NHS England Evidence Review:

Subcutaneous copper histidinate delivered prior to symptoms developing for classical Menkes disease

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Subcutaneous copper histidinate delivered prior to symptoms developing for classical Menkes disease

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Contents

1. Introduction

This evidence review examines the clinical effectiveness, safety and cost effectiveness of early subcutaneous copper histidinate delivered prior to symptoms developing compared with no subcutaneous copper histidinate in children with classical Menkes disease.

Classical Menkes disease, also known as kinky hair disease, is a recessive inherited metabolic disorder of copper transport. Early subcutaneous copper histidinate is delivered prior to symptoms developing to a neonate (28 days or younger). Without treatment, life expectancy is usually less than three years.

In addition, the review scope included the identification of possible subgroups of patients within the included studies who might benefit from subcutaneous copper histidinate delivered prior to symptoms developing more than others and the age at which patients received treatment.

2. Executive summary of the review

This evidence review examines the clinical effectiveness, safety and cost effectiveness of early subcutaneous copper histidinate delivered prior to symptoms developing compared with no subcutaneous copper histidinate in children with classical Menkes disease. The searches for evidence published since January 2008 were conducted on 20 April 2021 and identified 149 references. The titles and abstracts were screened and 14 full text papers were obtained and assessed for relevance.

Four papers were identified for inclusion. Two cohort studies, one prospective and one retrospective, compared children who received early copper histidinate prior to symptoms developing to children who received no early copper histidinate, but who did receive copper histidinate at a later stage. Two case series of patients who received early copper histidinate were also included. No studies comparing children who received early copper histidinate with no copper histidinate at any stage were identified. Each included study had between five and 35 children who received early treatment and the two cohort studies had between 22 and 39 children who received later treatment. There was some overlap between the populations in three of the studies. However, the approach to study selection and data extraction taken for this review has aimed to minimise duplication of patients included in the outcomes reported. Mean follow-up was reported as 4.6 years in one study. The other studies did not report mean follow-up but followed patients for up to three or six years or until time of death. Three of the studies were from one national centre in the United States and one study was from a national centre in Japan.

In terms of clinical effectiveness:

- **Survival (critical outcome).** Two cohort studies and one case series provided very low certainty evidence that survival ranged from 28.6% for death by three years old to 40.0% for death at a follow-up period of up to six years for children receiving early treatment. For children who received copper histidinate later, death by three years old was 50.0% and death at a follow-up period of up to six years was 65.5%. No statistical comparison of early compared to later treatment was reported.
- **Neurodevelopmental outcomes (critical outcome).** One cohort study provided very low certainty evidence of statistically significant better neurodevelopment at three years old or time of death in four areas[1] for children receiving early treatment compared to children who received later treatment. Two further studies (one case series and one cohort study) provided narrative descriptions of children's neurodevelopment with follow-up of up to six years. This ranged from normal to severely delayed (not further defined) for children who received early treatment in one case series. In one cohort study, the descriptions suggested that children who received copper histidinate later achieved fewer neurodevelopmental outcomes than children who received early treatment.
- **Clinical seizures (critical outcome).** Two case series reported very low certainty evidence that clinical seizures occurred in 12.5% and 16.7% of children receiving early treatment (timeframe not clear).
- **Growth measurements (important outcomes).** One cohort study provided very low certainty evidence that growth measurements were statistically significantly better in terms of occipitofrontal circumference at three years old or time of death for children receiving early treatment compared to children who received later treatment. There was no statistically significant difference between early and later treatment for weight and length in this study. A second cohort study provided descriptive information about body

[1] Gross motor function, fine motor-adaptive, personal-social and language as measured by the Denver Developmental Screening Test II

weight and height percentiles at different ages for children who received early or later treatment but did not report a statistical comparison.
- No evidence was identified for the important outcomes of health-related quality of life, number of hospital attendances/admissions, requirement for anti-convulsant medication and development of bladder diverticulae.

In terms of safety:
- **Drug-related serious adverse effects.** One case series reported very low certainty evidence that all children receiving early treatment with copper histidinate had increased levels of a marker of renal tubular damage during treatment.

In terms of cost effectiveness:
- No evidence was identified for cost effectiveness.

In terms of subgroups:
- No evidence was identified regarding any subgroups of patients that would benefit more from treatment with subcutaneous copper histidinate prior to symptoms developing.

Age at treatment:
- The two cohort studies reported that children received early treatment with copper histidinate at less than one month old. Their age was not further defined. In the two case series, the mean ± standard deviation age at treatment initiation was 10 ± 4 days (range 5 to 22) and 11.8 ± 9.6 days (range -3.5 weeks to 42 days[2]) respectively. In the two cohort studies, later treatment was described as starting after one month of age and after the appearance of symptoms respectively.

Please see the results table (section 5) in the review for further details of outcomes.

Limitations:
Several limitations reduced certainty in the outcomes reported. There was a lack of detail about the study populations, for example, limited details about baseline demographics and no information about whether any other interventions were received. Although some studies discussed potential confounding variables in general terms, such as age at first administration, differences in disease status at baseline, type of gene mutation and the function of copper enzymes, no studies adjusted for potential confounding variables in their analysis. One cohort study had incomplete follow-up and missing data for included patients and it is not clear if the patients without data for some outcomes differed from those who were included. In both case series it was unclear whether the recruitment of participants was consecutive and complete. Treatment duration was not stated in two studies.

Conclusion:
The studies identified for this review provide very low certainty evidence relating to the critical and important outcomes of survival, neurodevelopmental outcomes, clinical seizures and growth measurements. Very low certainty does not mean a paucity of evidence or no evidence. One study reported the results of statistical comparison between children receiving early treatment starting before the age of one month and later treatment, reporting statistically significantly better outcomes with early treatment for neurodevelopmental outcomes and one form of growth measurement (occipitofrontal circumference). Other outcomes were descriptive, for example, higher survival rates were reported in children receiving early treatment but there were no statistical comparisons with later treatment, and the majority of children receiving early treatment in two case series were reported not to

[2] Two of 24 children started treatment at more than 28 days old (one at 30 days and one at 42 days)

have clinical seizures. Safety outcomes were reported in one case series and showed that all patients had increased levels of a marker of renal tubular damage during treatment. No studies compared early treatment with copper histidinate to no copper histidinate at any stage and no evidence was identified for cost effectiveness. The limitations of the studies and descriptive nature and lack of comparative data for some outcomes reported limit the strength of the conclusions that can be drawn.

3. Methodology

Review questions

The review questions for this evidence review are:

1. In children with classical Menkes disease what is the clinical effectiveness of subcutaneous copper histidinate delivered prior to symptoms developing compared with no subcutaneous copper histidinate?

2. In children with classical Menkes disease what is the safety of subcutaneous copper histidinate delivered prior to symptoms developing compared with no subcutaneous copper histidinate?

3. In children with classical Menkes disease what is the cost effectiveness of subcutaneous copper histidinate delivered prior to symptoms developing compared with no subcutaneous copper histidinate?

4. From the evidence selected is there any data to suggest that there are particular subgroups of patients that would benefit from treatment with subcutaneous copper histidinate delivered prior to symptoms developing more than others?

5. From the evidence selected, at what age did patients receive treatment?

See Appendix A for the full review protocol.

Review process

The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2020).

The searches for evidence were informed by the PICO document and were conducted on 20th April 2021.

See Appendix B for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO framework. Full text references of potentially relevant evidence were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review.

See Appendix C for evidence selection details and Appendix D for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included studies and were critically appraised using a checklist appropriate to the study design. See Appendices E and F for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See Appendix G for GRADE Profiles.

4. Summary of included studies

Four papers were identified for inclusion, one retrospective cohort study (Gu et al 2014), one prospective cohort study (Kaler 2014) and two case series (Kaler et al 2008, Kaler et al 2010). The two cohort studies compared children who received early copper histidinate delivered prior to symptoms developing to children who received no early copper histidinate, but who did receive copper histidinate at a later stage. No studies compared early copper histidinate with no copper histidinate at any stage. Table 1 provides a summary of the included studies and full details are given in Appendix E.

No cost effectiveness studies were identified.

Table 1: Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported

Gu et al 2014
 	
Retrospective cohort study
 	
National review, Japan
	44 children with classical Menkes disease
	
	Early treatment: 5
	Later treatment: 39
	
	Male: 100%
	Age:
	• Early copper histidinate (age at start of treatment): < 1 month (not further defined)
	• Later copper histidinate (age at diagnosis): 8.0 ± 2.8 months and 7.5 ± 3.4 months (for oral feeding only and oral plus other feeding respectively)
	
	No subgroups reported
		Intervention
		Early treatment with copper histidinate (starting at <1 month old) following prenatal diagnosis
		
		Comparison
		Later treatment with copper histidinate starting after one month of age
		
		Children received approximately 375 mg/dose copper histidinate, administered parenterally[a] three times a week with adjustment to maintain serum copper and ceruloplasmin levels within a normal range. Duration of treatment not stated
		
		No information about any concomitant treatment
			Critical outcomes
			Mean follow-up not reported. Patients followed-up for up to 6 years
			• Survival
			  • Death by time of study
			• Neurodevelopmental outcomes
			  • Status at last follow-up or prior to death
			
			Important outcomes
			Mean follow-up not reported
			• Growth measurements up to 6 years
			  • Body weight percentile
			  • Height percentile

Kaler 2014
 	
Prospective cohort study
 	
1 national centre, USA
	57 children with classical Menkes disease
	
	Early treatment: 35
	Later treatment: 22
	
	No baseline characteristics reported
	
	No subgroups reported
		Intervention
		Early treatment with copper histidinate (starting at <1 month old) prior to symptoms developing
		
		Comparison
		Later treatment with copper histidinate after the appearance of symptoms
		
