

Multimodality evoked potentials and full-field electroretinography in neurological Wilson disease

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Abstract

Background

Copper deposition in Wilson disease (WD) extends beyond the basal ganglia to the brainstem, cerebellum, and retina, causing neural dysfunction that may not be evident on clinical examination.

Objective

To compare visual, brainstem auditory, somatosensory, and motor evoked potentials (EPs), together with scotopic and photopic full-field electroretinography (ERG), between patients with neurological WD and unrelated healthy controls (HC), and to relate these measures to copper studies, brain MRI, and disease severity.

Methods

Forty patients with neurological WD and 20 unrelated HC underwent standardised EP and ERG recording; this patient–control comparison was the prespecified primary analysis. Ten clinically asymptomatic at-risk siblings from five families were assessed with the same protocol but, because *ATP7B* genotyping was unavailable, were excluded from the primary analysis; their findings are reported separately as exploratory.

Results

Patients showed prolonged visual, brainstem auditory, and selected somatosensory latencies compared with controls, with preserved cortical amplitude and normal primary somatosensory and motor responses. Retinal dysfunction showed the greatest between-group difference, with scotopic and photopic b-wave amplitudes markedly reduced in patients and falling below laboratory reference limits. No EP or ERG measure correlated with clinical severity or brain MRI abnormality, and no correlation with the copper indices survived adjustment for multiple comparisons.

Conclusion

Retinal dysfunction observed in full-field ERG was the most significant subclinical electrophysiological abnormality in treated neurological WD. None of the recorded abnormalities was associated with corresponding symptoms, suggesting that EP and ERG may detect involvement missed during clinical assessment.

Introduction

Copper deposition in Wilson disease (WD) extends beyond the basal ganglia to the brainstem, cerebellum, and retina, causing neural dysfunction that may not be evident on routine clinical examination¹. Evoked potentials (EPs) and electroretinography (ERG) provide an objective, motor-independent method for detecting such subclinical involvement, and their use in WD dates back to the 1980s².

Early studies in WD identified central conduction delay across multiple pathways, with somatosensory, auditory, and visual abnormalities correlating with neurological severity; cortical responses were absent in the most advanced cases^{2,3}. Auditory dysfunction has been localised to the brainstem, with the III–V interpeak interval correlating with the burden of neurological signs in WD⁴. A more recent WD cohort confirmed high rates of auditory and visual abnormalities, restricted to neurological phenotypes⁵. These changes are responsive to treatment, as auditory and somatosensory latencies decrease with chelation⁶. Motor pathway findings have been less consistent: a systematic review reported wide variability in motor EP yield, whereas later series recorded preserved responses in most patients^{7,8}.

Electrophysiological data from the Indian WD cohort remain limited. In an early WD series, visual evoked potentials (VEP) were prolonged in 7 of 13 patients, and brainstem auditory interpeak latencies were prolonged in 8 of 12 patients⁹. Pattern-reversal VEP and flash electroretinography were subsequently combined in ten newly diagnosed patients at the same centre¹⁰. Clinical features, MRI, and four EP modalities were assessed in 18 patients, among whom VEP were abnormal in 57% and auditory and somatosensory responses in approximately half¹¹. Resting motor threshold (RMT) and central motor conduction time (CMCT) were both elevated in 13 patients examined at a tertiary centre in southern India¹². In 18 patients followed longitudinally at the same centre, RMT decreased significantly during chelation, whereas CMCT did not change¹³. However, no Indian study has combined all four EP modalities with scotopic and photopic electroretinography (ERG) in the same participants.

The retina is exposed to the same copper-handling defect because ATP7B is expressed in both the retinal pigment epithelium and photoreceptors¹⁴. Retinal thinning on optical coherence tomography and reduced full-field ERG responses have been reported in WD^{15–17}. However, whether rod- and cone-driven responses are comparably affected, and how retinal function relates to conduction along the classical afferent pathways in the same individuals, remain unclear.

