Clinical Commissioning Urgent Policy Statement Subcutaneous copper histidinate injections for presymptomatic neonates with classical Menkes disease (210507P) [URN 2104]

Publication date: June 2021 **Version number:** 1

Commissioning position

Summary

Subcutaneous copper histidinate injections are recommended to be available through routine commissioning as a treatment option for presymptomatic neonates with classical Menkes disease within the criteria set out in this document.

Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Executive summary

Plain language summary

Menkes disease is an inherited disorder of copper transport, which mainly affects males. 'Classical' Menkes disease is that which presents soon after birth and is a life-limiting disease, with affected children suffering seizures, growth failure and a poor quality of life. It is a progressive disease, with an average life expectancy of 3 years without early treatment. Current treatment focuses on treating the symptoms of the disease, as there is no cure.

Copper injections delivered under the skin are thought to reduce symptoms and treat the condition, as patients with Menkes disease cannot absorb copper normally from their diet. These injections are delivered twice a day for the first year and then once a day and is a lifelong treatment. These injections are expected to be delivered by the carers. For the treatment to be effective, it must be started within the first 28 days after birth.

Committee discussion

This was considered by the Clinical Panel as an urgent policy request. It was agreed that this did meet the criteria. The three evidence papers were considered and it was agreed to the policy would proceed based on these.

The condition

Classical Menkes disease is a recessive inherited metabolic disorder of copper transport caused by mutations in the ATP7A gene on the X-chromosome, affecting mainly males. Classical Menkes disease is a life-limiting, neurodegenerative disease with affected children suffering drug-resistant seizures, growth failure and a poor quality of life due to frequent hospitalisations. Classical Menkes disease is progressive, with an average life expectancy of 3 years without early treatment.

Symptoms are caused by copper deficiency due to the defective copper transporter in the gut, brain and other organs. Copper acts as a cofactor to activate copper-dependent enzymes. Serious and fatal effects may occur over time related to these enzymes not working correctly due to the lack of copper. These enzymes are important in the development of the brain, liver, bones, arteries and hair. Diagnosis of the condition is difficult, as newborn screening is not available in England and early detection is difficult as clinical abnormalities in affected newborns are absent or subtle. Furthermore, the usual biochemical markers (low serum copper and caeruloplasmin) are unreliable in the neonatal period, as the levels in healthy newborns are low and overlap with those in infants with classical Menkes disease. Molecular diagnosis is available, though complicated by the diversity of mutation types and the large size of ATP7A.

Although the incidence of Menkes disease in Western Europe is estimated to be between 1 in 250,000 and 1 in 300,000 many of these diagnoses will be made outside of the neonatal period, when symptoms have developed.

Current treatments

The current treatment for children with classical Menkes disease is symptomatic; treating seizures with anti-convulsant medication, and supportive, palliative care. If a pregnancy is identified as at risk of classical Menkes disease based on family history, antenatal testing is offered. The parents can then be offered genetic counselling and support if they choose to keep or terminate the pregnancy. If the pregnancy is continued, the child is discharged with early referral to neurology and palliative care services.

At the onset of symptoms, which are commonly seizures, frequent outpatient and inpatient attendances at a neurometabolic centre would be required. Early nasogastric feeding is usually required, with referral for gastrostomy insertion frequently made. Seizure control is usually poor with frequent, life-threatening hospital admissions (such as status epilepticus, even on anti-convulsant therapy). Other causes of hospital admissions (such as for respiratory infections) are also increased. Mainstream education is not normally achievable.

New treatment

Copper histidinate is a formulation of copper that can be delivered underneath the skin by subcutaneous injection. Patients with classical Menkes disease have a defect in the copper transporter in the gut, which affects the normal absorption of copper from the diet. There is evidence that delivering copper histidinate by subcutaneous injection can reduce the symptoms caused by copper deficiency if given before symptoms have developed in the neonatal period.

Subcutaneous copper histidinate injections are given at a dose of 250 micrograms twice daily in children under 1 year, then 250 micrograms once daily in children over 1 year. Treatment is initiated in a hospital setting, with training for the caregivers to continue treatment at home. Subcutaneous copper histidinate injections have Orphan Designation from the EMA (granted in August 2020) for use in patients with Menkes disease, it does not have marketing authorisation, therefore use in this condition is off-label. The injections are painful and can cause kidney damage with long-term use.

