Audit of in use reference ranges for homovanillic acid and vanillylmandelic acid for the diagnosis of neuroblastoma in the UK

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INTRODUCTION

Neuroblastoma is a rare childhood cancer, but it is the most common extracranial solid cancer within the first year of life. Homovanillic acid (HVA) and vanillylmandelic acid (VMA) are catecholamines that are measured in urine as part of the diagnostic workup of neuroblastoma.

STANDARDS/GUIDELINES

The European Society for Paediatric Oncology[1] recommends the measurement of both HVA and VMA as part of the diagnostic workup. The National Comprehensive Cancer Network guidelines[2] also state that HVA/VMA should both be offered as part of the work up of neuroblastoma but that they are not recommended for ongoing monitoring. Although there are guidelines for the diagnosis and management of neuroblastoma there are no specific recommendations for reference ranges or cut offs for HVA or VMA.

OBJECTIVE

The aim of this audit was to review our local reference ranges for HVA/VMA against those in use throughout the UK .

METHODOLOGY

The UKAS website was searched for accredited providers of HVA/VMA to identify UK based providers of these tests. Where clearly stated, the method in use was recorded from the UKAS scope document. Trust or laboratory websites were then searched for their reference range information including age delineations and any stated sources. Where this information was not publicly available, individual laboratories were contacted for their in-use ranges and sources. Since HVA/VMA are used in paediatric patients, only ranges per creatinine for random urines have been included in this audit as 24-hour collections are seldom performed for paediatric patients in routine practice.

RESULTS

11 UKAS accredited laboratories were identified. 9 laboratories offered both tests and were therefore compliant with guidelines. The majority of laboratories used HPLC for analysis. 5 laboratories stated that they used in house or historic reference ranges, 2 laboratories cited referenceable sources, 1 laboratory stated they did not know the source of their ranges and for 3 laboratories the source information was not able to be documented due to no response/available information. Table 1 demonstrates that there is widespread variation in both the age delineations and reference ranges in use in the UK for these tests even for laboratories using similar methodologies.

