Urine Catecholamines metabolites

The quantitative measurement of HMMA (4-hydroxy-3-methoxymandelic acid) and HVA (4-hydroxy-3-methoxy phenyl acetic acid) in urine, and the calculation of their ratio to creatinine, are used to aid with the diagnosis and post-treatment monitoring of neuroblastoma in children.

If Phaeochromocytoma is suspected, plasma metadrenalines should be requested (see separate entry).

Neuroblastoma, the most common solid tumour in children, derived from precursor sympathoadrenal cells so they can develop anywhere along the adrenal/spinal axis, rarely in the chest (Fisher and Tweddle, 2012). Around 120 new cases are diagnosed in the UK each year predominantly in children under 4 years old (http://www.ccrg.ox.ac.uk/datasets/registrations.shtml). Five year survival rates have improved since the 1970s from around 17% up to around 65% (http://www.ccrg.ox.ac.uk/datasets/survivalrates.shtml) resulting in more patients also being monitored for recurrence (in combination with MIBG scanning). Although there are several other biomarkers used as prognostic indicators, urine catecholamines (and plasma LDH) are the only ones considered to be diagnostic (Trigg, Shaw and Turner, 2019).

The paper by Erdelyi *et al* provides an excellent overview of the clinical use of urine catecholamines (Erdelyi, Elliott and Philips 2011). Neuroblastomas have high expression of tyrosine hydroxylase which converts tyrosine to L-DOPA which is then further metabolised to dopamine and HVA. Conversion of dopamine also takes place to adrenaline and noradrenaline which are converted to HMMA. Excess HVA and HMMA in particular are excreted as the end products of the metabolic pathways. Verly et al (Verly et al 2017) have proposed the best diagnostic sensitivity is achieved with a panel of 8 catecholamines and metabolites to identify those patients with non-MIBG avid tumours, tumours producing non-classical metabolite profiles (HMMA and HVA negative, approximately 1/6 of the cohort). HVA and HMMA out-perform noradrenaline and adrenaline in terms of percentage of patients with an elevation at diagnosis regardless of how the patients are grouped (INSS stage, risk group, age at diagnosis, primary tumour site etc.).

General information

Collection container: Random urine samples are suitable; collected into a 10mL Sarstedt (acidification not required) and must arrive at the laboratory within 3h.

24hr collections are also acceptable. 24hr urine bottle containing 5 mol/L hydrochloric acid, depending on age, up to a maximum of 25 mL. The laboratory can provide appropriate collection containers for 24h urine collection – telephone x64655.

Type and volume of sample: Spot or random specimens (10mL minimum volume), and 24-hour collections (10mL aliquot of a 24h acidified urine collection required) are suitable for investigation of neuroblastoma.

If a random sample is to be used, an early morning (concentrated) sample is best. Avoid first voided urine, as this may have been lying in the bladder for a number of hours and give falsely low results. Second morning urine is preferred.

External users providing spot urine samples: 5 mol/L hydrochloric acid added dropwise until the pH is less than 3.0.

Specimen transport/special precautions: Do not send in the pneumatic tube but ensure it is sent to the lab within 3h of collection.

External users: First class post is adequate but please contact the paediatric duty biochemist 0161 701 2255 if results are required urgently – we do not guarantee that an urgent result will be possible, but we will do our utmost to accommodate these requests.

Laboratory information

Method principle: HMMA and HVA are extracted from urine with ethyl acetate and determined by HPLC with electrochemical detection (ECD).

Biological reference range or cut off

All µmol/mmol creatinine

HMMA : creatinine ratio

Up to 3months	<18
3 to 9 months	<17
9 to 15 months	<15
15 to 21 months	<12
21m to 2.5y	<11
2.5 to 3.5y	<9
3.5 to 4.5y	<8
4.5 to 6.5y	<7
6.5 to 8.5y	<6
8.5 to 11y	<5.5
11 to 17y	<5

HVA : creatinine ratio

Up to 1y	<25
1 to 1.5y	<22
1.5 to 2y	<19
2 to 3y	<16
3 to 4 y	<13
4 to 5y	<12
5 to 8y	<9
8 to 10y	<7.5
10 to 11y	<7
11 to 12.5y	<6.5
12.5 to 15y	<6
15 to 17y	<5.5

Turnaround times: This analysis is usually performed once per week. Urgent analyses will be performed according to clinical need and/or after discussion with the Consultant Clinical Scientist.

Clinical information

Factors known to significantly affect the results: Catecholamines are unstable if not collected into acid therefore, if not collected into a pre-acidified bottle, the sample must reach the laboratory within 3 hrs to be acidified in the laboratory.

Dilute samples (creatinine <1.0mmol/L) cannot be analysed and will require repeat collection.

Clinical decision points: Any raised level may be significant and will be communicated to the requesting team. Isolated minor elevations in a single analyte may be related to diet.

References:

- Erdelyi, Elliott and Philips. Urine Catecholamines in paediatrics. Arch Dis Child Educ Pract Ed 2011; 96:107-111.
- Fisher JPH and Tweddle DA. Neonatal Neuroblastoma. Seminars in Fetal and Neonatal Medicine, 2012; 17: 207-215.
- https://www.sfnmjournal.com/article/S1744-165X(12)00057-1/abstract Trigg RM, Shaw JA, Turner SD. Opportunities and challenges of circulating biomarkers in neuroblastoma. Open Biol. 2019 May 31;9(5):190056. https://www.ncbi.nlm.nih.gov/pubmed/31088252
- Verly IR, van Kuilenburg AB, Abeling NG et al. Catecholamines profiles at diagnosis: Increased diagnostic sensitivity and correlation with biological and clinical features in neuroblastoma patients. Eur J Cancer. 2017 Feb;72:235-243. https://www.ncbi.nlm.nih.gov/pubmed/28061374

(Last updated April 2021)