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# Molecular correlates of epilepsy in early diagnosed and treated Menkes disease

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## Abstract

Epilepsy is a major feature of Menkes disease, an X-linked recessive infantile neurodegenerative disorder caused by mutations in *ATP7A*, which produces a copper-transporting ATPase. Three prior surveys indicated clinical seizures and electroencephalographic (EEG) abnormalities in a combined 27 of 29 (93%) symptomatic Menkes disease patients diagnosed at 2 months of age or older. To assess the influence of earlier, presymptomatic diagnosis and treatment on seizure semiology and brain electrical activity, we evaluated 71 EEGs in 24 Menkes disease patients who were diagnosed and treated with copper injections in early infancy (≤6 weeks of age), and whose *ATP7A* mutations we determined. Clinical seizures were observed in only 12.5% (3/24) of these patients, although 46% (11/24) had at least one abnormal EEG tracing, including 50% of patients with large deletions in *ATP7A*, 50% of those with small deletions, 60% of those with nonsense mutations, and 57% of those with canonical splice junction mutations. In contrast, five patients



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with mutations shown to retain partial function, either via some correct RNA splicing or residual copper transport capacity, had neither clinical seizures nor EEG abnormalities. Our findings suggest that early diagnosis and treatment improve brain electrical activity and decrease seizure occurrence in classical Menkes disease irrespective of the precise molecular defect. Subjects with *ATP7A* mutations that retain some function seem particularly well protected by early intervention against the possibility of epilepsy.

## Introduction

Menkes disease (OMIM#309400) is an X-linked recessive disorder involving defective copper metabolism and is characterized by infantile neurodegeneration, seizures, failure to thrive, and connective tissue abnormalities (Danks et al. 1972; Horn et al. 1992; Kaler 1994). The neuropathology of Menkes disease is caused by functional deficiency of a copper-transporting ATPase, ATP7A, which has roles in neuronal activation, axonal targeting, and synapse development (Schlief et al. 2005; El Meskini et al. 2007). In addition, reductions in the activities of numerous copper-dependent enzymes including cytochrome *c* oxidase, dopamine β-hydroxylase, lysyl oxidase, peptidylglycine alpha-amidating monooxygenase, superoxide dismutase, and tyrosinase contribute to the clinical signs and symptoms of this disorder (Kaler et al. 1993a, b; Kaler 1998). Affected infants appear healthy at birth and typically develop normally for 6 to 8 weeks. Subsequently, hypotonia, seizures, and failure to thrive develop, and affected patients often die by 3 years of age. However, early identification and institution of copper injections by 10 days of age enhances survival and can improve clinical outcomes, most dramatically in newborns with mutations that do not completely abrogate ATP7A function (Kaler et al. 2008).

Epilepsy is a major feature of Menkes disease; seizure types include focal or multifocal tonic-clonic, myoclonic, infantile spasms, and status epilepticus (Bahi-Buisson et al. 2006; Friedman et al. 1978; White et al. 1993). These three large series on EEG findings indicated that Menkes disease patients older than 2 months of age nearly always developed abnormal electrocerebral activity. EEG abnormalities included absence of age-appropriate features, background slowing and disorganization, polymorphic slow waves, focal or diffuse spike and waves, status epilepticus, and hypsarrhythmia.

The current study reports details on seizure semiology and serial EEG findings in a cohort of 24 patients confirmed as having Menkes disease by *ATP7A* molecular analysis and who began early copper injection treatment within 6 weeks of age.

## Methods

### Subjects

From 1992 to 2007, 24 newborn patients diagnosed with classical Menkes disease on clinical, neurochemical (Kaler et al. 1993a, b), or molecular grounds were referred to the National Institutes of Health (NIH). The patients' parents did not have epilepsy. Daily subcutaneous injections of 250–500 μg copper per day (copper histidine, U.S. Food and Drug Administration Investigational New Drug #34,166; holder S.G. Kaler) were begun in the absence of neurological symptoms under an NIH intramural clinical research protocol (ClinicalTrials.gov number NCT00001262), as previously described (Kaler et al. 1995, 1996, 2008; Kaler 1996). The study was approved by the NICHD and NINDS Institutional Review Boards and the NICHD Data Safety Monitoring Committee. Informed consent was obtained from the patients' parents. The subjects were evaluated at the NIH Clinical Center in a series of visits at which detailed histories including signs and symptoms of seizure activity were obtained from parents and neurodevelopmental progress was documented

using the Denver Developmental Screening Test II. EEGs were recorded at baseline (within the first 6 weeks of life), and approximately every 6 months up to 3 years of age except for nine patients who died during the trial (range of age at death: 5.5 months to 2.6 years), and seven patients who had some EEGs beyond 3 years of age (up to age 6 years).