Evidence summary

The three papers selected as best available evidence were reviewed and summarised. They presented the following outcomes:

Outcome	Summary
Survival / death	The three included papers reported survival for patients described as receiving early treatment (<1 month old) ranging from 62.5% to 92%. For patients described as receiving later treatment, survival ranged from 8.3% to 50%.
Neurodevelopment outcomes	One of the three included papers reported that patients receiving early treatment (<1 month old) had statistically significantly better improvement across four neurodevelopmental areas than patients receiving later treatment. The other two included papers provided narrative descriptions of patient's neurodevelopment which ranged from normal to seriously cognitively impaired for patients with a range of treatment onset ages.
Growth measurements	One of the included papers reported growth measurements and reported a statistically significantly better occipitofrontal circumference for patients receiving early treatment (<1 month old) compared to patients receiving later treatment (after the appearance of symptoms). There was no statistically significant difference between early and later treatment for weight or length.
Neurologic outcomes	Two of the included papers reported seizures in 12.5% and 16.7% of patients receiving early treatment, with electroencephalogram abnormalities in 46% and 58% of patients respectively. In one paper seizures and electroencephalogram abnormalities were reported for 87.5% to 100% of later treatment or untreated patients.
Safety	One of the included papers commented on safety, reporting increased levels of a marker of renal tubular damage in patients who received early treatment (<1 month old) with copper histidinate.

The full three paper summary is presented in Appendix 1.

Implementation

Criteria

Inclusion criteria

Neonates will be evaluated for the capacity to benefit from treatment if they meet all of the following inclusion criteria:

- Family history of classical Menkes disease
- Confirmed classical Menkes disease by the finding of a pathogenic mutation on ATP7A[1]
- 28 days or younger at the time of treatment onset

Exclusion criteria

Patients will not be considered for treatment who meet the following exclusion criteria:

- Symptomatic from classical Menkes disease

Starting criteria

Patients that meet all of the inclusion criteria and do not meet the exclusion criteria should be considered for treatment with subcutaneous copper histidinate injections. These patients should be treated under the care of a specialist neurometabolic multidisciplinary team (MDT) including

[1] In certain cases, it may be appropriate to make a diagnosis by biochemical means where the family index case has not previously had genetics testing.

at least a paediatric consultant specialising in metabolic diseases, a paediatric consultant specialising in neurology and specialist nurses. The specialist MDT should ensure that routine blood tests including full blood count, urea and electrolytes along with cystatin C, copper and caeruloplasmin[2] are measured at baseline. The specialist MDT should ensure that the patient has had a renal ultrasound, echocardiography and awake and sleep electroencephalogram at baseline.

Patients should be started on 250 micrograms of copper histidinate delivered subcutaneously twice daily until the age of 1 year. Treatment should be initiated as early after birth as possible and before 28 days after birth. When the patient is over 1 year old, the dose should be reduced to 250 micrograms of copper histidinate delivered subcutaneously once daily. Treatment should be initiated in hospital, with relevant training given to the caregivers to administer the injections at home.

Clinicians are encouraged to supply contact details for patient support organisations (such as Metabolic Support UK) to carers of patients who are started on treatment with subcutaneous copper histidinate.

Reassessment

Patients that are started on subcutaneous copper histidinate injections should remain under the care of the specialist neurometabolic MDT and follow-up should be determined by treatment success:

- For patients where treatment is successful and there are minimal symptoms, follow-up should be in an outpatient setting at least every 6 months
- For patients where treatment is partially successful, but symptoms develop, outpatient follow-up at the neurometabolic centre should be more frequent to consider further investigations and symptomatic treatments
- For patients where treatment is not successful, a patient-focused discussion should take place between the specialist MDT and the carers regarding the ongoing risk-benefit balance of treatment with copper histidinate

Patients should be monitored with:

- Urea and electrolytes and cystatin C measured every 6 months
- Renal ultrasounds every 12 months
- Echocardiography every 12 months
- Electroencephalogram every 6-12 months
- MRI brain between the ages of 2-3 years
- Developmental assessments every 12 months

For patients that develop symptoms of classical Menkes disease whilst on treatment with copper histidinate, additional investigations may be required with electroencephalogram combined with anticonvulsant medication.