		Children received 250µg copper histidinate, twice daily by subcutaneous injection up to one year old, then 250µg copper histidinate, once daily by subcutaneous injection
			Critical outcomes
			• Survival
			  • Death by 3 years old
			• Neurodevelopmental outcomes
			  • Neurodevelopmental level by 3 years old or time of death assessed by Denver Developmental Screening Test[b]
			
			Important outcomes
			• Growth measurement centile at 3 years old or time of death
			  • Body weight

		between one and three years old No information about any concomitant treatment	• Length • Occipitofrontal circumference
Kaler et al 2008 Case series 1 national centre, USA	12[c] children with classical Menkes disease Mean age at treatment initiation: 10 ± 4 days (range 5 to 22) No subgroups reported	**Intervention** Early treatment with copper histidinate (starting at ≤1 month old) prior to neurological symptoms developing **Comparison** No comparator Children received 250µg copper histidinate, twice daily by subcutaneous injection up to one year old then 250µg copper histidinate, once daily Eight children received treatment for 3 years and 3 children (aged < 3 years) were still being treated. 1 patient died during the study and received treatment for 1.6 years No information about any concomitant treatment	**Critical outcomes[d]** • Number of seizures • Number of patients experiencing clinical seizures (timeframe not clear) **Safety** • Drug-related serious adverse effects up to 3 years • Number with increased levels of urinary β2-microglobulin
Kaler et al 2010 Case series 1 national centre, USA	24[e,f] children with classical Menkes disease Mean age at treatment initiation: 11.8 ± 9.6 days (range -3.5 weeks to 42 days) No subgroups reported	**Intervention** Early treatment with copper histidinate (starting at <6 weeks old) prior to neurological symptoms developing **Comparison** No comparator Patients received 250-500µg copper histidinate per day by subcutaneous injection. Duration of treatment not reported No information about any concomitant treatment	**Critical outcomes** Mean follow-up not reported. Patients followed-up for up to 6 years • Survival • Death during the study • Neurodevelopmental outcomes • Neurodevelopmental status at last follow-up • Number of seizures • Number of patients experiencing clinical seizures

Abbreviations: µg: micrograms, mg: milligrams, USA: United States of America

a The authors state that the copper histidinate was parenterally administered. This could include subcutaneous administration, but it is not stated if the copper histidinate was administered subcutaneously
b The Denver Developmental Screening Test II assesses 4 areas: gross motor function, fine motor-adaptive, personal-social and language
c Kaler 2014 reported that the 12 patients from Kaler et al 2008 were included in Kaler 2014
d Kaler et al 2008 also reported survival and neurodevelopmental outcomes. However, these were not extracted as all of the patients who received early treatment with copper histidinate in this study were also included in the Kaler 2014 study population
e Kaler 2014 reported that 1 patient from Kaler et al 2010 was included in Kaler 2014
f Kaler et al 2010 reported that 10 patients from Kaler et al 2008 were included in Kaler et al 2010

5. Results

In children with classical Menkes disease, what is the clinical effectiveness and safety of subcutaneous copper histidinate delivered prior to symptoms developing compared with no subcutaneous copper histidinate?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	

Survival
 	
Certainty of evidence:
 	
Very low
	This outcome is important to patients because it reflects how long people live after treatment, although it does not provide information about patients' health and wellbeing during that time. Without treatment, life expectancy is usually less than three years.
	
	In total, three studies[3] (one prospective cohort study, one retrospective cohort study and one case series) provided evidence relating to survival with follow-up of up to six years for children with classical Menkes disease treated with subcutaneous copper histidinate. The two cohort studies compared children who received early copper histidinate delivered prior to symptoms developing with children who did not receive any early copper histidinate but did receive copper histidinate at a later stage. No studies compared early copper histidinate with no copper histidinate at any stage.
	
	At three years:
	• One prospective cohort study (Kaler 2014) reported death by three years old in ten of 35 children (28.6%) who received early copper histidinate and 11 of 22 children (50.0%) who received later copper histidinate. No statistical comparison reported. **(VERY LOW)**
	
	At follow-up of up to six years:
	• Two studies (one retrospective cohort study and one case series) reported survival with follow-up of up to six years.
	• One retrospective cohort study (Gu et al 2014) reported death by the time of the study for children who received early and later copper histidinate. Mean follow-up not reported. No statistical comparison reported. **(VERY LOW)**
	  • Two of five children (40.0%) who received early copper histidinate died. The mean (± SD) age at death was 53.5 ± 43.1 months (range 23 to 84). The mean (± SD) age of the three survivors at last follow-up was 55.7 ± 25.4 months (range 35 to 84).
	  • Nineteen of 29 children (65.5%) who received later copper histidinate died. Mean age at death and mean age of survivors was reported separately for children who received oral feeding only (n=7) or oral plus other feeding (n=22). Mean (± SD) age at death was 59 ± 10 months (n=3) and 46 ± 22 months (n=16) respectively (range not reported). Mean (± SD) age of survivors was 100 ± 44 months (n=4) and 21 ± 10 months (n=6) respectively (range not reported).
	• One case series (Kaler et al 2010) reported that nine of 24 children (37.5%) who received early treatment with copper histidinate died during the study. Mean follow-up not reported. Age at death ranged from 5.5 months to 2.6 years. **(VERY LOW)**
	
	These studies provided very low certainty evidence that survival for children receiving early treatment with copper histidinate ranges from 28.6% for death by three years old to 40.0% for death at a follow-up

[3] Kaler et al 2008 also reported survival and neurodevelopmental outcomes. However, these were not extracted as all of the patients who received early treatment with copper histidinate in this study were also included in the Kaler 2014 study population

	period of up to six years. For children who received copper histidinate later, death by three years old was 50.0% and death at a follow-up period of up to six years was 65.5%. No statistical comparison was reported comparing early to later treatment.

Neurodevelopmental outcomes
 	
Certainty of evidence:
 	
Very low
	Neurodevelopmental outcomes are important to patients as they are a marker of the development of the brain and the child's ability to meet milestones such as smiling, crawling, walking. These may be measured by tools such as the Denver Developmental Screening Test.
	
	In total, three studies (one prospective cohort study, one retrospective cohort study and one case series) provided evidence relating to neurodevelopmental outcomes with follow-up of up to six years for children with classical Menkes disease treated with subcutaneous copper histidinate. The two cohort studies compared children who received early copper histidinate delivered prior to symptoms developing with children who did not receive any early copper histidinate but did receive copper histidinate at a later stage. No studies compared early copper histidinate with no copper histidinate at any stage.
	
	At follow-up of up to three years:
	• One prospective cohort study (Kaler 2014) reported neurodevelopmental level achieved by three years old or time of death using the Denver Developmental Screening Test[4] (mean follow-up not reported). **(VERY LOW)**
	  • For gross motor function, children treated with early copper histidinate achieved a *statistically significantly better* neurodevelopmental level in months than children who received later copper histidinate (p<0.0001). Early copper histidinate (n=35) mean (SD; range) 13.743 (12.200; 1 to 36) compared to later copper histidinate (n=22) 2.455 (2.154; 1 to 10)
	  • For fine motor-adaptive, children treated with early copper histidinate achieved a *statistically significantly better* neurodevelopmental level in months than children who received later copper histidinate (p<0.0001). Early copper histidinate (n=35) mean (SD; range) 16.200 (12.762; 1 to 36) compared to later copper histidinate (n=22) 2.409 (1.652; 1 to 8)
	  • For personal-social, children treated with early copper histidinate achieved a *statistically significantly better* neurodevelopmental level in months than children who received later copper histidinate (p<0.0001). Early copper histidinate (n=35) mean (SD; range) 17.657 (13.482; 1 to 36) compared to later copper histidinate (n=22) 3.364 (3.499; 1 to 15)
	  • For language, children treated with early copper histidinate achieved a *statistically significantly better* neurodevelopmental level in months than children who received later copper histidinate (p<0.0001). Early copper histidinate (n=35) mean (SD; range) 15.800 (12.034; 1 to 36) compared to later copper histidinate (n=22) 3.227 (2.943; 1 to 12)
	
	At follow-up of up to six years:
	• Two studies (one retrospective cohort study and one case series) reported neurodevelopmental outcomes with follow-up of up to six years.
	• One retrospective cohort study (Gu et al 2014) reported status at last follow-up or prior to death (mean follow-up not reported). Of five children who received early treatment with copper histidinate, four were described as "could lift head from a prone position, sit well unsupported, stand without help and walk" and one was described as "could lift head from a prone position and sit with support". All 39 children who received later copper histidinate were described as