We therefore compared visual, brainstem auditory, somatosensory, and motor EPs, together with scotopic and photopic full-field ERG, between patients with neurological WD and unrelated healthy controls, and examined the relationship of these measures with copper studies, brain MRI, and a validated severity scale.

Methods

This prospective study was conducted in the Departments of Neurology at the All India Institute of Medical Sciences, New Delhi, between February 2024 and March 2025. We screened 44 symptomatic patients from 44 unrelated families, with four declining participation. Twenty unrelated healthy volunteers served as controls. The primary analysis compared the symptomatic patients to the control group. We recruited and evaluated asymptomatic siblings of the index patients at the same time. Since *ATP7B* sequencing for these siblings was incomplete at the time of analysis, their genetic status remained unknown, preventing classification as presymptomatic carriers. We describe their electrophysiological recordings in the Supplementary Material.

Patients required a definite diagnosis of WD by a modified Leipzig score of 4 or more together with neurological involvement, and were eligible irrespective of treatment status¹⁸. Siblings of index patients were eligible if they had no clinical abnormality, with or without biochemical or radiological abnormality. We excluded a purely hepatic phenotype, as well as any other neurological, ophthalmological, or systemic condition that could alter EP recordings, contraindications to any study procedure, and inability to cooperate with testing.

All patients underwent history taking, general and neurological examination by the investigators, slit-lamp examination, and copper studies comprising serum ceruloplasmin, serum copper and 24-hour urinary copper excretion. Clinical severity was scored with the Movement Disorder Society Global Assessment Scale (GAS) for Wilson's disease¹⁹.

Evoked Potentials

EP recording followed established clinical recommendations^{20–23}. A latency above or an amplitude below the laboratory reference limit was classified as abnormal. Pattern-reversal VEPs used a black-and-white checkerboard with a 1° check size, reversing at 1–2 Hz, with the active electrode at Oz, referenced to Fz, and a forehead ground. N75, P100 and N145 latencies and P100 amplitude were measured against reference limits of 70–90 ms, below 110 ms, 140–160 ms and above 5 µV, respectively. Brainstem auditory evoked potentials (BAEPs) were elicited by monaural rarefaction clicks of 100 µs duration at 70–90 dB above threshold, delivered via headphones, and recorded from mastoid electrodes referenced to Cz; reference limits for waves I, III and V were 1.417–1.797, 3.41–3.91 and 5.22–5.76 ms.

Somatosensory evoked potentials (SSEPs) were recorded following median nerve stimulation at the wrist with 0.2 ms pulses at 3–5 Hz and supramaximal intensity, from Erb's point, the cervical spine and the contralateral parietal cortex, and N9, N13, N20, P25 and N30 latencies were measured. Motor EPs were obtained using transcranial magnetic stimulation with a Magstim 200 stimulator and a 70 mm coil, with surface electromyography recorded from the abductor pollicis brevis; RMT was expressed as a percentage of maximum stimulator output (reference range 35–60%), and motor response amplitude was recorded.

Electroretinography

Full-field ERG was performed in accordance with International Society for Clinical Electrophysiology of Vision standards²⁴. Pupils were dilated with 1% tropicamide, and electrodes were applied after topical anaesthesia. Dark adaptation lasted 45 minutes before scotopic recording, and light adaptation lasted 15 minutes before photopic recording. The b-wave amplitude was the primary outcome, with lower laboratory reference limits of 8 μ V for the scotopic response and 24 μ V for the photopic response.

Neuroimaging

Brain MRI was acquired at 1.5 T using T1-weighted, T2-weighted, fluid-attenuated inversion recovery, diffusion-weighted, and susceptibility-weighted sequences. MRI was performed wherever feasible; it was deferred in patients who refused the scan or required general anaesthesia to complete it, as poor cooperation or dystonia-related movement artefact precluded image acquisition. Two radiologists reported each study independently, and findings were recorded region by region as present or absent.