TABLE 1

Method	Offer both HVA/VMA?	Reference range source	UKAS accredited	VMA ranges (µmol/mmol creatinine)	HVA ranges (µmol/mmol creatinine)
HPLC-ECD	Y	Soldin S & Hill G. Liquid-Chromatographic Analysis for Urinary 4-Hydroxy-3-Methoxymandelic Acid and 4-Hydroxy-3-Methoxyphenylacetic Acid , and its Use in Investigation of Neural Crest Tumors, *Clinical Chemistry* 1981; 27 (3) 502-503	Y	0-1Y <11 2-4Y <6 5-9Y <5 10-19Y <5	0-1Y <20 2-4Y <14 5-9Y <9 10-19Y <8
UPLC-ECD	Y	In house historic	Y	0-6M <17 >6-12M <15 >1-2Y <10 >2-3Y <9 >3-4Y <8 >4-6Y <7 >6-8Y <6 >6-12Y <5.5 >12-16 <5	0-6M <23 >6-12M <21 >1-2Y <17.5 >2-3Y <15 >3-4Y <13 >4-5Y <11 >5-6Y <10 >6-8Y <8 >8-10Y <7 >10-13Y <6 >13-16Y <5
GCMS	Y	Unable to ascertain/no response	Y	Infant (2m-1Y) 2-12 1-5Y 2-9 >5Y 1-7	Infant (2m-1Y) 4-25 1-5Y 2-15 >5Y 2-13
HPLC Chromsystems	Y	Davidson DF, Hammond PJ, Murphy D, Carachi R. Age-related medical decision limits for urinary free (unconjugated) metadrenalines, catecholamines and metabolites in random urine specimens from children. *Ann Clin Biochem* . 2011 Jul;48(Pt 4):358-66.	Y	Under 1 1.1 -12.9 1 or 2 4.9 - 12.3 3 or 4 3.9 - 8.9 5 to 7 0.2 - 7.9 8 to 10 0.1 - 5.0 11 to 13 0.3 - 5.6 14 to 19 0.9 - 5.5	Under 1 0.7-23.1 1 or 2 0.5- 18.0 3 or 4 1.1-12.0 5 to 7 0.1-10.5 8 to 10 0.1-9.8 11 to 13 0.2-5.9 14 to 19 0.2-5.0
Unknown	Y	In house historic	Y	<1Y <20 1Y <17 2Y <12.5 3Y <11.4 4Y <9.5 5Y <8.2 6Y <7.3 7Y <6 8Y <5.5 9Y <5 10Y <4.3 11Y <4 12Y <3.8 13Y <3.6 14Y <3.1 15Y <2.8 ≥16Y <2.5	<1Y <35 1Y <30 2Y <25 3Y <19.8 4Y <17 5Y <15.5 6Y <10.8 7Y <9.9 8Y <9 9Y <7.5 10Y <6.6 11Y <6.5 12Y <6.3 13Y <6 14Y <5.4 15Y <4.5 ≥16Y <4.4
HPLC-ECD	Y	In house historic	Y	<1w 0-22.8 1w - <30w 0-9.7 30w - <1Y 0-8.6 1Y-<3Y 0-11 3Y-<5Y 0-10.5 5Y-<8Y 0-10 8Y-<12Y 0-7.5 ≥12Y 0-3.5	<1w 0-31 1w - <30w 0-25 30w - <1Y 0-19 1Y-<3Y 0-17 3Y-<5Y 0-16 5Y-<8Y 0-14 8Y-<12Y 0-11 ≥12Y 0-7
GC-MS	Y	In house historic	Y	<2Y 0.0 - 11.8 2-7Y 0.0 - 8.6 ≥8Y 0.0 - 3.6	<2Y 0.0-20.3 2-7Y 0.0-12.3 8-15Y 0.0-5.3 ≥16Y 0.0-4.4
HPLC Chromsystems	N (HVA only)	Unknown	Y	N/A	0 - <4Y <20 ≥4 - <7Y <9 ≥7 - <10Y <5 ≥10 - ≤16Y <4
HPLC-ECD	Y	Established in house and correlated with other centres	Y	0-1Y <15 1-2Y <12 3-4Y <7.5 5-10Y <7.0 >11Y <7.0	0-1Y <22 1-2Y <17 3-4Y <16 5-10Y <10 >11Y <7.7
HPLC	N (VMA only)	Unable to ascertain/no response	Y	Unable to source ranges from handbook/online	N/A
GC-MS	Y	Unable to ascertain/no response	Y	Unable to source ranges from handbook/online	Unable to source ranges from handbook/online

CONCLUSION

Given there is limited consensus and wide variations in age delineations in use in the UK, further validation and harmonisation of reference ranges is required, particularly amongst laboratories using similar or identical methods. Davidson *et al*[3] established their local ranges using a large clinical dataset. There is generally good agreement between methods on EQA schemes for HVA and VMA. For SWLP, it is proposed that that the Davidson *et al*[3] reference ranges be implemented for both HVA and VMA based on the rationale that this is a UK multi-centre evidence based referenceable source. Further work will be carried out to validate these reference ranges in our local population using local clinical data.

REFERENCES

1 SIOP Europe, The European Society for Paediatric Oncology, European Reference Network, Low-Risk Neuroblastoma Standard Clinical Practice Recommendation. https://siope.eu/media/documents/low-risk-neuroblastoma-standard-clinical-practice-recommendations.pdf
2 Bagatell R, Park JR, Acharya S, *et al*. Neuroblastoma, Version 2.2024, NCCN Clinical Practice Guidelines in Oncology. *Journal of National Comprehensive Cancer Network*. 2024 Aug;22(6):413-433
3 Davidson DF, Hammond PJ, Murphy D, Carachi R. Age-related medical decision limits for urinary free (unconjugated) metadrenalines, catecholamines and metabolites in random urine specimens from children. *Annals of Clinical Biochemistry: International Journal of Laboratory Medicine*. 2011;48(4):358-366