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

	"normalised scalp hair and capable of smiling back but could not lift head from a prone position". No numerical data or statistical comparison reported. **(VERY LOW)** • One case series (Kaler et al 2010) reported neurodevelopmental status in 14 survivors who received early treatment with copper histidinate with data at last follow-up (mean follow-up not reported). Three children (21.4%) were described as having normal development, one (7.1%) was mildly delayed, three (21.4%) were moderately delayed and seven (50.0%) were severely delayed. Neurodevelopmental status was assessed using the Denver Developmental Screening test, however the categories were not further described. **(VERY LOW)** **One study provided very low certainty evidence of statistically significantly better outcomes in four neurodevelopmental areas at up to three years follow-up for children receiving early treatment with copper histidinate compared to children who received later treatment. Two further studies provided narrative descriptions of children's neurodevelopment at up to six years follow-up. One described outcomes ranging from normal to severely delayed for children who received early treatment with copper histidinate. In the other study, the descriptions given suggested that children who received copper histidinate later achieved fewer neurodevelopmental outcomes than children who received early treatment.**
Number of seizures **Certainty of evidence:** Very low	The absence or reduction in the number of seizures is important to patients as they may develop drug-resistant seizures requiring hospital attendance and admission with status epilepticus. In total, two case series provided evidence relating to seizures with follow-up of up to six years for children with classical Menkes disease treated with early subcutaneous copper histidinate delivered prior to symptoms developing. No studies compared early copper histidinate with no copper histidinate. At follow-up of up to six years: • One case series (Kaler et al 2008) reported that two of 12 children (16.7%) who received early treatment with copper histidinate had clinical seizures. The study mean follow-up was 4.6 years (range 1.5 to 8.6 years). The timeframe for this outcome was unclear. **(VERY LOW)** • One case series (Kaler et al 2010) reported that three of 24 children (12.5%) who received early treatment with copper histidinate had clinical seizures. Patients were followed-up for up to six years. Mean follow-up was not reported. Mean age at first seizure was 20.3 ± 9.3 weeks (range 14 to 31). **(VERY LOW)** **Two studies reported very low certainty evidence that clinical seizures occurred in 12.5% and 16.7% of children receiving early treatment with copper histidinate.**
Important outcomes	
Health-related quality of life **Certainty of evidence:** Not applicable	Quality of life is important to patients and their carers as it provides a holistic evaluation and indication of the patient's general health and their and their carer's perceived well-being. Quality of life for patients with classical Menkes disease can be measured with tools such as Peds-QL (Paediatric Quality of Life Inventory) or the EQ-5D-Y. **No evidence was identified for this outcome.**
Growth measurements **Certainty of evidence:** Very low	Growth measurements such as weight, length and head circumference are important outcomes to patients and their carers as they can be a marker of treatment success. In total, two studies (one prospective cohort study and one retrospective cohort study) provided evidence relating to growth measurements with follow-up of up

	to six years for children with classical Menkes disease treated with subcutaneous copper histidinate. The two cohort studies compared children who received early copper histidinate delivered prior to symptoms developing with children who did not receive any early copper histidinate but did receive copper histidinate at a later stage. No studies compared early copper histidinate with no copper histidinate at any stage.
	
	At follow-up of up to three years:
	• One prospective cohort study (Kaler 2014) reported growth measurement (weight, length, occipitofrontal circumference) centiles at three years old or time of death (mean follow-up not reported). **(VERY LOW)**
	  • For weight, there was *no statistically significant difference* between children treated with early copper histidinate and children who received later copper histidinate (p=0.8735). Early copper histidinate (n=35) mean (SD; range) centile 12.086 (19.589; 0 to 80) compared to later copper histidinate (n=22) 11.273 (17.097; 0 to 50)
	  • For length, there was *no statistically significant difference* between children treated with early copper histidinate and children who received later copper histidinate (p=0.1453). Early copper histidinate (n=35) mean (SD; range) centile 8.286 (13.501; 0 to 25) compared to later copper histidinate (n=22) 15.455 (23.192; 0 to 75)
	  • For occipitofrontal circumference, children treated with early copper histidinate had a *statistically significantly better* measurement than children who received later copper histidinate (p<0.0009). Early copper histidinate (n=35) mean (SD; range) centile 33.286 (27.060; 0 to 90) compared to later copper histidinate (n=22) 11.136 (14.551; 0 to 50)
	
	At follow-up of up to six years:
	• One retrospective cohort study (Gu et al 2014) reported growth measurement (body weight and height) percentiles based on national data, with follow-up of up to six years. The specific timepoints for which outcomes were reported varied and are specified below. For children who received later copper histidinate, body weight and height were reported separately for children who received oral feeding only or oral plus other feeding. All children who received early treatment with copper histidinate received oral feeding only.
	• For body weight up to 12 months **(VERY LOW)**:
	  • At six to 12 months, three children who received early treatment were all <3rd percentile
	  • At five to seven months, one of three children who received later copper histidinate and oral feeding only was between the 10th and 25th percentiles and the other two children were between the 50th and 75th percentiles
	  • At four to seven months, three of eight children who received later copper histidinate and oral plus other feeding were between the 3rd and 10th percentiles, three were between the 10th and 25th percentiles, one was between the 75th and 90th percentiles and one was >97th percentile
	• For body weight after 12 months **(VERY LOW)**:
	  • At 13 to 60 months, four children who received early treatment were all <3rd percentile
	  • At 24 to 25 months, two children who received later copper histidinate and oral feeding only were both <3rd percentile
	  • At 22 to 59 months, five children who received later copper histidinate and oral plus other feeding were all <3rd percentile
	• For height up to 12 months **(VERY LOW)**:
	  • At six to 12 months, three children who received early treatment were all <3rd percentile

	• At five to seven months, one child who received later copper histidinate and oral feeding only was <3rd percentile • At four to seven months, one of six children who received later copper histidinate and oral plus other feeding was <3rd percentile, two were between the 3rd and 10th percentiles, one was 10th percentile, one was between the 25th and 50th percentiles and one was between the 75th and 90th percentiles • For height after 12 months **(VERY LOW)**: • At 13 to 60 months, three children who received early treatment were <3rd percentile and one child was <10th to 25th percentile • At 24 to 25 months, two children who received later copper histidinate and oral feeding only were both <3rd percentile • At 22 to 59 months, three of five children who received later copper histidinate and oral plus other feeding were <3rd percentile and the other two children were between the 3rd and 10th percentiles. **One study provided very low certainty evidence that children receiving early treatment with copper histidinate had statistically significantly better growth measurements in terms of occipitofrontal circumference than children who received later treatment. There was no statistically significant difference between early and later treatment for weight and length in this study. A second study provided descriptive information about body weight and height percentiles at different ages for children who received early or later treatment.**
Number of hospital attendances/admissions **Certainty of evidence:** Not applicable	Patients with classical Menkes disease often require frequent admissions to hospital, including paediatric intensive care units. The reduction of hospital admissions is an important outcome for patients and their carers as it is a marker that treatment is working. **No evidence was identified for this outcome.**
Requirement for anti-convulsant medication **Certainty of evidence:** Not applicable	Patients with classical Menkes disease often require anti-convulsant medication to help control their seizures. A reduction in the requirement of these medications is preferred by patients as they can have negative side effects. Increased requirement for anticonvulsant medication may also be an indicator of treatment resistance. **No evidence was identified for this outcome.**
Development of bladder diverticulae **Certainty of evidence:** Not applicable	Not developing bladder diverticulae is an important outcome for patients as bladder diverticulae can cause an increased risk of infection, bladder stones, vesico-ureteric reflux and difficulty passing urine. **No evidence was identified for this outcome.**
Safety	
Drug-related serious adverse effects **Certainty of evidence:** Very low	This can include kidney damage and cardiomyopathy. Kidney damage may be monitored by the use of urine beta-2 microglobulin or other markers for early renal tubular dysfunction. In total, one case series provided evidence relating to drug-related serious adverse effects for children with classical Menkes disease treated with early subcutaneous copper histidinate prior to symptoms developing. This involved measurement of levels of urinary β2-microglobuln (a sensitive marker of renal tubular damage) whilst children were receiving copper histidinate (up to three years). The reference range was stated as 0.0 to 0.3 mg/L. No studies compared early copper histidinate with no copper histidinate. • One case series (Kaler et al 2008) reported that 11 children (100%) who received early treatment with copper histidinate had increased

	levels of urinary β2-microglobuln. The median maximum measured concentration was 27.4 mg/L (range 1.2 to 60.9). **(VERY LOW)** **One paper reported very low certainty evidence that all children receiving early treatment with copper histidinate had increased levels of a marker of renal tubular damage during treatment.**
Abbreviations L: litre, mg: milligrams, SD: standard deviation	

In children with classical Menkes disease, what is the cost effectiveness of subcutaneous copper histidinate delivered prior to symptoms developing compared with no subcutaneous copper histidinate?

Outcome	Evidence statement
Cost effectiveness	**No evidence was identified for cost effectiveness.**

From the evidence selected, is there any data to suggest that there are particular subgroups of patients that may benefit from treatment with subcutaneous copper histidinate delivered prior to symptoms developing more than others?

Outcome	Evidence statement
Subgroups	**No evidence was identified regarding any subgroups of patients that would benefit more from early treatment with subcutaneous copper histidinate.**

From the evidence selected, at what age did patients receive treatment?

Outcome	Evidence statement
Age at treatment	In Gu et al 2014 and Kaler 2014, children received early treatment with copper histidinate at less than one month old. Their age was not further defined. In Kaler et al 2008 and Kaler et al 2010 the mean ± standard deviation age at treatment initiation was 10 ± 4 days (range 5 to 22) and 11.8 ± 9.6 days (range -3.5 weeks to 42 days[5]) respectively. In Gu et al 2014, children were described as receiving later treatment with copper histidinate, starting after one month of age. Their age at the start of treatment was not further defined. However, their age at diagnosis was stated as 8.0 ± 2.8 months and 7.5 ± 3.4 months for children who received oral feeding only and oral plus other feeding respectively. In Kaler 2014 the age at treatment initiation of children receiving later treatment with copper histidinate was not specified, only that it was after the appearance of symptoms.

[5] Two of 24 children started treatment at more than 28 days old (one at 30 days and one at 42 days)

6. Discussion

This evidence review considered the clinical effectiveness and safety of early subcutaneous copper histidinate delivered prior to symptoms developing compared with no subcutaneous copper histidinate in children with classical Menkes disease. The modality, timing (in the first month after birth) and capacity to benefit the most were the primary focus of the evidence review. The critical outcomes of interest were survival, neurodevelopmental outcomes and clinical seizures. Important outcomes were growth measurements, health-related quality of life, number of hospital attendances/admissions, requirement for anti-convulsant medication, development of bladder diverticulae and drug-related serious adverse effects. Evidence on cost effectiveness was also sought.