### Electroencephalography

Subjects had 21-channel EEGs carried out during wakeful and sleep states, using the international 10/20 system for electrode replacement. Photic stimulation was performed in all patients. The duration of EEG recordings was 30–45 min. All EEG recordings were read by a board-certified electroencephalographer (S.S.), who was aware of the diagnosis of Menkes disease and patient treatment status.

### Mutation analysis

Genomic DNA from the patients was screened for ATP7A mutations, as previously described (Liu et al. 2002).

### Statistical analysis

We used the chi-square test for independence to compare the proportion of clinical seizures, electroencephalographic abnormalities, and survival in this cohort with those of three previously studied groups (Bahi-Buisson et al. 2006; Friedman et al. 1978; White et al. 1993) combined.

## Results

Patient characteristics including age at start of treatment, *ATP7A* mutation, EEG findings, seizure semiology and frequency, and neurologic outcome are summarized in Table 1. Mean age at initiation of treatment was 11.8±9.6 days. *ATP7A* mutations included four large deletions, four small deletions, five nonsense mutations, two missense mutations, and nine splice junction defects (Table 2). The splice junction defects included two that predict amino acid substitutions (Q724H and K1037N) but which both involved a G to T transversion at the final base of an exon, the 1 splice donor site position, an alteration that severely disrupts proper mRNA splicing (Kaler et al. 1995). Five of the seven other splice junction mutations affected highly conserved, canonical bases, whereas two (IVS8 AS dup5 and IVS9 DS +6, t→g) did not and were shown previously to generate some transcripts that maintained a proper translational reading frame (Kaler et al. 1996, 2008).

Among 71 total EEGs, 20 tracings showed one or more abnormalities, including slowed or disorganized background, focal slowing, focal spike and wave, and diffuse spike and wave (Table 3). While 11 of 24 patients had at least one abnormal EEG, only 3 (#16, 17, and 20) had clinical seizures; these included apneic, tonic-clonic, and myoclonic types, with onset at 16, 14, and 31 months of age, respectively (Tables 1 and 4). Compared to data combined from three studies of older Menkes patients ($n$= 29) who had already suffered neurologic problems, group differences in seizure occurrence, EEG abnormalities, and survival rate were highly statistically significant ($P$=3.8× $10^{-9}$, 5.0×$10^{-4}$, and 5.0×$10^{-3}$, respectively, Table 4).

Nine patients in the present cohort died, including four from acute respiratory syncytial virus (RSV) pneumonia, noted by superscript “c” in Table 1 (Neurologic outcome column), one from severe pulmonary emphysema (Grange et al. 2005) and one from congestive heart failure related to congenital pulmonic stenosis (Hicks et al., unpublished data). One patient was lost to follow-up after 6 months of age. Neurodevelopmental outcomes in the remaining

14 patients ranged from normal (*n*=3), to mildly (*n*=1), moderately (*n*=3), or severely (*n*=7) delayed.

Grouped by mutation class, 50% of the Menkes patients with large *ATP7A* deletions, 50% of those with small deletions, 60% of those with nonsense mutations, and 57% of those with canonical splice junction mutations had one or more abnormal EEG recordings. In contrast, none of the four patients with missense mutations or leaky splice junction defects had abnormal EEGs (Tables 1 and 2).

