Clinical Commissioning Policy:

Subcutaneous copper histidinate injections for presymptomatic neonates with classical Menkes disease [2105]

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Commissioning position

Summary

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

The policy is restricted to certain age groups and it is not recommended to be used in those age groups not included in the policy.

Equality statement

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

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

Executive summary

This policy is focused on presymptomatic neonates with classical Menkes disease and the use of copper histidinate in this population.

The independent evidence review returned evidence for copper histidinate, which is presented for a routine commissioning position.

Plain language summary

Menkes disease is an inherited disorder of copper transport, which mainly affects males. 'Classical' Menkes disease presents soon after birth and is a life-limiting disease, with affected children suffering seizures, growth failure and a poor quality of

life. It is a progressive disease, with an average life expectancy of 3 years without early treatment. Current treatment focuses on treating the symptoms of the disease, as there is no cure.

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

What we have decided

NHS England has carefully reviewed the evidence to treat neonates diagnosed with classical Menkes disease who are presymptomatic (i.e. not yet displaying symptoms) with subcutaneous copper histidinate. We have concluded that there is enough evidence to make the treatment available at this time.

Links and updates to other policies

This document updates and replaces the Clinical Commissioning Urgent Policy Statement: Subcutaneous copper histidinate injections for presymptomatic neonates with classical Menkes disease.

Committee discussion

See the committee papers on the (on the NHS England website) for full details of the evidence.

The condition

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

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

Current treatments

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

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

Proposed treatments

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

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

Epidemiology and needs assessment

Although the incidence of Menkes disease in Western Europe is estimated to be between 1 in 250,000 and 1 in 300,000 (Rangahr and Kohli, 2018) many of these diagnoses will be made outside of the neonatal period, when symptoms have developed.

Evidence summary

An independent evidence review was conducted for the use of subcutaneous copper histidinate for presymptomatic neonates with classical Menkes disease. NHS England has concluded that there is sufficient evidence to support a policy for the routine commissioning of this treatment for the indication. The evidence review which informs this commissioning position can be accessed on the NHS England website).

Implementation

Criteria

Inclusion criteria

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

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

Exclusion criteria

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

- Symptomatic from classical Menkes disease

Starting criteria

Patients that meet all of the inclusion criteria and do not meet the exclusion criteria should be considered for treatment with subcutaneous copper histidinate injections. These patients should be treated under the care of a specialist neurometabolic multidisciplinary team (MDT) including at least a paediatric consultant specialising in metabolic diseases, a paediatric consultant specialising in neurology and specialist nurses. The specialist MDT should ensure that routine blood tests including full blood count, urea and electrolytes along with cystatin C, copper and caeruloplasmin[2] are measured at baseline.