Statistical analysis

Continuous variables are summarised as mean $\pm$ standard deviation. For the paired-organ modalities, VEP, BAEP and ERG, each side was recorded separately; because the two eyes or ears of one participant are not independent observations, right-sided recordings were used for analysis, and left-sided recordings were inspected for consistency of direction. We compared the groups using one-way analysis of variance with Bonferroni-adjusted pairwise comparisons, and categorical variables with the chi-square or Fisher exact test; the patient–control contrast is the analysis reported here, and the corresponding sibling comparisons are reported in the Supplementary Material as exploratory. Within the patient group, we examined associations between each EP and ERG measure and the baseline GAS score and the three copper indices (serum ceruloplasmin, serum copper, and 24-hour urinary copper excretion) using the Pearson correlation coefficient; we report all 64 coefficients in Supplementary Table S6 and treated them as exploratory. We considered a two-sided p-value below 0.05 significant. Analyses used Stata 17 (StataCorp, College Station, TX, USA).

Ethics

The Institute Ethics Committee at the All India Institute of Medical Sciences, New Delhi, approved the protocol (Ref No. IEC PG-525/20.9.23, RT-21/26.10.23), and the study followed the principles of the Declaration of Helsinki. We obtained written informed consent from each participant or from a legally authorised representative if the participant was a minor.

Results

Forty patients were evaluated at a mean age of 19.8 ± 5.4 years (median, 19 years; range, 10–37 years); 26 (65%) were male. The mean age at symptom onset was 15.3 ± 5.9 years, and the mean disease

duration at presentation was 4.3 ± 5.0 years. Movement disorder was the predominant presenting syndrome, most commonly dystonia. All patients had extrapyramidal manifestations at recruitment, with dystonia in 34 (85%) and parkinsonism in 13 (32.5%). Kayser–Fleischer rings were observed in 32 (80%) patients, and cognitive or behavioural involvement occurred in 14 (35%). All patients received chelation therapy, predominantly penicillamine-based (38/40, 95%). No patient reported visual, auditory, or sensory symptoms, and none had clinical evidence of peripheral neuropathy. The mean GAS score was 17.5 ± 9.8 (median, 16; range, 1–45) (Table 1).

Table 1
Demographic, clinical and biochemical characteristics of the participants

Characteristic	Patients (n = 40)	Controls (n = 20)
Age, years	19.8 ± 5.4	36.5 ± 10.6
Male sex, n (%)	26 (65.0)	10 (50.0)
Age at symptom onset, years	15.3 ± 5.9	—
Disease duration, years	4.3 ± 5.0	—
Dystonia, n (%)	34 (85.0)	0
Parkinsonism, n (%)	13 (32.5)	0
Cognitive or behavioural involvement, n (%)	15 (37.5)	0
Seizures, n (%)	5 (12.5)	0
Myoclonus, n (%)	2 (5.0)	0
Ataxia, n (%)	2 (5.0)	0
Kayser–Fleischer ring, n (%)	32 (80.0)	0
Positive family history, n (%)	4 (10.0)	0
GAS score	17.5 ± 9.8	—
Serum ceruloplasmin, mg/dL	9.54 ± 4.76	—
Serum copper, $\mu\text{g/dL}$	42.87 ± 27.21	—
24-hour urinary copper, $\mu\text{g/24 h}$	94.45 ± 72.37	—
On chelation therapy, n (%)	40 (100)	0
<i>Values are mean $\pm$ standard deviation unless stated otherwise. Copper studies were not performed in controls. Corresponding data for the at-risk siblings are given in Supplementary Table S1. GAS, Global Assessment Scale for Wilson's disease; —, not applicable.</i>		

The 20 controls comprised 10 men and 10 women with a mean age of 36.5 ± 10.6 years and had no personal or family history of liver or neurological disease (Table 1). The 10 at-risk siblings, drawn from 5

families, had a mean age of 16.6 ± 4.4 years (median 16, range 11–24) and comprised six males and four females; all had a normal neurological examination and normal copper studies (Supplementary Table S1).