These four patients with normal or nearly normal neurologic outcomes had 19/19 EEGs with no abnormalities (Table 1). The mutations in two of these patients were IVS8 AS dup5 and IVS9 DS +6, t→g, for which we previously documented the molecular bases for partial copper transport function (Kaler et al. 1996, 2008). In the two other patients with successful developmental outcomes and no epilepsy, we confirmed that their mutations (R201X and G727R) possessed residual copper transport activity, as revealed by *in vitro* expression and/or yeast complementation analyses (Kaler et al. 2009; Tang et al. 2008).

## Discussion

In contrast to its allelic variants, occipital horn syndrome (Kaler et al. 1994) and *ATP7A*-related distal motor neuropathy (Kennerson et al. 2010), Menkes disease is characteristically associated with epilepsy. Here, we evaluated 71 EEGs in 24 Menkes disease patients who were diagnosed early before neurological symptoms occurred, and who were treated with copper injections beginning at less than 6 weeks of age. This cohort includes some subjects whom we have previously reported, however, without a detailed analysis of findings relevant to epilepsy. For example, ten patients (denoted in Table 1 by an “a” superscript) were part of prospective study (Kaler et al. 2008) to evaluate sensitivity and specificity of a plasma neurochemical assay for early diagnosis of Menkes disease in newborn infants accrued during a specific time frame and which did not present detailed EEG features. The current report provides an in-depth analysis of the EEG findings in those subjects and for other Menkes disease patients accrued outside the temporal boundaries of the prospective study. (Two subjects from Kaler et al. 2008 were excluded from the present analysis due to a family history of epilepsy, and a medical history of a seizure within 48 h of diphtheria-pertussis-tetanus immunization, respectively.)

We compared EEG findings in this large NIH cohort (*n*= 24) diagnosed and treated from early infancy with those found by others in older symptomatic Menkes disease patients from three previously published series (Bahi-Buisson et al. 2006; Friedman et al. 1978; White et al. 1993), one of which (White et al. 1993) also originated from our center. Table 4 indicates that the age at onset of clinical seizures in subjects from all four studies covered a similar range, from 9 weeks to as late as 52 weeks. The mean age at first seizure was later in both U.S. cohorts (roughly 20 weeks of age) compared to 12.5 and 14 weeks in the European cohorts (Bahi-Buisson et al. 2006; Friedman et al. 1978), for which there is no clear explanation.

In contrast, the strikingly decreased frequency of seizures, reduction of EEG abnormalities, and enhanced survival in the cohort with presymptomatic diagnosis and early treatment suggests that these latter factors improve brain electrical activity in Menkes disease patients irrespective of precise molecular defect. Information about the *ATP7A* mutations in the patients reported by Friedman et al. (1978), White et al. (1993), and Bahi-Buisson et al. (2006) is not available from those reports, although we since have determined the mutations in the subjects reported by White et al. (1993), and the spectrum of defects (one large deletion, one small deletion, two nonsense, one missense, and four splicing mutations) is

similar to that in the large cohort reported here. In fact, because of recurrences within families, four of the mutations represented in the present cohort (del exon 1, R201X, Q724H, and IVS8 AS dup) occurred in five of the nine subjects from White et al. (1993) whose EEG data we reference (Table 4). In terms of copper treatment, 8 of the older symptomatic subjects reported received copper EDTA injections while under study (Friedman et al. 1978), 9 had not received copper injections (White et al. 1993), and no information about copper treatment was provided for 12 (Bahi-Buisson et al. 2006). Thus, the major clinical distinctions between the cohort discussed here and the previously reported patients are absence of neurologic symptoms, and younger age at diagnosis and initiation of treatment.

A caveat to our findings is that the length of the individual EEG monitoring period (30–45 min) was shorter for subjects in this study than in two of the earlier series (Friedman et al. 1978; Bahi-Buisson et al. 2006), which may have affected the likelihood of detecting EEG abnormalities. We recorded during both wakeful and sleep states, however, and found no evidence for epileptic encephalopathy, a condition associated with high rates of epileptic seizures or subclinical epileptic activity in sleep (Neville 2007), among our patients with poor neurodevelopmental outcomes.