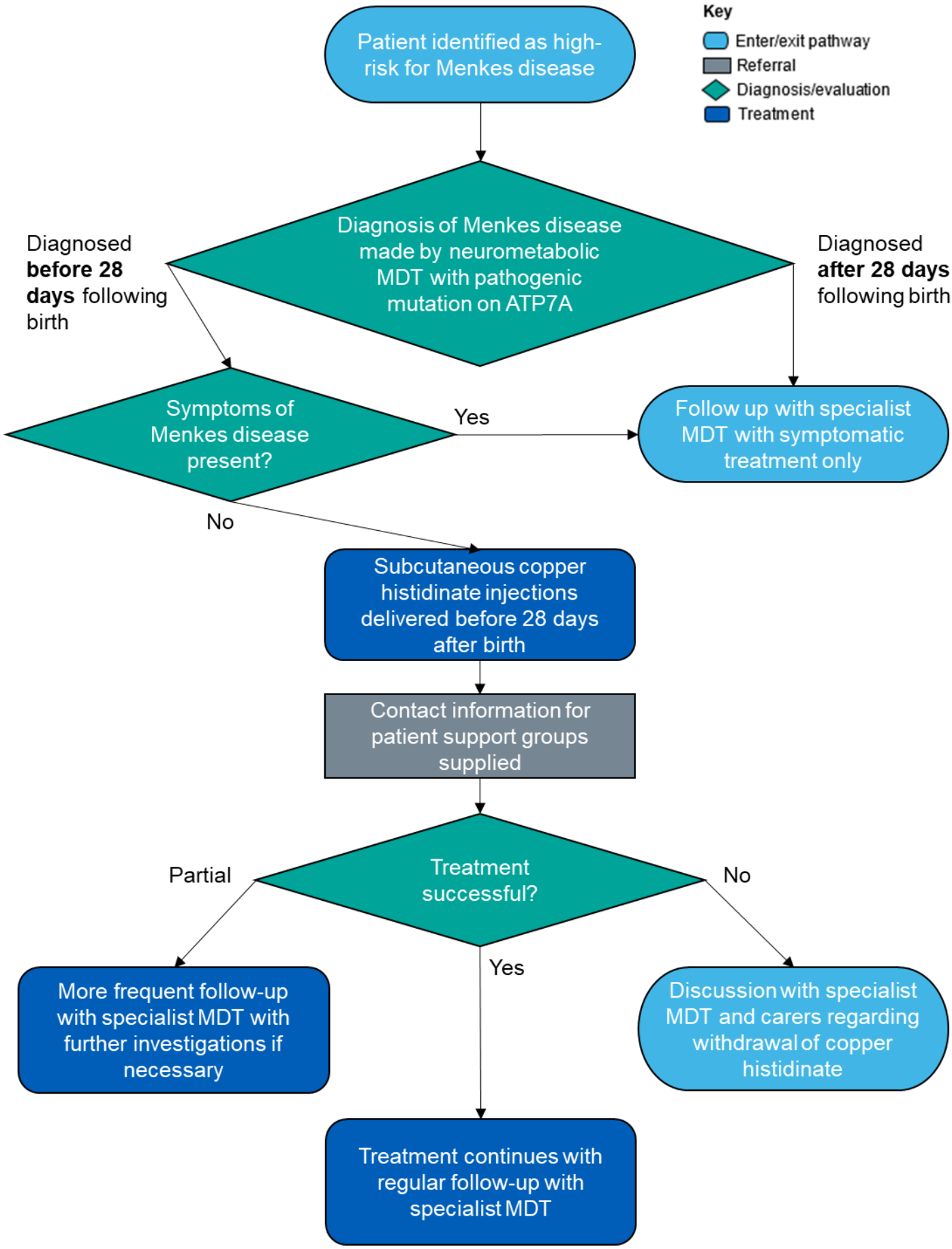
Stopping criteria

The specialist MDT, with support from an external specialist neurometabolic MDT, should stop treatment with copper histidinate in any of the following circumstances:

- Adverse events where harm exceeds the benefit at any time during treatment
- No clinical improvement despite treatment for 6 months, and should be reassessed every 6 months, this may be measured by:
    - Worsening seizure control (with concurrent anticonvulsant medication)

[2] The results of copper and caeruloplasmin should not impact on decision to treat, and the results may not be back at the time treatment is initiated.