Evidence was available from two cohort studies (one prospective (Kaler 2014) and one retrospective (Gu et al 2014)) and two case series (Kaler et al 2008, Kaler et al 2010). The two cohort studies compared children who received early copper histidinate prior to symptoms developing to children who received no early copper histidinate, but who did receive copper histidinate at a later stage. The two case series included only children who received early copper histidinate for the outcomes of interest. No studies compared early treatment with copper histidinate to no copper histidinate at any stage. No evidence was identified for the important outcomes of health-related quality of life, number of hospital attendances/admissions, requirement for anti-convulsant medication and development of bladder diverticulae, or for cost effectiveness.

In the cohort studies, early treatment was given to children who were less than one month old. Their age was not further defined. However, in one study patients were diagnosed prenatally (Gu et al 2014) and the other study specified that treatment was initiated prior to symptoms developing (Kaler 2014). The two case series reported mean age at treatment initiation as 10 ± 4 days (range 5 to 22) (Kaler et al 2008) and 11.8 ± 9.6 days (range -3.5 weeks to 42 days) (Kaler et al 2010) respectively. As indicated by the range, the second case series included two patients who were more than 28 days old at treatment initiation (one was 30 days and the other 42 days old). However, in both case series treatment was delivered prior to the development of neurological symptoms.

Later treatment was described as starting after one month of age (Gu et al 2014) and after the appearance of symptoms (Kaler 2014) in the two cohort studies. In one study the mean age at diagnosis was around eight months old although age at treatment initiation was not reported (Gu et al 2014), while in the second study the ages at diagnosis or starting treatment were not reported (Kaler 2014).

Between them, the four included studies reported outcomes on a total of 76 children who received early treatment with copper histidinate, but there was some overlap in the populations included in the three studies from one centre in the USA which means that the actual total included was less than this. The approach used for study selection and the decisions made about which outcomes to extract from each study have sought to minimise any duplication of patients in the results reported in this review. There were 61 children who received later treatment in the cohort studies. However, most of the outcomes reported in Gu et al's 2014 retrospective review did not include all 39 of the children receiving later treatment who were included in their study. The authors stated that data from some patients treated during the 16-year study period would have been lost due to the duration for which medical records are maintained (five years). The small number of children included in the studies reflects the rarity of classical Menkes disease.

The follow-up period or timepoint for some of the outcomes reported was clear. For example, Kaler 2014 reported outcomes at three years old or time of death. The other

studies either reported a mean follow-up or stated that patients were followed-up for up to six years.

The two cohort studies reported outcomes for children who received early and later treatment for the critical outcomes of survival and neurodevelopmental outcomes and the important outcome of growth measurements. The percentages of children who survived were higher for patients receiving early treatment, however no statistical analysis comparing survival between early and later treatment was reported. Only one study (Kaler 2014) reported any statistical comparison between the groups for two outcomes (neurodevelopmental outcomes and growth measurements). These results reported statistically significantly better outcomes for children who received early treatment in the four neurodevelopmental areas assessed by the Denver Developmental Screening Test (gross motor, fine motor-adaptive, personal-social and language). For example, the mean neurodevelopmental level in the four areas achieved by three years old or time of death was approximately 14 to 18 months in the children who received early treatment and approximately two to four months in the children who received later treatment. Although the other cohort study (Gu et al 2014) only reported a narrative description of neurodevelopmental status, the descriptions also suggest that children who received copper histidinate later achieved fewer neurodevelopmental outcomes than children who received early treatment. In terms of growth measurements, children receiving early treatment had statistically significantly better occipitofrontal (head) circumference at three years old or time of death. However, there was no statistically significant difference between early and late treatment for weight or length.

The case series provided non-comparative evidence on clinical seizures and safety. The proportion of patients receiving early treatment with copper histidinate who had clinical seizures was 12.5% and 16.7% in the two case series. All the patients assessed in one case series (Kaler et al 2008) had increased levels of a marker of renal tubular damage during treatment with copper histidinate. No other details on safety outcomes were reported.

The outcomes reported were objective. None of the studies commented on what minimal clinically important thresholds would be for any of the outcomes considered.

The certainty in the outcomes reported was very low. There are a number of potential confounding variables which could affect both the comparison of children who received treatment at different stages and the outcomes within a population of children who received early treatment. Although some of the studies discussed potential confounding variables in general terms, such as age at first administration, differences in disease status at baseline, type of gene mutation and the function of copper enzymes, no studies adjusted for potential confounding variables in their analysis. Other factors that reduced confidence in the outcomes included lack of detail about the study populations, for example, limited details about baseline demographics and characteristics and a lack of information on whether any other interventions were received. Incomplete follow-up and missing data for included patients was a particular limitation of the study by Gu et al 2014. It is not clear if the patients without data for some outcomes differed from those who were included. In both case series it was unclear whether the recruitment of study participants was consecutive and complete. The duration of treatment was not stated in Gu et al 2014 or Kaler et al 2010. No studies reported any subgroup analysis about patients who might benefit more from treatment for the outcomes of interest.

Three of the studies were from one national centre in the United States (USA) and one study was from a national centre in Japan. It is not clear how generalisable these might be to other settings.

7. Conclusion

This review included two cohort studies which compared children with classical Menkes disease who received early subcutaneous copper histidinate delivered prior to symptoms developing with children who received no early copper histidinate, but who did receive copper histidinate at a later stage. Two case series of children with classical Menkes disease who received early subcutaneous copper histidinate delivered prior to symptoms developing were also included. No studies compared early treatment with copper histidinate to no copper histidinate at any stage. These studies provide very low certainty evidence relating to the critical and important outcomes of survival, neurodevelopmental outcomes, clinical seizures and growth measurements. Only one study reported the results of statistical comparison between children receiving early and later treatment. This study reported statistically significantly better outcomes with early treatment for neurodevelopmental outcomes and one form of growth measurement (occipitofrontal circumference). Other outcomes were descriptive, for example higher survival rates were reported in children receiving early treatment but there were no statistical comparisons, and the majority of children receiving early treatment in two case series were reported not to have clinical seizures. Safety outcomes were reported in one case series and showed that all patients had increased levels of a marker of renal tubular damage during treatment. There was no evidence on cost effectiveness or on any subgroups of patients who may benefit more than others from early treatment delivered prior to symptoms developing.

Limitations reducing the certainty in the outcomes included lack of detail about the study populations, lack of clear identification of and adjustment for potential confounding variables, incomplete follow-up and missing data and uncertainty about whether the recruitment of study participants was consecutive and complete. The duration of treatment was not stated in two studies.

The studies identified for this review therefore provide very low certainty evidence that early treatment with subcutaneous copper histidinate delivered prior to symptoms developing may improve neurodevelopmental outcomes and some growth measurements compared to later treatment. Very low certainty does not mean a paucity of evidence or no evidence. However, the limitations of the studies and descriptive nature and lack of comparative data for the other outcomes reported limit the strength of the conclusions that can be drawn.

Appendix A PICO document

The review questions for this evidence review are:

1. In children with classical Menkes disease what is the clinical effectiveness of subcutaneous copper histidinate delivered prior to symptoms developing compared with no subcutaneous copper histidinate?

2. In children with classical Menkes disease what is the safety of subcutaneous copper histidinate delivered prior to symptoms developing compared with no subcutaneous copper histidinate?

3. In children with classical Menkes disease what is the cost effectiveness of subcutaneous copper histidinate delivered prior to symptoms developing compared with no subcutaneous copper histidinate?

4. From the evidence selected is there any data to suggest that there are particular subgroups of patients that would benefit from treatment with subcutaneous copper histidinate delivered prior to symptoms developing more than others?

5. From the evidence selected, at what age did patients receive treatment?

P-Population and Indication	Children with classical Menkes disease [Also known as kinky hair disease] [Diagnosis made with a family history and either: 1. Genetic testing (pathogenic mutation in *ATP7A*) or 2. Biochemical testing (Plasma dopamine/norepinephrine ratio >0.2 or dihydroxyphenylacetic acid/dihydroxyphenylglycol ratio >5 with or without reduction in plasma copper and/or caeruloplasmin to below a laboratory's reference range)] [Patients with occipital horn disease (a milder form of Menkes disease) should be excluded]
I-Intervention	Early subcutaneous copper histidinate delivered prior to symptoms developing to a neonate (28 days or younger)
C-Comparator	No copper histidinate
O-Outcomes	Response to treatment for all of the clinical effectiveness outcomes would be expected by 1 year, though longer-term follow-up is preferred. There are no known standard MCIDs for any of the outcome measures for patients with classical Menkes disease. **Clinical effectiveness** *Critical to decision-making:* • Survival This outcome is important to patients because it reflects how long people live after treatment, although it does not provide information about patients' health and wellbeing during that time. Without treatment, life expectancy is usually less than 3 years. • Neurodevelopmental outcomes Neurodevelopmental outcomes are important to patients as they are a marker of the development of the brain and the child's ability to meet milestones such as smiling, crawling, walking. These may be measured by tools such as the Denver Developmental Screening Test.

	• Number of seizures The absence or reduction in the number of seizures is important to patients as they may develop drug-resistant seizures requiring hospital attendance and admission with status epilepticus. *Important to decision-making*: • Health-related quality of life Quality of life is important to patients and their carers as it provides a holistic evaluation and indication of the patient's general health and their and their carer's perceived well-being. Quality of life for patients with classical Menkes disease can be measured with tools such as Peds-QL (Paediatric Quality of Life Inventory) or the EQ-5D-Y. • Growth measurements Growth measurements such as weight, length and head circumference are important outcomes to patients and their carers as they can be a marker of treatment success. • Number of hospital attendances/admissions Patients with classical Menkes disease often require frequent admissions to hospital, including paediatric intensive care units. The reduction of hospital admissions is an important outcome for patients and their carers as it is a marker that treatment is working. • Requirement for anti-convulsant medication Patients with classical Menkes disease often require anti-convulsant medication to help control their seizures. A reduction in the requirement of these medications is preferred by patients as they can have negative side effects. Increased requirement for anticonvulsant medication may also be an indicator of treatment resistance. • Development of bladder diverticulae Not developing bladder diverticulae is an important outcome for patients as bladder diverticulae can cause an increased risk of infection, bladder stones, vesico-ureteric reflux and difficulty passing urine. **Safety** • Drug-related serious adverse effects (including kidney damage[6] and cardiomyopathy) **Cost effectiveness**
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher-level quality evidence is found, case series can be considered.
Language	English only
Patients	Human studies only

[6] Kidney damage may be monitored by the use of urine beta-2 microglobulin or other markers for early renal tubular dysfunction.

