temporal sequence (20-year latency following exposure cessation), biological plausibility (established mechanisms linking nitrobenzene/aniline to tau modification), and phenotypic concordance with genetic susceptibility (*MAPT* H1/H1 homozygosity). These findings underscore the necessity of obtaining detailed occupational and environmental exposure histories in patients with non-familial CBD, particularly recognizing that the specific nature, duration, and intensity of chemical exposure, may be the critical etiologic factor. Moreover, they demonstrate that genetic risk factors alone, even high-risk genotypes such as *MAPT* H1/H1, may be insufficient to cause disease, with environmental modifiers potentially serving as critical

determinants of clinical penetrance. While *MAPT* H1 haplotype and other genetic risk factors have been extensively characterized, the role of environmental determinants in 4R tauopathy pathogenesis remains inadequately investigated. Systematic case-control studies examining occupational exposures in nonfamilial CBD and PSP cohorts, stratified by *MAPT* haplotype, could clarify whether environmental neurotoxins such as nitrobenzene and aniline function as disease triggers, accelerants, or penetrance modifiers in genetically susceptible individuals.

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Author Contributions

Y. Chen: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. H. Pham: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. L. Rabkina: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. A.J. Weigand: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. C. Lane-Donovan: drafting/revision of the manuscript for content, including medical writing for content. A. Snyder: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. P.A. Ljubenkova: drafting/revision of the manuscript for content, including medical writing for content. J.C. Rojas: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. S.E. Lee: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. G.D. Rabinovici: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. J.S. Yokoyama: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. L. Dratch: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. C.T. McMillan: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. E. Suh: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. V.M. Van Deerlin: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. D.-J. Irwin: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. H. Ulugut: drafting/revision of the manuscript for content, including medical writing for content. B.L. Tee:

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