Visual and brainstem auditory evoked potentials

VEP latencies were prolonged in patients compared with controls (N75: 90.17 ± 14.09 vs 66.15 ± 6.98 ms; P100: 135.56 ± 25.97 vs 98.40 ± 6.79 ms; N145: 168.88 ± 28.54 vs 135.60 ± 4.51 ms; all $p < 0.001$), whereas P100 amplitude was preserved ($p = 1.000$) (Table 2). BAEP absolute latencies were also prolonged, most prominently for waves III and V (both $p < 0.001$), with a smaller prolongation of wave I ($p = 0.043$). Left-sided recordings showed the same direction of difference.

Table 2
Visual and brainstem auditory evoked potential findings of participants

Measure	Patients (n = 40)	Controls (n = 20)	Reference limit	p
VEP N75 latency, ms	90.17 ± 14.09	66.15 ± 6.98	70–90	< 0.001
VEP P100 latency, ms	135.56 ± 25.97	98.40 ± 6.79	< 110	< 0.001
VEP N145 latency, ms	168.88 ± 28.54	135.60 ± 4.51	140–160	< 0.001
VEP P100 amplitude, μV	7.65 ± 2.18	7.88 ± 1.00	> 5	1.000
BAEP wave I latency, ms	1.60 ± 0.25	1.44 ± 0.20	1.417–1.797	0.043
BAEP wave III latency, ms	4.07 ± 0.53	3.53 ± 0.20	3.41–3.91	< 0.001
BAEP wave V latency, ms	6.09 ± 0.69	5.36 ± 0.19	5.22–5.76	< 0.001
<i>Values are mean $\pm$ standard deviation of right-sided recordings. Reference limits are those of the recording laboratory. p values are Bonferroni-adjusted pairwise comparisons derived from one-way analysis of variance across the three groups recruited; the corresponding sibling values and comparisons are given in Supplementary Table S2. BAEP, brainstem auditory evoked potential; VEP, visual evoked potential.</i>				

Somatosensory and motor evoked potentials

SSEP abnormalities were limited to N9 and N30 latencies, both of which were prolonged in patients (8.75 ± 1.56 vs 6.84 ± 1.36 ms and 36.02 ± 5.08 vs 27.69 ± 1.40 ms, respectively; both $p < 0.001$) (Table 3). N13, N20 and P25 latencies did not differ between groups (all $p \geq 0.113$). RMT and motor

response amplitude were within laboratory reference limits and comparable between patients and controls ($p = 0.244$ and $p = 0.540$, respectively).

Table 3
Somatosensory and motor evoked potential findings of participants

Measure	Patients (n = 40)	Controls (n = 20)	p
SSEP N9 latency, ms	8.75 ± 1.56	6.84 ± 1.36	< 0.001
SSEP N13 latency, ms*	13.13 ± 1.84	12.26 ± 0.64	0.113
SSEP N20 latency, ms	18.46 ± 3.37	17.92 ± 0.98	1.000
SSEP P25 latency, ms	25.94 ± 3.46	25.31 ± 1.69	1.000
SSEP N30 latency, ms	36.02 ± 5.08	27.69 ± 1.40	< 0.001
Resting motor threshold, % MSO	47.00 ± 6.58	43.15 ± 10.98	0.244
Motor response amplitude, μV	487.11 ± 128.99	527.89 ± 77.33	0.540
<i>Values are mean $\pm$ standard deviation. p values are Bonferroni-adjusted pairwise comparisons derived from one-way analysis of variance across the three groups recruited; the corresponding sibling values and comparisons are given in Supplementary Table S3. *n = 39 patients. MSO, maximum stimulator output; SSEP, somatosensory evoked potential.</i>			

Electroretinography

ERG demonstrated the largest between-group differences. Both scotopic and photopic b-wave amplitudes were markedly reduced in patients (4.33 ± 1.75 vs $13.61 \pm 2.28 \mu V$ and 5.52 ± 1.44 vs $39.68 \pm 7.15 \mu V$, respectively; both $p < 0.001$), and both patient-group means were below laboratory lower reference limits (Table 4).