Age	All ages
Date limits	2008-2021
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials and guidelines
Study design	Case reports, resource utilisation studies

Appendix B Search strategy

Medline, Embase, PsycINFO and the Cochrane Library were searched limiting the search to papers published in English language in the last 13 years. Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre-publication prints, guidelines, case reports and resource utilisation studies were excluded.

Search dates: 1 January 2008 to 20 April 2021

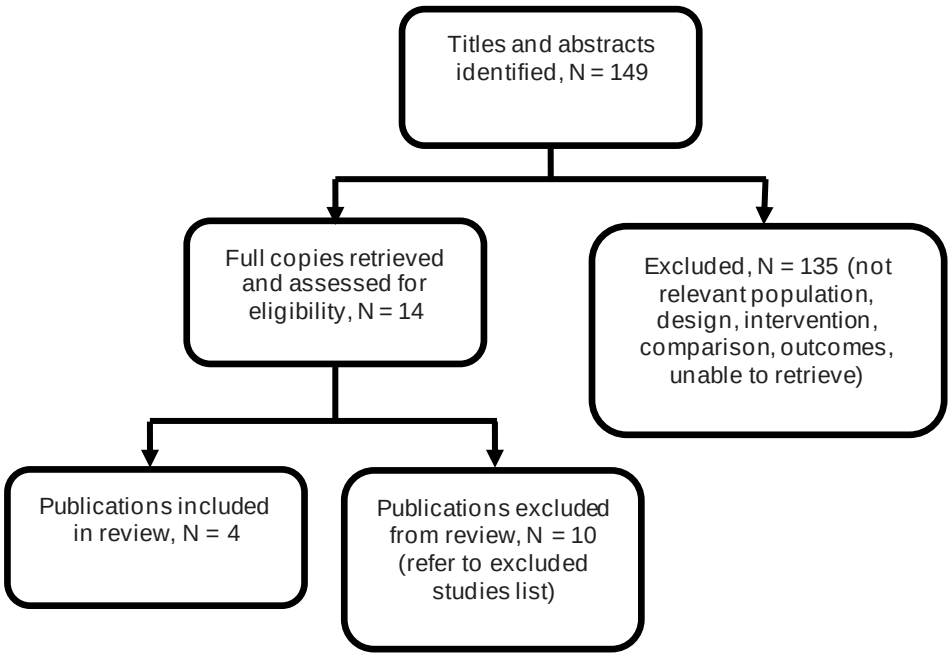
Medline search strategy:

1	Menkes Kinky Hair Syndrome/
2	((menke* or kinky hair or steely hair) adj2 (disease? or syndrome? or disorder?)).ti,ab,kw.
3	((xlinked or x-linked) adj2 copper deficienc*).ti,ab,kw.
4	(copper adj2 (transport disorder? or transport disease? or transport syndrome?)).ti,ab,kw.
5	(atp7a adj2 mutation?).ti,ab,kw.
6	1 or 2 or 3 or 4 or 5
7	Copper/tu [Therapeutic Use]
8	(injections/ or injections, subcutaneous/) and Copper/
9	(copper adj2 histidin*).ti,ab,kw.
10	(copper adj5 (injection* or intravenous or intra-venous)).ti,ab,kw.
11	(copper adj5 (therapy or treatment)).ti,ab,kw.
12	7 or 8 or 9 or 10 or 11
13	6 and 12
14	exp animals/ not humans/
15	13 not 14
16	limit 15 to (english language and yr="2008 -Current")

Appendix C Evidence selection

The literature search identified 149 references. These were screened using their titles and abstracts and 14 references were obtained in full text and assessed for relevance. Of these, four references are included in this evidence review. The 10 references excluded are listed in Appendix D.

Figure 1- Study selection flow diagram



References submitted with Preliminary Policy Proposal

Reference	Paper selection decision and rationale if excluded
Kaler SG, Holmes CS, Goldstein DS, Tang J, Godwin SC, Donsante A, Liew CJ, Sato S, Patronas N (2008) Neonatal diagnosis and treatment of Menkes disease. New England Journal of Medicine. 358(6): 605-614. doi: 10.1056/NEJMoa070613.	Included
Kaler SG (2014) 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. 28(4): 427-430. doi: 10.1016/j.jtemb.2014.08.008.	Included
Vairo FPE, Chwal BC, Perini S, Ferreira MAP, Lopes ACF, Saute JAM (2019) A systematic review and evidence-based guideline for diagnosis and treatment of Menkes disease. Molecular Genetics and Metabolism. 126(1): 6-13. doi: 10.1016/j.ymgme.2018.12.005.	Review with narrative presentation of results. No pooled analysis. Individual studies considered separately

Appendix D Excluded studies table

Study reference	Reason for exclusion
Flores-Pulido AA, Jimenez-Perez VM, Garcia-Chong NR. Sintesis y uso de histidinato de cobre en ninos con enfermedad de Menkes en Mexico. Gaceta Medica de Mexico. 2019;155(2):191-5.	No patients received early subcutaneous copper histidinate
Gu YH, Kodama H, Kato T. Congenital abnormalities in Japanese patients with Menkes disease. Brain & Development. 2012;34(9):746-9.	Not clear if any patients received early subcutaneous copper histidinate. No separate reporting of results by age of treatment initiation
Gu YH, Kodama H, Ogawa E, Izumi Y. Lactate and pyruvate levels in blood and cerebrospinal fluid in patients with Menkes disease. Journal of Pediatrics. 2014;164(4):890-4.	No patients received early subcutaneous copper histidinate
Kim JH, Lee BH, Kim YM, Choi JH, Kim GH, Cheon CK, et al. Novel mutations and clinical outcomes of copper-histidine therapy in Menkes disease patients. Metabolic Brain Disease. 2015;30(1):75-81.	Case series n=11 with 2 patients who received early treatment. No results for outcomes which are not already reported by larger case series
Kralik L, Flachsova E, Hansikova H, Saudek V, Zeman J, Martasek P. Molecular Diagnostics of Copper-Transporting Protein Mutations Allows Early Onset Individual Therapy of Menkes Disease. Folia Biologica. 2017;63(5-6):165-73.	No patients received early subcutaneous copper histidinate
Ogawa E, Kodama H. Effects of disulfiram treatment in patients with Menkes disease and occipital horn syndrome. Journal of Trace Elements in Medicine & Biology. 2012;26(2-3):102-4.	No patients received early subcutaneous copper histidinate
Tang J, Donsante A, Desai V, Patronas N, Kaler SG. Clinical outcomes in Menkes disease patients with a copper-responsive ATP7A mutation, G727R. Molecular Genetics & Metabolism. 2008;95(3):174-81.	N=2 early treatment patients, both included in Kaler 2014. No additional outcomes reported in this paper
Vairo FPE, Chwal BC, Perini S, Ferreira MAP, de Freitas Lopes AC, Saute JAM. A systematic review and evidence-based guideline for diagnosis and treatment of Menkes disease. Mol Genet Metab. 2019;126(1):6-13.	Review with narrative presentation of results. No pooled analysis. Individual studies considered separately
Verrotti A, Cusmai R, Darra F, Martelli P, Accorsi P, Bergamo S, et al. Epilepsy in Menkes disease: an electroclinical long-term study of 28 patients. Epilepsy Research. 2014;108(9):1597-603.	No patients received early subcutaneous copper histidinate
Yoganathan S, Sudhakar SV, Arunachal G, Thomas M, Subramanian A, George R, et al. Menkes disease and response to copper histidine: An Indian case series. Annals of Indian Academy of Neurology. 2017;20(1):62-8.	No patients received early subcutaneous copper histidinate

Appendix E Evidence table

For abbreviations see list after table

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
Gu YH, Kodama H, Ogawa E, Sato Y, Motoyama K, Yagi M, Yoshida S, Ohkubo T. Changes in body weight and height in survivors of Menkes disease. Journal of Trace Elements in Medicine & Biology. 2014;28(4):470-473. **Study location** National review, Japan **Study type** Retrospective cohort study **Study aim** The study aim was to explore the changes in the body weight and height of Japanese patients with classical Menkes disease treated with copper histidinate and compare these changes between patients who received early and late treatment	Children with classical Menkes disease **Inclusion criteria** Male children with records of growth parameters, diagnosed as having classical Menkes disease by clinical examination, laboratory data including catecholamine tests, measurement of copper concentrations in cultured cells and/or genetic analysis **Exclusion criteria** Female patients, occipital horn disease, Menkes patients with onset at over 12 months of age, one Brazilian patient, repeat cases, patients without description of growth parameters and patients born before 1994	**Intervention** Early copper histidinate delivered following prenatal diagnosis to children starting at <1 month old **Comparison** Children who received no early copper histidinate, but who did receive copper histidinate later starting after one month of age Some outcomes for children who received later treatment were reported separately for children who received oral feeding only or oral plus other feeding (see outcomes for n) Patients received approximately 375 mg/dose copper histidinate, administered	Patients were followed-up for up to 6 years. Mean follow-up not reported **Critical outcomes** **Survival** Death by time of study • Early copper histidinate: 2/5 (40.0%) • Later copper histidinate: 19/29 (65.5%) No statistical comparison between early and later treatment Mean (± SD) age at death • Early copper histidinate, oral feeding only, (n=2): 53.5 ± 43.1 months (range 23 to 84) • Later copper histidinate, oral feeding only (n=3): 59 ± 10 months (range not stated) • Later copper histidinate, oral plus other feeding (n=16): 46 ± 22 months (range not stated) Mean (± SD) age survivors at last follow-up • Early copper histidinate, oral feeding only, (n=3): 55.7 ± 25.4 months (range 35 to 84)	This study was appraised using the JBI checklist for cohort studies 1. No 2. Yes 3. No 4. No 5. Not applicable 6. Not applicable 7. Yes 8. Yes 9. No 10. No 11. No **Other comments**: This was a retrospective review of patients nationally with data obtained from medical records or summaries retrospectively written by paediatricians. The authors state that data for some classical Menkes patients treated during the study period would have been lost due to the duration for which medical records are maintained (5 years).