Patient pathway



Governance arrangements

Any provider organisation treating patients including children with this intervention will be required to assure itself that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the Trust's Drugs and Therapeutics committee (or similar) and NHS England may ask for assurance of this process.

Provider organisations must register all patients using prior approval software and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined.

Policy review date

This is an urgent policy statement, which means that the full process of policy production has been abridged: a full independent evidence review has not been conducted; and public consultation has not been undertaken. If a review is needed due to a new evidence base then a new Preliminary Policy Proposal needs to be submitted by contacting england.CET@nhs.net.

Links and updates to other policies

This document does not update any other policies.

References

Kaler SG. Neurodevelopment and brain growth in classic Menkes disease is influenced by age and symptomatology at initiation of copper treatment. Journal of Trace Elements in Medicine and Biology. 2014;28(4):427-430. doi: 10.1016/j.jtemb.2014.08.008. Available from https://pubmed.ncbi.nlm.nih.gov/25281031/

Kaler SG, Holmes CS, Goldstein CS, Tang J, Godwin SC, Donsante A, Liew CJ, Sato S, Patronas N. Neonatal diagnosis and treatment of Menkes disease. New England Journal of Medicine. 2008;358(6):605-614. doi: 10.1056/NEJMoa070613. Available from https://pubmed.ncbi.nlm.nih.gov/18256395/

Tønnesen T, Kleijer WJ, Horn N. Incidence of Menkes disease. Human Genetics. 1991;86(4):408-410. doi: 10.1007/BF00201846. Available from https://pubmed.ncbi.nlm.nih.gov/1999344/

Vairo FP, Chwal BC, Perini S, Ferreira MAP, Lopes ACF, Saute JAM. A systematic review and evidence-based guideline for diagnosis and treatment of Menkes disease. Molecular Genetics and Metabolism. 2019;126(1):6-13. doi: 10.1016/j.ymgme.2018.12.005. Available from https://pubmed.ncbi.nlm.nih.gov/30594472/

Appendix 1 – Clinical trial evidence

Three papers were presented for review by NHS England. Paper 1 is an uncontrolled clinical trial of infants assessed for Menkes disease at a national centre in the United States (US). Twelve patients received early treatment (<1 month old) with copper histidinate and survival outcomes were compared to 15 historical controls who had received treatment with copper histidinate at a later age. Paper 2 is a phase I/II uncontrolled trial of copper histidinate in 60 patients with Menkes disease treated at a national centre in the US. Outcomes were compared between patients who received early (<1 month old) and later (after the appearance of symptoms) treatment. Paper 3 is a systematic review and evidence-based guideline on the diagnosis and treatment of Menkes disease. The review of studies on the effectiveness of intervention included nine studies with between four and 57 patients. Study country, when stated, included the US, Italy, England and India. Outcomes reported in the review focused on early compared to later treatment.

Paper 1: Kaler et al 2008. Neonatal diagnosis and treatment of Menkes disease
This paper reports an uncontrolled clinical trial of infants who were identified as being at risk for Menkes disease between May 1997 and July 2005. Patients were assessed at the National Institutes of Health Clinical Center in the United States. The eligibility criteria to receive early treatment with copper histidinate were one month of age or less and no neurologic symptoms. These patients also had high ratios of both dopamine to norepinephrine and dihydroxyphenylacetic acid to dihydroxyphenylglycol. Twelve patients met the eligibility criteria and began treatment at a mean ± standard deviation (SD) age of 10 ± 4 days (range 5 to 22). Patients received 250µg copper histidinate by subcutaneous injection twice daily up to one year of age and then 250µg once daily. Eight patients received treatment for three years, one patient died during the study and received treatment for 1.6 years and three patients (aged < 3 years) were still being treated. Patients were assessed approximately every six months. Median follow-up was 4.6 years (range 1.5 to 8.6).

A 'late-treatment' historical control group consisted of 15 patients with a mean (± SD) age of 163 ± 113 days at diagnosis (range 42 to 390). These patients were treated at the same national centre and received the same copper histidinate regimen as the early treatment patients. Five patients received treatment for three years and 10 patients died before three years with a mean length of treatment of 12.2 months (range 4.0 to 18.0). Median follow-up was 1.8 years (range not reported).