Table 4
Full-field electroretinographic b-wave amplitudes of participants

Measure	Patients (n = 40)	Controls (n = 20)	Lower reference limit	p
Scotopic b-wave amplitude, μV	4.33 ± 1.75	13.61 ± 2.28	8	< 0.001
Photopic b-wave amplitude, μV	5.52 ± 1.44	39.68 ± 7.15	24	< 0.001
Values are mean $\pm$ standard deviation of right-eye recordings. p values are Bonferroni-adjusted pairwise comparisons derived from one-way analysis of variance across the three groups recruited; the corresponding sibling values and comparisons are given in Supplementary Table S4. Reference limits are those of the recording laboratory				

Neuroimaging and association with severity

Among the 24 patients imaged, the putamen and midbrain were most often abnormal (37.5% each), followed by the globus pallidus, pons, caudate nucleus and thalamus (Supplementary Table S5). Cerebral atrophy was present in 20.8%. Nineteen controls were imaged, and all studies were normal.

Baseline GAS score did not correlate with any VEP, BAEP, SSEP, MEP or ERG measure in the patient group (Pearson $r = -0.30$ to 0.26 , all $p \geq 0.061$). Three of the 48 coefficients involving the copper indices reached nominal significance: serum ceruloplasmin with VEP P100 amplitude ($r = -0.46$, $p = 0.003$) and with SSEP N20 latency ($r = 0.48$, $p = 0.002$), and serum copper with SSEP N9 latency ($r = 0.48$, $p = 0.002$). None survived correction for the 64 comparisons performed (Bonferroni threshold $p < 0.00078$; smallest false discovery rate q value 0.11). Ceruloplasmin associations showed opposite trends to the anticipated copper-mediated effects. The full matrix is given in Supplementary Table S6.

Discussion

In the present study, we recorded four EP modalities and full-field ERG in the same participants, an approach seldom undertaken in neurological WD. Patients showed prolonged latencies along the visual and brainstem auditory pathways and at the peripheral N9 and late N30 somatosensory components, alongside a marked reduction in scotopic and photopic b-wave amplitudes. Among these abnormalities, retinal dysfunction was the most pronounced, while the primary cortical somatosensory response and cortical excitability remained intact. Notably, none of the participants reported visual, auditory, or other sensory symptoms, indicating that all identified electrophysiological abnormalities were subclinical.

The reduction in retinal responses was the largest difference between patients and controls, exceeding every latency difference in magnitude. Because all patients were established on chelation, this reduction reflects dysfunction that persisted despite treatment rather than an untreated state. The finding is consistent with the known expression of *ATP7B* in the retinal pigment epithelium and photoreceptors and with copper-dependent redistribution of its protein product¹⁴, and it complements the structural changes demonstrated by optical coherence tomography^{14–16}. The present findings extend the earlier electrophysiological series in which reduced full-field responses were reported by comparing rod- and cone-driven responses directly within the same cohort^{10,17}. Both rod- and cone-driven responses were affected. The proportional reduction was greater for the photopic response, although scotopic and photopic amplitudes are obtained under different adaptation conditions and are therefore not directly comparable. We recorded reductions of similar magnitude in the asymptomatic at-risk siblings assessed in parallel; because their genetic status could not be established, we do not interpret them further here.

The distribution of abnormalities within the patient group merits comment. Prolongation of all three visual peaks with preserved P100 amplitude, together with prolongation of brainstem auditory latencies from wave I onwards, is consistent with earlier reports^{3–5,9}. Somatosensory involvement, by contrast, spared the primary cortical response: N13, N20 and P25 latencies were within normal limits, whereas N9 and N30 latencies were prolonged, a pattern that differs from the cervicocortical delay originally described by Chu². Prolongation of N9 with a normal N13 latency suggests conduction delay distal to

the cervical cord that was not apparent on clinical examination, while delay of the N30 component is compatible with the frontal and striatal generators known to contribute to this response, consistent with the putaminal and midbrain lesions observed on imaging in this cohort^{25,26}. RMT remained within normal limits in both groups, unlike the elevated thresholds reported in predominantly untreated or mixed cohorts^{7,12}. Because RMT has been shown to decrease with effective de-coppering while CMCT remains unchanged, normal thresholds would be expected in a fully chelated cohort such as the present one¹³.