Study details	Population	Intervention	Study outcomes	Appraisal and Funding

Study dates
1994 to 2010
	Total sample size
	n=44
	
	Early treatment: n=5
	Late treatment: n=39
	
	Baseline characteristics
	• Male: 100%
	• Age
	  • Early copper histidinate (age at start of treatment): < 1 month (not further defined)
	  • Later copper histidinate (age at diagnosis): 8.0 ± 2.8 months and 7.5 ± 3.4 months (for oral feeding only and oral plus other feeding respectively)
		parenterally[7] three times a week with adjustment to maintain serum copper and ceruloplasmin levels within a normal range
		
		Duration of treatment not stated
		
		No detail about whether patients received any concomitant treatments
			• Later copper histidinate, oral feeding only (n=4): 100 ± 44 months (range not stated)
			• Later copper histidinate, oral plus other feeding (n=6): 21 ± 10 months (range not stated)
			
			Neurodevelopmental outcomes
			Status at last follow-up or prior to death
			
			Early copper histidinate (n=5):
			• Could lift head from a prone position, sit well unsupported, stand without help and walk: 4/5
			• Could lift head from a prone position and sit with support: 1/5
			
			Later copper histidinate (n=39):
			• Normalised scalp hair and capable of smiling back but could not lift head from a prone position: 39/39
			
			No numerical data or statistical comparison between early and later treatment
			
			Important outcomes
			
			Growth measurements
			Body weight and height of classical Menkes patients with follow-up of up to 6 years were presented as percentiles based on national data
				Limited clinical and demographic information was provided about the participants at baseline and patients who received later treatment were older and are likely to have been diagnosed after the development of symptoms, although this is not clearly stated. Information was provided about the dosing regimen but not about the duration of treatment.
				
				Outcomes were objective. Patients were followed-up for up to 6 years, although mean follow-up was not stated. Potential cofounding factors were not clearly identified.
				
				The study included only 5 patients who received early treatment with copper histidinate. The number of patients included in the outcomes reported varied, with missing data for some patients, particularly patients who received later treatment. The number of patients included in the growth measurement outcomes reported was low. It is not clear if the patients without

[7] The authors state that the copper histidinate was parenterally administered. This could include subcutaneous administration, but it is not stated if this was the means by which the copper histidinate was administered

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			Weight Early copper histidinate (all oral feeding only) • At 6-12 months (n=3): 3/3 <3rd percentile • At age range 13 to 60 months (n=4): 4/4 <3rd percentile Later copper histidinate (oral feeding only) • At age 5-7 months (n=3): 1/3 10th -25th percentile, 2/3 50th -75th percentile • At age 24-25 months (n=2): 2/2 <3rd percentile Later copper histidinate (oral plus other feedings) • At age 4-7 months (n=8): 3/8 3rd -10th percentile, 3/8 10th -25th percentile, 1/8 75th -90th percentile, 1/8 >97th percentile • At age 22-59 months (n=5): 5/5 <3rd percentile *Height* Early copper histidinate (all oral feeding only) • At 6-12 months (n=3): 3/3 <3rd percentile • At age range 13 to 60 months (n=4): 3/4 <3rd percentile, 1/4 <10th -25th percentile Later copper histidinate (oral feeding only) • At age 5-7 months (n=1): 1/1 <3rd percentile	data for some outcomes differed from those who were included. Outcomes are reported for patients who received early treatment with copper histidinate and for patients who did not receive early copper histidinate but who did receive treatment later on. No statistical comparison is made between patients who did or did not receive early treatment. It is not clear how these groups may have differed at baseline apart from age at diagnosis. It is difficult to interpret any differences observed between early and later treatment. The authors state that the copper histidinate was parenterally administered. This could include subcutaneous administration, but it is not stated if this was the means by which the copper histidinate was administered. All patients were referred to one national centre. It is not clear how generalisable these might be to other settings. **Source of funding:**

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			• At age 24-25 months (n=2): 2/2 <3rd percentile Later copper histidinate (oral plus other feedings) • At age 4-7 months (n=6): 1/6 <3rd percentile, 2/6 3rd -10th percentile, 1/6 10th percentile, 1/6 25th -50th percentile, 1/6 75th -90th percentile • At age 22-59 months (n=5): 3/5 <3rd percentile, 2/5 3rd -10th percentile No statistical comparison between early and later treatment	The work was supported by the Japan Foundation for Pediatric Research, the Mother and Child Health Foundation of Japan and the Specified Disease Treatment Research Program of the Ministry of Health, Labour and Welfare of Japan
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. **Study location** 1 national centre, USA **Study type** Prospective cohort study **Study aim** The study aim was to evaluate the effects of a	Children with classical Menkes disease **Inclusion criteria** Children identified as having classical 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 **Exclusion criteria** None stated **Total sample size**	**Intervention** Early subcutaneous copper histidinate delivered prior to symptoms developing to children starting at <1 month old **Comparison** Children who received no copper histidinate prior to symptoms developing, but who did receive copper histidinate starting later after the appearance of symptoms (age not specified) Patients received 250µg copper histidinate, twice	Patients followed-up at 4 to 6-month intervals by a single investigator for up to 3 years **Critical outcomes** **Survival** Death by three years old • Early copper histidinate: 10/35 (28.6%) • Later copper histidinate: 11/22 (50.0%) No statistical comparison between early and later treatment **Neurodevelopmental outcomes** Neurodevelopmental level in months achieved by age three years or time of death	This study was appraised using the JBI checklist for cohort studies 1. No 2. Yes 3. Yes 4. No 5. No 6. Not applicable 7. Yes 8. Yes 9. Yes 10. Not applicable 11. No **Other comments**: This was a prospective, uncontrolled cohort study comparing a group of children who had received early

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
specific copper treatment regimen on neurodevelopment and somatic growth in patients with a proven diagnosis of classical Menkes disease **Study dates** Study dates not stated	n=57 Early treatment: n=35 Late treatment: n=22 **Baseline characteristics** No baseline characteristics reported No detail on the age of the children at treatment initiation reported other than that early treatment was at < 1 month old	daily by subcutaneous injection up to one year old then 250µg copper histidinate, once daily by subcutaneous injection between one and three years old No detail about whether patients received any concomitant treatments	using the Denver Developmental Screening Test[8] (mean follow-up not reported) *Gross motor (mean (SD; range) months)* • Early copper histidinate (n=35): 13.743 (12.200; 1 to 36) • Later copper histidinate (n=22): 2.455 (2.154; 1 to 10) p<0.0001 *Fine motor-adaptive (mean (SD; range) months)* • Early copper histidinate (n=35): 16.200 (12.762; 1 to 36) • Later copper histidinate (n=22): 2.409 (1.652; 1 to 8) p<0.0001 *Personal-social (mean (SD; range) months)* • Early copper histidinate (n=35): 17.657 (13.482; 1 to 36) • Later copper histidinate (n=22): 3.364 (3.499; 1 to 15) p<0.0001 *Language (mean (SD; range) months)* • Early copper histidinate (n=35): 15.800 (12.034; 1 to 36) • Later copper histidinate (n=22): 3.227 (2.943; 1 to 12) p<0.0001 **Important outcomes**	treatment with a group of children who did not receive early copper histidinate but who did receive copper histidinate later on. Limited clinical and demographic information was provided about the participants other than differences in symptomatic status at baseline. It is not clear if all patients treated at the centre in a time period were included. Year of recruitment or treatment was not reported. Objective measures were used to assess outcomes and patients were followed-up for up to 3 years. Statistical analysis comparing the groups was reported for some outcomes. However, potential cofounding factors were not clearly identified and no adjustments were made for potential confounding factors between the groups. All patients were referred to one national centre. It is not clear how generalisable these might be to other settings.