Paper 2: Kaler 2014. Neurodevelopment and brain growth in classic Menkes disease is influenced by age and symptomatology at initiation of copper treatment
This paper reports a phase I/II uncontrolled trial of copper histidinate in 60 patients[3] with Menkes disease. Patients were treated at the National Institutes of Health Clinical Center in the United States (treatment years not stated). Most included patients (n=57) were identified as having classic Menkes disease based on evidence of disturbed copper transport including biochemical findings of reduced dopamine-beta-hydroxylase activity and clinical stigmata of reduced lysyl oxidase activity. The three remaining patients were described as older subjects with milder Menkes disease phenotypes whose treatment with copper histidinate began late after the onset of milder symptoms. Patients received 250µg copper histidinate by subcutaneous injection twice daily up to one year of age and then 250µg once daily for up to three years. Patients were assessed at four to six-month intervals by a single investigator for up to three years.

For the reporting of outcomes, patients were grouped as either early treatment (starting at <1 month old) (n=35), later treatment (after the appearance of symptoms) (n=22) or milder Menkes disease phenotypes (n=3).

[3] These 60 patients included the 12 early treatment patients included in Kaler et al 2008

Paper 3: Vairo et al 2019. A systematic review and evidence-based guideline for diagnosis and treatment of Menkes disease

This paper reports a systematic review and evidence-based guideline on the prenatal and neonatal diagnosis of Menkes disease and on disease-modifying treatment. The review included studies published in English, Portuguese or Spanish up to June 2018. The inclusion criteria were a population with a diagnosis or known risk (25% to 50%) of Menkes disease and either a systematic review, randomised controlled trial, cohort, case-control or case series study design. The exclusion criteria were populations with other ATP7A-related disorders[4], <10 individuals with Menkes disease (for diagnostic studies) or <4 individuals with Menkes disease (for therapeutic studies). Therapeutic studies were also excluded if they had <48 weeks follow-up to assess outcomes or had a cross-sectional study design. The systematic review included nine intervention studies[5], published between 1978 and 2017 and including between four and 57 patients. When reported, the dosing regimen was subcutaneous copper histidinate 250-500 µg/day. Duration of treatment and age at treatment onset was reported for few studies (see outcomes for details where available). Study country, when stated, included the US, Italy, England and India.

The review authors stated that most of the intervention studies compared early (asymptomatic) treatment with copper histidinate to late treatment (after the appearance of symptoms). No pooled analysis of the intervention studies was reported. A narrative description of eight of the nine intervention studies and some of their results was provided[6]. Figures for relative risk and absolute risk reduction, calculated by the review authors, was presented for a small number of studies (between 1 and 3) for different outcomes.

Effectiveness

Survival / death

Kaler et al 2008 reported 92% survival for 12 patients who received early treatment (<1 month old) with copper histidinate at a median follow-up of 4.6 years (range 1.5 to 8.6). For a historical control group of 15 patients who received treatment with copper histidinate at a later age (mean age at diagnosis 163 ± 113 days), survival was 13% at a median follow-up of 1.8 years (range not reported). No statistical comparison between groups was reported.

Kaler 2014 reported that death by three years of age was 28.6% (10/35) for patients who received early treatment (<1 month old) and 50.0% (11/22) for patients who received later treatment (after the appearance of symptoms). None of the three patients with milder Menkes disease phenotypes died by three years of age. No statistical comparison between groups was reported.

Vairo et al 2019 reported details of survival for five of the nine intervention studies:

- Survival was 92% at a median follow-up of 4.6 years for 12 patients who received early treatment (by 22 days old) and 13% at a median follow-up of 1.8 years for 15 patients who received later treatment. The relative risk[7] was calculated as 10.4 (95% confidence interval (CI) 1.57 to 68.63). The absolute risk reduction was calculated as 78.4 (95%CI 55.1 to 100). The number needed to treat to avoid one death with early treatment was 1.27 (95%CI 0.98 to 1.81). (This study is Kaler et al 2008, reported above)
- Survival was 62.5% for 24 patients who received early treatment (mean ± SD age at onset of treatment 11.8 ± 9.6 days) (timeframe not reported). This was compared to data

[4] Menkes disease is caused by mutations in the copper transport gene ATP7A

[5] These nine studies included both Kaler et al 2008 and Kaler 2014

[6] The ninth study was mentioned in a table in the paper but no results were provided for this study