The molecular correlations presented here suggest that Menkes disease patients with *ATP7A* mutations that preserve partial function are particularly amenable to prevention of epilepsy in the context of early copper treatment. For example, the R201X nonsense mutation represents a rare example of native translational readthough that appears to be related to the sequence context associated with amino acid position 201 of the *ATP7A* coding sequence (Kaler et al. 2009). The allele harboring G727R, located in the second transmembrane segment of *ATP7A*, complemented a *Saccharomyces cerevisiae* copper transport mutant, although Western blots of fibroblast protein showed markedly reduced quantities of ATP7A, suggesting a misfolded protein response. The latter was confirmed by comparing degradation rates of mutant and wild-type ATP7A via cycloheximide treatment of cultured fibroblasts; half-life of the G727R mutant was 2.9 h and for the wild-type, 11.4 h. (Tang et al. 2008).

Notably, neither status epilepticus nor infantile spasms with hypsarrythmia on EEG were identified in any of the 24 subjects we report, compared with 10/12 Menkes patients who suffered status epilepticus and 11/12 who later manifested infantile spasms in the retrospective study by Bahi-Buisson et al. (2006). The mechanisms for improved brain electrical activity associated with presymptomatic copper injection therapy are unclear but may involve a salutary effect on neuronal excitotoxicity. Copper has been shown to act as a noncompetitive antagonist of the N-methyl-D-aspartate (NMDA) receptor (Vlachova et al. 1996), and impairment of NMDA receptor-mediated copper efflux in Menkes disease may directly alter receptor function and contribute to seizures (Schlief et al. 2005). Modulation of NMDA-mediated excitotoxocity by early copper treatment in Menkes disease may explain the overall results reported here. While most efficient delivery of copper across the blood-brain and blood-cerebrospinal fluid barriers is believed to require functional ATP7A, alternative copper transport systems could be activated in Menkes patients with severe loss-of-function mutations (Kaler 2010). In this context, normalization of blood copper levels attained by daily injections would facilitate copper transport into the brain.

The overall survival rate found in this cohort (62.5%) is lower than that in our recent prospective study, 92% (Kaler et al. 2008). This difference, in part, reflects the impact of several unexpected deaths from medical complications (acute RSV pneumonitis, and right heart failure as a long-term sequela of surgically treated congenital pulmonic stenosis) that are not generally considered features of Menkes disease.

The diagnosis of classical Menkes disease in the newborn period by plasma neurochemical levels (Kaler et al. 1993a, b, 2008) or genomic DNA-based techniques (Liu et al. 2002) affords the possibility of early copper therapy. The reduced seizure frequency and improved EEG pattern reported for this large cohort confirm the value of early diagnosis and treatment of affected infants and provide evidence for the desirability of population-based newborn screening for this condition.

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**Table 1**

Seizure semiology and EEG findings in 24 early diagnosed and treated Menkes disease patients