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

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			Growth measurements Growth measurements (weight, length, occipitofrontal circumference), centile at age three years or time of death (mean follow-up not reported) *Weight (mean (SD; range) centile)* • Early copper histidinate (n=35): 12.086 (19.589; 0 to 80) • Later copper histidinate (n=22): 11.273 (17.097; 0 to 50) p=0.8735 *Length (mean (SD; range) centile)* • Early copper histidinate (n=35): 8.286 (13.501; 0 to 25) • Later copper histidinate (n=22): 15.455 (23.192; 0 to 75) p=0.1453 *Occipitofrontal circumference (mean (SD; range) centile)* • Early copper histidinate (n=35): 33.286 (27.060; 0 to 90) • Later copper histidinate (n=22): 11.136 (14.551; 0 to 50) p<0.0009	Outcomes for 3 patients with milder forms of Menkes disease were not extracted. **Source of funding:** The study was funded by the Intramural Research Programs of NICHD and NINDS and grants from the International Copper Association and Children's National Medical Center, Washington DC
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	Children with classical Menkes disease **Inclusion criteria** Patients at risk of classical Menkes disease because of a	**Intervention** Early subcutaneous copper histidinate delivered prior to neurological symptoms developing to children	Mean follow up: 4.6 years (range 1.5 to 8.6) **Critical outcomes** **Number of seizures**	This study was appraised using the JBI checklist for case series 1. Yes 2. Yes 3. Yes 4. Unclear

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
England Journal of Medicine. 2008; 358(6):605-614. **Study location** 1 national centre, USA **Study type** Case series **Study aim** The study aim included determining the clinical effect of early diagnosis and treatment **Study dates** May 1997 to July 2005	positive family history or suggestive clinical or biochemical findings. Patients eligible to receive copper histidinate were ≤ 1 month old with no neurologic symptoms. These patients also had high ratios of both dopamine to norepinephrine and dihydroxyphenylacetic acid to dihydroxyphenylglycol **Exclusion criteria** None stated **Total sample size** n=12[9] Baseline characteristics • Mean age at treatment initiation: 10 ± 4 days (range 5 to 22)	≤1 month old (mean 10 ± 4 days) **Comparison** No comparator Patients received 250µg copper histidinate, twice daily by subcutaneous injection up to one year old then 250µg copper histidinate, once daily Eight patients received treatment for 3 years and 3 patients (aged < 3 years) were still being treated. 1 patient died during the study and received treatment for 1.6 years No detail about whether patients received any concomitant treatments	Evidence of clinical seizures: 2/12 (16.7%) (not further defined) Timeframe unclear **Safety** Increased levels of urinary β2-microglobulin (a sensitive marker of renal tubular damage): 11/11 (100%) Maximum measured concentration: Median 27.4 mg/L (range 1.2 to 60.9) (reference range 0.0 to 0.3) Measurements taken whilst patients were receiving copper histidinate (up to 3 years)	5. Unclear 6. Yes 7. Yes 8. Yes 9. Yes 10. Not applicable **Other comments**: This study reviewed patients treated at one national centre in the USA. It is not clear if all patients treated at the centre in a time period were included. This study did not include a comparator for the outcomes extracted for this review. As all the patients who received early treatment in this study were also included in Kaler 2014, outcomes included Kaler in 2014 (survival and neurodevelopmental outcomes) have not been extracted from this paper. Data from a historical group of patients who received later treatment was only reported for survival and was therefore not extracted. Urinary β2-microglobulin levels were stated as 'not measured' in one of the surviving 12 patients

[9] Kaler 2014 stated that the 12 patients from Kaler et al 2008 were included in Kaler 2014. Kaler et al 2010 reported that 10 patients from Kaler et al 2008 were included in Kaler et al 2010 (please see comment in study summary table)

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
				included in this study. No reason is given for why this measurement was not reported. 10 of the 12 patients included in this paper were included in Kaler et al 2010. It is unclear if the 2 patients who had clinical seizures in this paper are amongst the patients reported as having clinical seizures in Kaler et al 2010. All patients were referred to one national centre. It is not clear how generalisable these might be to other settings. **Source of funding:** The study was supported by funding from the Intramural Research Program of the National Institutes of Health
Kaler SG, Liew CJ, Donsante A, Hicks JD, Sato S, Greenfield JC. Molecular correlates of epilepsy in early diagnosed and treated Menkes disease. Journal of Inherited Metabolic Disease. 2010;33(5):583-9. **Study location**	Children with classical Menkes disease **Inclusion criteria** Children identified as having classical Menkes disease based on clinical, neurochemical or molecular grounds **Exclusion criteria**	**Intervention** Early subcutaneous copper histidinate delivered prior to neurological symptoms developing to children <6 weeks old (mean 11.8 ± 9.6 days) **Comparison** No comparator	Patients followed-up for up to 6 years. Mean follow-up not reported **Critical outcomes** **Survival** 9/24 patients (37.5%) died during the study (mean follow-up not reported). Age range at death 5.5 months to 2.6 years **Neurodevelopmental outcomes**	This study was appraised using the JBI checklist for case series 1. Yes 2. No 3. Yes 4. Unclear 5. Unclear 6. Yes 7. Yes 8. Yes 9. Yes

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
1 national centre, USA **Study type** Case series **Study aim** The study aim was to assess the influence of earlier, presymptomatic diagnosis and treatment on seizure semiology and brain electrical activity **Study dates** 1992 to 2007	2 patients were excluded from the analysis due to a family history of epilepsy and a medical history of seizure respectively **Total sample size** n=24[10] **Baseline characteristics** • Mean age at treatment initiation: 11.8 ± 9.6 days (range -3.5 weeks to 42 days)	Patients received 250-500µg copper histidinate per day by subcutaneous injection Duration of treatment not reported No detail about whether patients received any concomitant treatments	Neurodevelopmental outcomes were assessed using the Denver Developmental Screening Test Neurodevelopmental development status in survivors with data at last follow-up (n=14) (mean follow-up not reported)[11]: • Normal: 3 (21.4%) • Mildly delayed: 1 (7.1%) • Moderately delayed: 3 (21.4%) • Severely delayed: 7 (50.0%) Categories not further defined **Number of seizures** Clinical seizures: 3/24 (12.5%) In these 3 patients, seizures were described as: • Apnea/cyanosis 2-3 episodes/day starting at approximately 4 months (n=1) • One tonic-clonic seizure at 3.5 months (n=1) • Myoclonic jerks 10-20/day, starting at 31 months (n=1) Mean age at first seizure: 20.3 ± 9.3 weeks (range 14 to 31)	10. Not applicable **Other comments**: This study reviewed patients treated at one national centre in the USA. It is not clear if all patients treated at the centre in a time period were included. Two of the 24 patients received treatment starting at more than 28 days old, one at 30 days and one at 42 days. However, all patients were described as starting treatment prior to the development of neurological symptoms. Information was provided about the dosing regimen but not about the duration of treatment. One patient was lost to follow-up after 6 months of age. The study did not include a comparator group. Details of a comparison between the results of this study and previously studied groups were not extracted.

[10] Kaler 2014 reported that 1 patient from Kaler et al 2010 was included in Kaler 2014. Kaler et al 2010 reported that 10 patients from Kaler et al 2008 were included in Kaler et al 2010

[11] Figures taken from the study text which differs from the number of patients in the different categories presented in a table (7 patients compared to 6 patients severely delayed; 3 patients compared to 4 patients moderately delayed)

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
				All patients were referred to one national centre. It is not clear how generalisable these might be to other settings. **Source of funding:** The study was supported by the National Institutes of Health Intramural Research Program of the National Institutes of Health

Abbreviations

L: litre, µg: micrograms, mg: milligrams, SD: standard deviation, USA: United States of America

Appendix F Quality appraisal checklists

JBI Critical Appraisal Checklist for Cohort Studies

1. Were the two groups similar and recruited from the same population?
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?
3. Was the exposure measured in a valid and reliable way?
4. Were confounding factors identified?
5. Were strategies to deal with confounding factors stated?
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?
7. Were the outcomes measured in a valid and reliable way?
8. Was the follow-up time reported and sufficient to be long enough for outcomes to occur?
9. Was follow-up complete, and if not, were the reasons to loss to follow-up described and explored?
10. Were strategies to address incomplete follow-up utilized?
11. Was appropriate statistical analysis used?

JBI Critical Appraisal Checklist for Case Series

1. Were there clear criteria for inclusion in the case series?
2. Was the condition measured in a standard, reliable way for all participants included in the case series
3. Were valid methods used for the identification of the condition for all participants included in the case series?
4. Did the case series have consecutive inclusion of participants?
5. Did the case series have complete inclusion of participants?
6. Was there clear reporting of the demographics of the participants in the study?
7. Was there clear reporting of clinical information of the participants?
8. Were the outcomes or follow up results of cases clearly reported?
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?
10. Was statistical analysis appropriate?

Appendix G GRADE profiles

Table 1. In children with classical Menkes disease, what is the clinical effectiveness and safety of subcutaneous copper histidinate delivered prior to symptoms developing compared with no subcutaneous copper histidinate?

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Early copper histidinate	Later copper histidinate	Result		
Survival (2 cohort studies and 1 case series)									
Death by three years old									
1 prospective cohort study Kaler 2014	Very serious limitations[1]	No serious indirectness	Not applicable	Not calculable	35	22	• Early copper histidinate: 10/35 (28.6%) • Later copper histidinate: 11/22 (50.0%) No comparison between early and later treatment	Critical	Very low
Death by time of study (patients followed-up for up to 6 years, mean follow-up not reported)									
1 retrospective cohort study Gu et al 2014	Very serious limitations[2]	No serious indirectness	Not applicable	Not calculable	5	29	• Early copper histidinate: 2/5 (40.0%) • Later copper histidinate: 19/29 (65.5%) No comparison between early and later treatment	Critical	Very low
Death during the study (patients followed-up for up to 6 years, mean follow-up not reported)									
1 case series Kaler et al 2010	Very serious limitations[3]	Serious indirectness[4]	Not applicable	Not calculable	24	---	9/24 (37.5%)	Critical	Very low

Neurodevelopmental outcomes (2 cohort studies and 1 case series)									
Gross motor level in months by 3 years old or time of death (mean (SD; range)) assessed by DDST[A] (benefit indicated by higher result)									
1 prospective cohort study Kaler 2014	Very serious limitations[5]	No serious indirectness	Not applicable	Not calculable	35	22	• Early copper histidinate: 13.743 (12.200; 1 to 36) • Later copper histidinate: 2.455 (2.154; 1 to 10) p<0.0001	Critical	Very low
Fine motor-adaptive level in months by 3 years old or time of death (mean (SD; range)) assessed by DDST (benefit indicated by higher result)									
1 prospective cohort study Kaler 2014	Very serious limitations[5]	No serious indirectness	Not applicable	Not calculable	35	22	• Early copper histidinate: 16.200 (12.762; 1 to 36) • Later copper histidinate: 2.409 (1.652; 1 to 8) p<0.0001	Critical	Very low
Personal-social level in months by 3 years old or time of death (mean (SD; range)) assessed by DDST (benefit indicated by higher result)									
1 prospective cohort study Kaler 2014	Very serious limitations[5]	No serious indirectness	Not applicable	Not calculable	35	22	• Early copper histidinate: 17.657 (13.482; 1 to 36) • Later copper histidinate: 3.364 (3.499; 1 to 15) p<0.0001	Critical	Very low
Language level in months by 3 years old or time of death (mean (SD; range)) assessed by DDST (benefit indicated by higher result)									
1 prospective cohort study Kaler 2014	Very serious limitations[5]	No serious indirectness	Not applicable	Not calculable	35	22	• Early copper histidinate: 15.800 (12.034; 1 to 36) • Later copper histidinate: 3.227 (2.943; 1 to 12) p<0.0001	Critical	Very low
Neurodevelopmental status at last follow-up or prior to death (patients followed-up for up to 6 years, mean follow-up not reported)									
1 retrospective cohort study Gu et al 2014	Very serious limitations[6]	No serious indirectness	Not applicable	Not calculable	5	39	Early copper histidinate: • Could lift head from a prone position, sit well unsupported, stand without help and walk: 4/5 • Could lift head from a prone position and sit with support: 1/5	Critical	Very low