[7] Relative risk considered the incidence of the outcome in the control group/ incidence of the outcome in the early treatment group

from three previous studies of 29 late-treated or untreated patients (not further defined) with survival ranging from 8.3% to 37.5% (timeframe not reported). The relative risk was calculated as 2.02 (95%CI 1.16 to 3.52). The absolute risk reduction was calculated as 38.3 (95%CI 11.6 to 58.6). The number needed to treat to avoid one death with early treatment was 2.6 (95%CI 1.59 to 7.25)

- Mortality by the age of three years was 28.5% for 35 patients who received early treatment (presymptomatic) and 50% for 22 patients who received treatment after the development of symptoms. The relative risk was calculated as 1.75 (95%CI 0.89 to 3.42). The absolute risk reduction was calculated as 21.4 (95%CI -4.27 to 47.13). (This study is Kaler 2014, reported above)
- In the remaining two studies: seven of 12 patients (58.3%) died before the age of five years (mean age at onset of treatment 7.3 months, range 15 days to 27 months); and one of four patients (25%) died aged 10 years (stated treatment by 4 weeks old) with the other three patients alive at the age of 10, 18 and 20 years (2 patients stated treatment by 4 weeks old, 1 patient at 7 weeks old).

The three included papers reported survival for patients described as receiving early treatment (<1 month old) ranging from 62.5% to 92%. For patients described as receiving later treatment, survival ranged from 8.3% to 50%.

Neurodevelopmental outcomes

Kaler et al 2008 reported neurodevelopmental outcomes using the Denver Developmental Screening Test II[8] for 12 patients who received early treatment (<1 month old) with copper histidinate. Results were only reported graphically for individual patients with details of the patient's associated mutation. The text summarising the neurodevelopmental outcomes stated that:

- 2 patients had "completely normal neurodevelopment" during the three-year treatment period and have "normal neurological function" at their present age (5 and 7 years) and do not require special education
- 1 patient showed "some delay in all neurodevelopmental spheres at 36 months of age". This patient was also described at eight years old as being able to ride a tricycle, walk with support and very socially interactive
- 9 patients were described as having "less dramatic responses to early treatment".

Kaler 2014 reported the neurodevelopmental levels (in months) achieved by age three years or by time of death using the Denver Developmental Screening Test (mean follow-up not reported). The early treatment (<1 month old) group (n=35) results were statistically significantly better than the later treatment (after the appearance of symptoms) group (n=22) for all four neurodevelopmental areas (p<0.0001). The results for the three patients with milder Menkes disease phenotypes were also reported but no statistical comparison with the other groups was provided. The results are summarised in Table 1.

Table 1: Denver Developmental Screening Test results (in months) at three years old or at death (Kaler 2014)

	Gross motor	**Fine motor-adaptive**	**Personal-social**	**Language**
Early treatment Mean (SD; range)	13.743 (12.200; 1 to 36)	16.200 (12.762; 1 to 36)	17.657 (13.482; 1 to 36)	15.800 (12.034; 1 to 36)

[8] The Denver Developmental Screening Test II assesses 4 areas: gross motor, fine motor-adaptive, personal-social and language

Later treatment Mean (SD; range)	2.455 (2.154; 1 to 10)	2.409 (1.652; 1 to 8)	3.364 (3.499; 1 to 15)	3.227 (2.943; 1 to 12)
Milder Menkes disease phenotypes Mean (SD; range)	15.667 (9.815; 10 to 27)	17.667 (13.204; 6 to 32)	17.667 (15.308; 6 to 35)	21.000 (9.539; 12 to 31)

Vairo et al 2019 reported some information on neurodevelopmental outcomes for four of the nine intervention studies:

- Two of 12 patients who received early treatment (by 22 days old) were described as having normal neurological development (no further details provided). (This study is Kaler et al 2008, reported above)
- Patients who received early treatment (presymptomatic) (n=35) were described as having an improvement ($p<0.0001$) in the acquisition of the four major neurodevelopmental domains (no further details provided) compared to 22 patients who received treatment after the development of symptoms. (This study is Kaler 2014, reported above)
- Five (of 12) patients who survived to at least five years old were all described as having serious cognitive impairment (mean age at onset of treatment 7.3 months, range 15 days to 27 months)
- Three (of four) patients who survived to at least 10 years old were described respectively as having normal cognitive development at the age of 20 years, mild to moderate cognitive impairment at the age of 18 years and mild cognitive impairment at the age of 10 years (2 patients started treatment by 4 weeks old, 1 patient at 7 weeks old).