| | Age at start of treatment | *ATP7A* mutation | Number of EEGs | Number of abnormal EEGs | EEG abnormalities (age) | Seizure semiology and frequency | Neurologic outcome |
|---|---|---|---|---|---|---|---|
| 1. | 8 days | Del ex 7–19 | 2 | 2 | Excessive beta activity; bilateral spike and wave (6 years) | No known seizures | Severe delays[a] |
| 2. | 7 days | Del 20–23 | 7 | 2 | Central vertex and mid-frontal small sharp waves (9 months); background slowing (32 months) | No known seizures | Severe delays[a] |
| 3. | 5 days | Del 13–14 | 1 | 0 | No abnormalities found | No known seizures | Died at age 5 months[b] |
| 4. | 14 days | Del exon 1 | 2 | 0 | No abnormalities found | No known seizures | Severe delays[a] |
| 5. | 10 days | Del 4246–4260 | 3 | 2 | Multifocal spikes (6 weeks); R frontal small sharp waves (21 months) | No known seizures | Moderate delays[a] |
| 6. | 7 days | 2757delAG | 1 | 0 | No abnormalities found | No known seizures | Died at age 19 months[a,c] |
| 7. | 5 days | 3936/7 delT | 3 | 0 | No abnormalities found | No known seizures | Moderate delays[a] |
| 8. | 10 days | 3060delT | 3 | 1 | Monorhythmic (10 months) | No known seizures | Severe delays[a] |
| 9. | 7 days | Q197X | 2 | 0 | No abnormalities found | No known seizures | Moderate delays[d] |
| 10. | 8 days | R201X | 5 | 0 | No abnormalities found | No known seizures | Normal[e] |
| 11. | 16 days | L625X | 4 | 3 | Bilateral posterior spike and wave 2 (1 year); diffuse spike and wave (18 months); general slowing (30 months) | No known seizures | Died at age 2.5 years[f,g] |
| 12. | 10 days | W1187X | 3 | 2 | Generalized rhythmic alpha activity (13 days); R frontotemporal spike and wave (2 months) | No known seizures | Died at age 17 months[h] |
| 13. | 12 days | Q1385X | 2 | 2 | Asymmetric frequency/amplitude (9 months); diffuse beta activity (19 months) | No known seizures | Severe delays[a] |
| 14. | 22 days | G666R | 4 | 0 | No abnormalities found | No known seizures | Moderate delays[a] |
| 15. | 25 days | G727R | 4 | 0 | Normal | No known seizures | Minimal delays[i] |
| 16. | −3.5 weeks | Q724H[j] | 2 | 1 | R central and L temporal spike and wave (4.5 months) | Apnea/cyanosis 2–3 episodes/ day starting≈4 months | Died at age 5.5 months[c,k] |
| 17. | 30 days | K1037N[j] | 1 | 0 | No abnormalities found | One tonic-clonic seizure at 3.5 months | Died at age 14 months[l,m] |
| 18. | 28 days | IVS7 AS -1, g→c | 2 | 1 | L occipital spike and wave, L posterior slowing (7 months) | No known seizures | Died at age 18 months[n] |
| 19. | 10 days | IVS7 AS -1, g→c | 1 | 1 | L occipital spike and wave; L focal slowing (6 months) | No known seizures | Moderate delays[o] |

| | Age at start of treatment | *ATP7A* mutation | Number of EEGs | Number of abnormal EEGs | EEG abnormalities (age) | Seizure semiology and frequency | Neurologic outcome |
|---|---|---|---|---|---|---|---|
| 20. | 6 days (Corrected for gestational age) | IVS11 AS -1, g→a | 3 | 3 | Diffuse spike and wave (7 months); diffuse background slowing; diffuse spike and wave + bilateral temporal and R occipital multifocal spikes (2 years); disorganized background, bilateral temporal spike and wave (3 years) | Myoclonic jerks 10–20/day (onset at age 31 months) | Severe delays[p] |
| 21. | 6 days | IVS15 AS -1 g→a | 5 | 0 | No abnormalities found | No known seizures | Died at age 2 years 7 months[c,q] |
| 22. | 42 days | IVS12 DS +1 g→a | 1 | 0 | No abnormalities found | No known seizures | Died at age 6.5 months[c,r] |
| 23. | 6 days | IVS8 AS dup5[j] | 4 | 0 | No abnormalities found | No known seizures | Normal[s] |
| 24. | 8 days | IVS9 DS +6, t→g | 6 | 0 | No abnormalities found | No known seizures | Normal[a] |
| Total | | | 71 | 20 | | | |

[a] Detailed neurodevelopmental outcome reported in Kaler et al. 2008

[b] Detailed neurodevelopmental outcome reported in Desai et al. 2010

[c] Primary cause of death was RSV pneumonitis

[d] At age 31 months, gross motor: 12–13 months; fine motor: 12–15 months; language: 19–27 months; personal-social: 18–22 months. Lost to later follow-up

[e] Kaler et al. 2009

[f] At age 30 months, gross motor: 9–11 months; fine motor: 12–15 months; language: 18–20 months; personal-social: 16–18 months

[g] Primary cause of death was congestive heart failure related to congenital pulmonic stenosis (Hicks et al., unpublished data)

[h] At age 17 months, gross motor: 5 months; fine motor: 4 months; language: 3–6 months; personal-social: 5–8 months

[i] Tang et al. 2008

[j] Missense mutation or small duplication that affects a splice junction (please see text and specific references for details).