							Later copper histidinate: • Normalised scalp hair and capable of smiling back but could not lift head from a prone position: 39/39 No numerical data or comparison between early and later treatment		
Neurodevelopmental status at last follow-up assessed using the DDST (patients followed-up for up to 6 years, mean follow-up not reported)									
1 case series Kaler et al 2010	Very serious limitations[3]	Serious indirectness[4]	Not applicable	Not calculable	14	---	• Normal: 3/14 (21.4%) • Mildly delayed: 1/14 (7.1%) • Moderately delayed: 3/14 (21.4%) • Severely delayed: 7/14 (50.0%)	Critical	Very low
Number of seizures (2 case series)									
Number of patients with clinical seizures (study mean follow-up 4.6 years (range 1.5 to 8.6). Timeframe for this outcome unclear)									
1 case series Kaler et al 2008	Serious limitations[7]	Serious indirectness[4]	Not applicable	Not calculable	12	---	2/12 (16.7%)	Critical	Very low
Number of patients with clinical seizures (patients followed-up for up to 6 years, mean follow-up not reported)									
1 case series Kaler et al 2010	Very serious limitations[3]	Serious indirectness[4]	Not applicable	Not calculable	24	---	3/24 (12.5%)	Critical	Very low
Growth measurements (2 cohort studies)									
Weight centile at 3 years old or time of death (mean (SD; range)) (benefit indicated by higher result)									
1 prospective cohort study Kaler 2014	Very serious limitations[5]	No serious indirectness	Not applicable	Not calculable	35	22	• Early copper histidinate: 12.086 (19.589; 0 to 80) • Later copper histidinate: 11.273 (17.097; 0 to 50) p=0.8735	Important	Very low

Body weight percentile at time period up to 12 months old (benefit indicated by higher result)									
1 retrospective cohort study Gu et al 2014	Very serious limitations[2]	No serious indirectness	Not applicable	Not calculable	3	11	• Early[B] copper histidinate at 6-12 months: <3rd percentile 3 • Later copper histidinate, oral feeding only at 5-7 months (n=3): 1/3 10th -25th percentile, 2/3 50th -75th percentile • Later copper histidinate, oral feeding plus other feeding at 4-7 months (n=8): 3/8 3rd -10th percentile, 3/8 10th -25th percentile, 1/8 75th -90th percentile, 1/8 >97th percentile No comparison between early and later treatment	Important	Very low
Body weight percentile at time period from over 12 months to 60 months old (benefit indicated by higher result)									
1 retrospective cohort study Gu et al 2014	Very serious limitations[2]	No serious indirectness	Not applicable	Not calculable	4	7	• Early copper histidinate at 13-60 months: <3rd percentile 4 • Later copper histidinate, oral feeding only at 24-25 months (n=2): 2/2 <3rd percentile • Later copper histidinate, oral feeding plus other feeding at 22-59 months (n=5): 5/5 <3rd percentile No comparison between early and later treatment	Important	Very low
Length centile at 3 years old or time of death (mean (SD; range)) (benefit indicated by higher result)									
1 prospective cohort study	Very serious limitations[5]	No serious indirectness	Not applicable	Not calculable	35	22	• Early copper histidinate: 8.286 (13.501; 0 to 25) • Later copper histidinate: 15.455 (23.192; 0 to 75)	Important	Very low

Kaler 2014							p=0.1453		
Body height percentile at time period up to 12 months old (benefit indicated by higher result)									
1 retrospective cohort study Gu et al 2014	Very serious limitations[2]	No serious indirectness	Not applicable	Not calculable	3	7	• Early copper histidinate at 6-12 months: <3rd percentile 3/3 • Later copper histidinate, oral feeding only at 5-7 months (n=1): 1/1 <3rd percentile • Later copper histidinate, oral feeding plus other feeding at 4-7 months (n=6): 1/6 <3rd percentile, 2/6 3rd -10th percentile, 1/6 10th percentile, 1/6 25th -50th percentile, 1/6 75th -90th percentile No comparison between early and later treatment	Important	Very low
Body height percentile at time period from over 12 months to 60 months old (benefit indicated by higher result)									
1 retrospective cohort study Gu et al 2014	Very serious limitations[2]	No serious indirectness	Not applicable	Not calculable	4	7	• Early copper histidinate at 13-60 months: 3/4 <3rd percentile, 1/4 <10th -25th percentile • Later copper histidinate, oral feeding only at 24-25 months (n=2): 2/2 <3rd percentile • Later copper histidinate, oral feeding plus other feeding at 22-59 months (n=5): 3/5 <3rd percentile, 2/5 3rd -10th percentile No comparison between early and later treatment	Important	Very low

Occipitofrontal circumference centile at 3 years old or time of death (mean (SD; range)) (benefit indicated by higher result)									
1 prospective cohort study Kaler 2014	Very serious limitations[5]	No serious indirectness	Not applicable	Not calculable	35	22	• Early copper histidinate: 33.286 (27.060; 0 to 90) • Later copper histidinate: 11.136 (14.551; 0 to 50) p<0.0009	Important	Very low
Safety (1 case series)									
Increased level of urinary β2-microglobulin[C] during treatment with copper histidinate (up to 3 years)									
1 case series Kaler et al 2008	Serious limitations[7]	Serious indirectness[4]	Not applicable	Not calculable	11	---	11/11 (100%)	Important	Very low

Abbreviations: DDST: Denver Developmental Screening Test, SD: standard deviation

1 Risk of bias: Very serious limitations due to lack of detail about the study population, lack of similarity between the groups at baseline, lack of identification of and adjustment for potential confounding factors and lack of statistical analysis
2 Risk of bias: Very serious limitations due to lack of detail about the study population, lack of similarity between the groups at baseline, lack of information about duration of treatment, lack of identification of confounding factors, incomplete follow-up and lack of statistical analysis
3 Risk of bias: Very serious limitations due to unclear reporting of study participants in relation to consecutive and complete recruitment and lack of information about duration of treatment
4 Indirectness: Serious indirectness due to lack of a comparator[D]
5 Risk of bias: Very serious limitations due to lack of detail about the study population, lack of similarity between the groups at baseline and lack of identification of and adjustment for potential confounding factors
6 Risk of bias: Very serious limitations due to lack of detail about the study population, differences between the groups at baseline, lack of information about duration of treatment, lack of identification of potential confounding factors and lack of statistical analysis
7 Risk of bias: Serious limitations due to unclear reporting of study participants in relation to consecutive and complete recruitment

A The Denver Developmental Screening Test (DDST) II assesses 4 areas: gross motor, fine motor-adaptive, personal-social and language
B All early copper histidinate patients in Gu et al 2014 had oral feeding only
C An increased level is a sensitive marker of renal tubular damage
D This study had not been downgraded in relation to the population as although 2 patients started treatment at >28 days, one at 30 days and one at 42 days, all patients were described as starting treatment prior to the development of neurological symptoms

Glossary

Adverse event	Any undesirable event experienced by a person while they are having a drug or any other treatment or intervention, regardless of whether or not the event is suspected to be related to or caused by the drug, treatment or intervention.
Case series	Reports of several patients with a given condition, usually covering the course of the condition and the response to treatment. There is no comparison (control) group of patients.
Comparative cohort study	An observational study with two or more groups (cohorts) of people with similar characteristics. One group has a treatment, is exposed to a risk factor or has a particular symptom and the other group does not.
GRADE (Grading of recommendations assessment, development and evaluation)	A systematic and explicit approach to grading the quality of evidence and the strength of recommendations developed by the GRADE working group.
Minimal clinically important difference	The smallest change in a treatment outcome that people with the condition would identify as important (either beneficial or harmful), and that would lead a person or their clinician to consider a change in treatment.
Objective measure	A measurement that follows a standardised procedure which is less open to subjective interpretation by potentially biased observers and people in the study.
PICO (population, intervention, comparison and outcome) framework	A structured approach for developing review questions that divides each question into 4 components: the population (the population being studied); the interventions (what is being done); the comparators (other main treatment options); and the outcomes (measures of how effective the interventions have been).
Prospective study	A research study in which the health or other characteristic of patients is monitored (or 'followed up') for a period of time, with events recorded as they happen. This contrasts with retrospective studies.
P-value (p)	The p value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing 2 treatments found that 1 seems to be more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance), it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 0.1% probability that the results occurred by chance), the result is seen as highly significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.
Retrospective study	A research study that focuses on the past and present. The study examines past exposure to suspected risk factors for the disease or condition. Unlike prospective studies, it does not cover events that occur after the study group is selected.
Standard deviation (SD)	A measure of the spread, scatter or variability of a set of measurements. Usually used with the mean (average) to describe numerical data.
Statistical significance	A statistically significant result is one that is assessed as being due to a true effect rather than random chance.

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