The clinical severity did not predict the electrophysiological measures recorded in this cohort. The GAS score showed no association with any EP or ERG variable, which is not unexpected, given that this instrument is weighted toward dystonia, tremor, and functional disability¹⁹ rather than sensory or visual impairment, particularly in patients who reported no such symptoms. Other rating scales used in this disease share the same limitation, as none incorporates a dedicated sensory or visual domain^{27,28}. Imaging was described by region and was not statistically related to the electrophysiological measures, so we cannot determine how structural and functional abnormalities relate in these patients. The cohort was small, but we recruited patients and controls simultaneously and recorded five electrophysiological modalities. Because recordings from the two eyes or ears of the same individual are not independent, we analysed only right-sided recordings and used left-sided recordings solely to verify the consistency of the results, thereby preventing the inflation of findings that can occur when averaging or pooling data from both sides.

Certain limitations still need to be acknowledged. The study was conducted at a single centre, which may limit generalisability. Controls were matched for sex but, on average, were older than patients. Since latencies lengthen and b-wave amplitudes decline with age, this imbalance would, if anything, be expected to narrow rather than widen the observed group differences, making it unlikely that the abnormalities recorded in patients can be attributed to age. This age imbalance does, however, constrain interpretation of the measures on which patients and controls did not differ, as a modest, true difference could conceivably have been masked by the direction of the age effect. Genotyping of the at-risk siblings was still in progress, so their *ATP7B* status could not be established. Brain MRI was available in 24 of the 40 patients and was scored region by region as present or absent rather than using a validated severity index, and it was not statistically related to the electrophysiological measures. The correspondence between structural and functional abnormality therefore remains unexamined. Optical coherence tomography was not performed alongside electroretinography, precluding correlation of retinal structure with retinal function in the same individuals. The correlation analysis comprised 64 coefficients; the corresponding multiplicity thresholds are reported, but these analyses remain exploratory rather than confirmatory. Finally, as all patients were established on chelation at the time of assessment, the findings reported here characterise a treated rather than a treatment-naïve cohort.

Conclusion

Retinal dysfunction, measured by scotopic and photopic full-field ERG, was the most consistent electrophysiological abnormality in treated neurological WD, showing a greater magnitude than conduction delays in the visual, auditory, and somatosensory pathways. None of these delays was accompanied by corresponding symptoms, and clinical severity did not predict any of them. Prospective work combining full-field ERG with retinal imaging, serial recording during chelation, and, where feasible, genotyping is needed to establish whether these measures can serve as markers of neural involvement and treatment response.

Declarations

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Author Contributions

Author contributions

A. Research project

1. Conception: DMR, RD, AG
2. Organization: DMR, AA, RD, Shalimar, BK, AG
3. Execution: KK, AG, RR, EA, AD, DG

B. Statistical Analysis

1. Design: SP
2. Execution: KK, SP
3. Review and Critique: DMR

C. Manuscript Preparation:

1. Writing of the first draft: DMR, KK
2. Review and Critique: AA, AKP, AKS

Ethical Compliance Statement

1. The Institutional Ethics Committee approved the study (Ref No. IEC PG-525/20.9.23, RT-21/26.10.23), and it was conducted in accordance with the Declaration of Helsinki.

2. Written informed consent to publish the clinical data was obtained from adult participants; for minors, written consent to publish was obtained from a parent or legal guardian, and assent was obtained where applicable.

3. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Data Availability Statement

The data supporting the findings of this study are not publicly available because they contain potentially identifiable participant information and/or are subject to ethical restrictions. De-identified data may be made available by the corresponding author upon reasonable request, subject to approval by the study investigators and institutional ethics requirements.

Sources of funding

This study received no specific funding from any agency in the public, commercial or not-for-profit sectors.

Conflicts of interest

The authors have no potential conflicts of interest to disclose.

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