[k] Detailed neurodevelopmental outcome reported in Kaler et al. 1995

[l] Severe neurodevelopmental delays, as reported by Grange et al. 2005

[m] Primary cause of death was severe emphysema (Grange et al. 2005)

[n] At age 17 months, gross motor: 5 months; fine motor: 4 months; language: 4 months; personal-social: 4 months

[o] At age 6 months, gross motor: 3 months; fine motor: 3 months; language: 4–5 months; personal-social: 5 months. Lost to later follow-up

[p] At age 3 years, gross motor: 2–4 months; fine motor: 2 months; language: 3 months; personal-social: 4 months

[q] At age 31 months, gross motor: 9–12 months; fine motor: 13–17 months; language: 21–25 months; personal-social: 15–18 months

[r] At age 6.5 months, gross motor: 2 months; fine motor: 3 months; language: 5 months; personal-social: 4 months

[s] Kaler et al. 1996

**Table 2**

Spectrum of *ATP7A* molecular defects and electroencephalographic abnormalities

| ***ATP7A* mutation type** | **Large deletions** | **Small deletions** | **Nonsense** | **Missense** | **Canonical splice junction** | **Leaky splice junction** |
|---|---|---|---|---|---|---|
| Number of patients | 4 | 4 | 5 | 2 | 7 | 2 |
| Number of patients with abnormal EEGs (%) | 2 (50%) | 2 (50%) | 3 (60%) | 0 (0%) | 4 (57%) | 0 (0%) |

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**Table 3**

Classification of EEG abnormalities

| Type of EEG abnormality | Background slowing/ disorganization | Focal slowing | Focal spike and wave | Diffuse spike and wave |
|---|---|---|---|---|
| Frequency | 10 | 1 | 10 | 4 |
| Number of patients | 8 | 1 | 7 | 3 |

## Table 4

Age at onset of clinical seizures and rates of seizures, abnormal EEG, and survival in large studies of epilepsy in Menkes disease

| Subject number[a] | Friedman et al. (1978) (*n*=8) | White et al. (1993) (*n*=9) | Bahi-Buisson et al. (2006) (*n*=12) | Current study (*n*=24) |
|---|---|---|---|---|
| Age at onset of clinical seizures (weeks) | | | | |
| 1 | No seizures | N.A. | 12 | No seizures |
| 2 | 10 | 10 | 11 | No seizures |
| 3 | 9 | 15 | 10 | No seizures |
| 4 | 9 | 10 | 11 | No seizures |
| 5 | 11 | 12 | 20 | No seizures |
| 6 | 10 | 24 | 22 | No seizures |
| 7 | 14 | 14 | 10 | No seizures |
| 8 | 24 | 52 | 11 | No seizures |
| 9 | | No seizures | 32 | No seizures |
| 10 | | 32 | 11 | No seizures |
| 11 | | | 21 | No seizures |
| 12 | | | 12 | No seizures |
| 13–15, 18, 19, 21–24 | | | | No seizures |
| 16 | | | | 16 |
| 17 | | | | 14 |
| 20 | | | | 31 |
| Mean±SD age at 1st seizure (weeks) | 12.4±5.4 | 21.1±14.6 | 14 (SD not given) | 20.3±9.3 |
| Range (weeks) | 9–24 | 10–52 | 10–32 | 14–31 |
| Percentage with seizures | 87.5% | 88.9% | 100% | 12.5%[b] |
| Percentage with EEG abnormalities | 87.5% | 88.9% | 100% | 45.8%[c] |
| Percent survival | 37.5% | 33.3% | 8.3% | 62.5%[d] |
| Early copper treatment | No | No | No | Yes |

*N.A.* Not applicable

[a] Subject number refers to patients listed in Friedman et al. (1978), White et al. (1993), and in Table 1 of this paper. Mean (*n*=12) and range for age at onset of seizures were available from Bahi-Buisson et al. (2006), and we estimated individual ages (weeks) from Fig. 4 of that paper. For White et al., age at onset seizures and survival were not included in the original paper and are provided here from our records on these patients

[b] $P=3.8\times10^{-9}$

[c] $P=5.0\times10^{-4}$

[d] $P=5.0\times10^{-3}$

*P* values represent comparison of the present cohort (*n*=24) with three prior studies combined (*n*=29)