One of the three included papers reported that patients receiving early treatment (<1 month old) had statistically significantly better improvement across four neurodevelopmental areas than patients receiving later treatment. The other two included papers provided narrative descriptions of patient's neurodevelopment which ranged from normal to seriously cognitively impaired for patients with a range of treatment onset ages.

Growth measurements

Kaler 2014 reported growth measurements (in centiles) achieved by age three years or by time of death (mean follow-up not reported). The early treatment (<1 month old) group (n=35) results for occipitofrontal circumference were statistically significantly better than the later treatment (after the appearance of symptoms) group (n=22) ($p<0.0009$). There was no statistically significant difference between the early and later treatment groups for weight ($p=0.8735$) and length ($p=0.1453$). The results for the three patients with milder Menkes disease phenotypes were also reported but no statistical comparison with the other groups was provided. The results are summarised in Table 2.

Table 2: Growth measurement results (in centiles) at three years old or at death (Kaler 2014)

	Weight	**Length**	**Occipitofrontal circumference**
Early treatment Mean (SD; range)	12.086 (19.589; 0 to 80)	8.286 (13.501; 0 to 25)	33.286 (27.060; 0 to 90)
Later treatment	11.273	15.455	11.136

Mean (SD; range)	(17.097; 0 to 50)	(23.192; 0 to 75)	(14.551; 0 to 50)
Milder Menkes disease phenotypes Mean (SD; range)	5.000 (8.660; 0 to 15)	28.333 (40.723; 0 to 75)	18.333 (27.538; 0 to 50)

One of the included papers reported growth measurements and reported a statistically significantly better occipitofrontal circumference for patients receiving early treatment (<1 month old) compared to patients receiving later treatment (after the appearance of symptoms). There was no statistically significant difference between early and later treatment for weight or length.

Neurologic outcomes

Kaler et al 2008 reported electroencephalogram abnormalities[9] in seven of 12 patients (58%) who received early treatment (<1 month old) with copper histidinate. Two of these patients (16.7%) had evidence of clinical seizures. Distinct abnormalities[10] on brain magnetic resonance imaging (MRI) were found in six of nine patients (66.7%) assessed. Two patients had normal serial brain MRI scans. Timeframes for neurologic outcomes not reported.

Vairo et al 2019 reported some information on neurologic outcomes for three of the nine intervention studies:

- Seizures occurred in 12.5% of 24 patients who received early treatment (mean ± SD age at onset of treatment 11.8 ± 9.6 days) and 46% had at least one abnormal (not further defined) electroencephalogram after a minimum follow-up of three years. This was compared to data from three previous studies of 29 late-treated or untreated patients (not further defined) in which 87.5% to 100% of patients reported seizures and electroencephalogram abnormalities (timeframe not reported). The relative risk was calculated as 4.33 (95%CI 1.44 to 13.04). The absolute risk reduction was calculated as 80.6 (95%CI 56.7 to 90.1)
- There was no difference in neurological evaluation between 16 symptomatic patients who received late treatment and 12 symptomatic patients who received no copper histidinate treatment at four years follow-up
- Late treatment (not further defined) was described as not having an impact on clinical course and electroencephalogram abnormalities for eight patients.

Two of the included papers reported seizures in 12.5% and 16.7% of patients receiving early treatment, with electroencephalogram abnormalities in 46% and 58% of patients respectively. In one paper seizures and electroencephalogram abnormalities were reported for 87.5% to 100% of later treatment or untreated patients.

Safety

Kaler et al 2008 reported that all 12 patients who received early treatment (<1 month old) with copper histidinate showed increased levels of urinary β_2-microglobulin, described as a sensitive marker of renal tubular damage (timeframe not reported).

[9] Abnormal findings included background slowing or disorganisation, focal slowing (mainly in the posterior head region), focal spike waves or polyspikes (predominantly in the occipital region) and diffuse spike-and-slow-wave complexes

[10] MRI abnormalities included cortical cerebral and cerebellar atrophy and delayed myelination

One of the included papers commented on safety, reporting increased levels of a marker of renal tubular damage in patients who received early treatment (<1 month old) with copper histidinate.