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

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

Reassessment

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

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

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

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

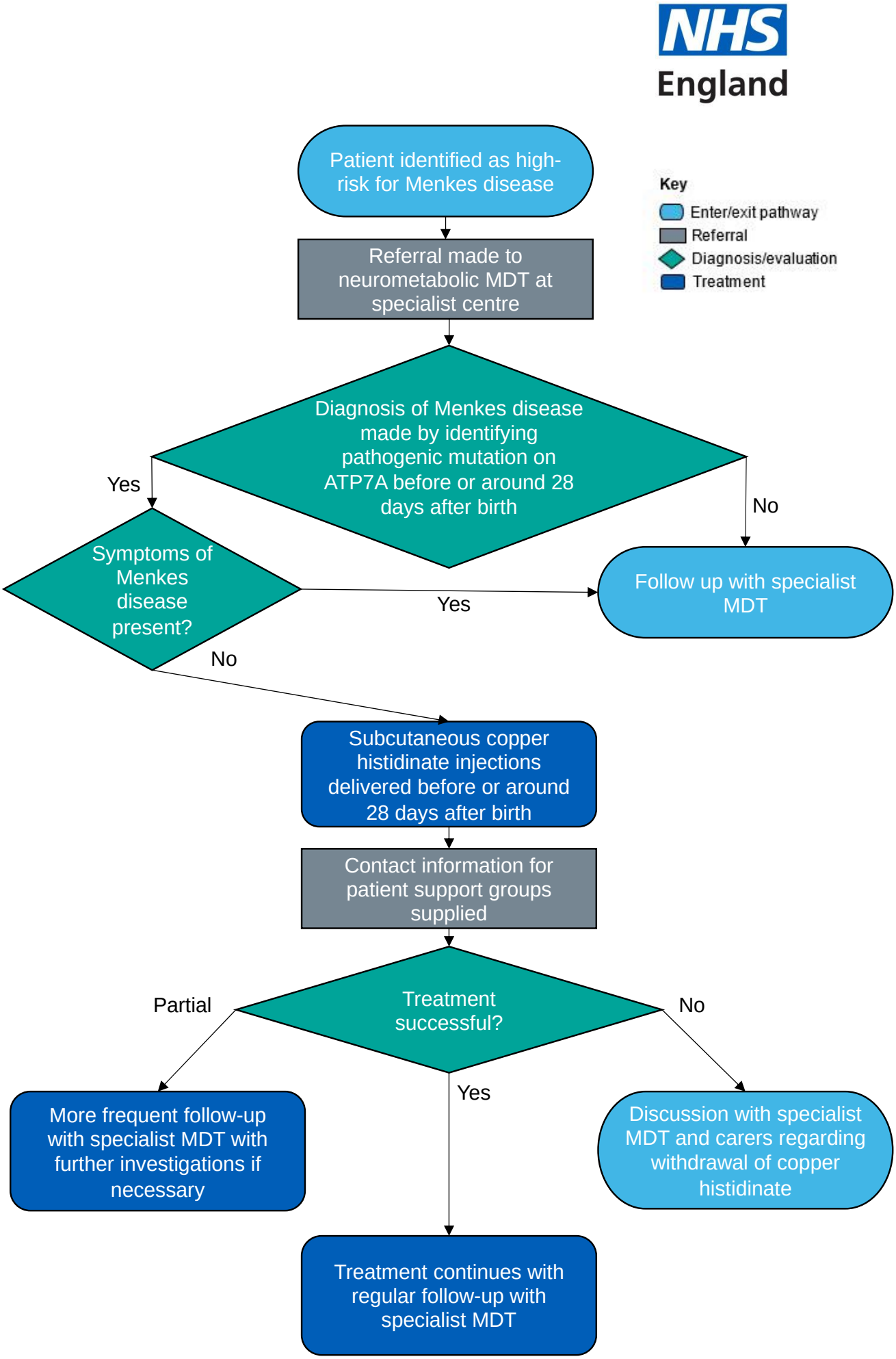
Stopping criteria

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

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

NHS England

Patient path


NHS England
Key
Enter/exit pathway
Referral
Diagnosis/evaluation
Treatment
Patient identified as high-risk for Menkes disease
Referral made to neurometabolic MDT at specialist centre
Diagnosis of Menkes disease made by identifying pathogenic mutation on ATP7A before or around 28 days after birth
Yes
No
Symptoms of Menkes disease present?
Yes
No
Follow up with specialist MDT
Subcutaneous copper histidinate injections delivered before or around 28 days after birth
Contact information for patient support groups supplied
Treatment successful?
Partial
Yes
No
More frequent follow-up with specialist MDT with further investigations if necessary
Discussion with specialist MDT and carers regarding withdrawal of copper histidinate
Treatment continues with regular follow-up with specialist MDT

Governance arrangements

This policy should be used in conjunction with the Metabolic Disorders (Children) Service Specification (E06/S/b, NHS England 2013).

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

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

Mechanism for funding

Subcutaneous copper histidinate will be routinely commissioned by NHS England through specialist metabolic units and in a formal shared care arrangement with such a centre. The activity will be invoiced through the contracts that the specialist trust has with NHS England.

Policy review date

This document will be reviewed when information is received which indicates that the policy requires revision. If a review is needed due to a new evidence base then a new Preliminary Policy Proposal needs to be submitted by contacting england.CET@nhs.net.

Our policies provide access on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to review policies where the supplier of an intervention is no longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies.

Definitions

Classical Menkes disease	A progressive genetic disorder of copper transport, which is life limiting and mainly affects males. It presents soon after birth.
Copper histidinate	A treatment for classical Menkes disease, delivered subcutaneously.

References

NHS England. 2013. E06/S/b 2013/2014 NHS Standard Contract: Metabolic Disorders (Children). Available at https://www.england.nhs.uk/wp-content/uploads/2013/06/e06-metab-disorders-child.pdf. Accessed 7 July 2021.

Rangahr P, Kohli N. 2018. Neuroimaging findings in Menkes disease: a rare neurodegenerative disorder. BMJ Case Reports. bcr2017223858.