S Pervana

Department of Pathology Euromedica Geniki Kliniki,
Thessaloniki, GreeceCorrespondence to: Dr D Miliaras, Laboratory of
Histology and Embryology, Medical School, Aristotle
University of Thessaloniki, GR54006 Thessaloniki,
Greece; dmiliaras@med.auth.gr

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Catecholamine and metanephrene excess in intracerebral haemorrhage: revisiting an obscure yet common “pseudophaeochromocytoma”

We prospectively recruited five patients with CT evidence of intracerebral haemorrhage (ICH), having excluded trauma, a history of phaeochromocytoma (PHEO) and sympathomimetics/antihypertensives capable of increasing catecholamines (CATS)/metanephrenes (METS). Informed consent was obtained from the next of kin. Plasma METS are superior to plasma CATS, although both are unavailable locally. Urinary CATS/METS, which integrate CATS/

Figure 2 24 h urinary metanephrenes (METS; ie, sum of metanephrene and normetanephrene) of five patients with intracerebral haemorrhage. Using a metanephrene cut-off of >8300 nmol/day, patients who exceeded these values would be deemed to have a positive screen for phaeochromocytoma. Pt, patient.

METS secretion and has greater sensitivity than plasma CATS in the absence of PHEO spells, was used.¹ 24 h urinary CATS/METS were sampled on days 1 and 7 and before discharge. Catheterised urine was transferred into bottles containing 10 ml 6 N HCl, and analysed by high-performance liquid chromatography (HPLC)–electrochemical detection. Patients with increases in CATS/METS underwent abdominal CT. ICH volume was estimated from CT. This research was ethically approved by our hospital's institutional review board.

Four of five cases had urinary METS and/or CATS exceeding twice the upper normal limit. On day 1, CATS were not measured for patients 2–4, and METS were not measured for patients 1 and 2 before discharge owing to logistic difficulties. Generally, CATS/METS peaked on day 7, and then declined (figs 1 and 2). On day 7, the average CATS/METS (reference intervals within parentheses) values were as follows: epinephrine 328.8 (9.3–122) nmol/day, norepinephrine 1079.3 (72–505) nmol/day, metanephrene 2075 (264–1729) nmol/day and normetanephrene 7029.8 (480–2424) nmol/day.

Patients 4 and 5 with massive “day 7” total CATS (1070 and 2505 nmol/day, respectively) and METS (10 365 and 12 392 nmol/day, respectively) had normal total CATS (44 and 165 nmol/day, respectively) and METS (2154 and 1189 nmol/day, respectively) when re-evaluated 2 years later.

The PHEO suspects revealed no adrenal/extra-adrenal lesions on abdominal CT and were unlikely to harbour PHEO. All four false

positives (patients 2–5) had larger ICH (cerebral haematoma >25 ml with or without intraventricular extension) requiring extra-ventricular drainage/craniotomy, whereas patient 1 with normal CATS/METS had a basal ganglia haematoma of 11.8 ml treated conservatively.

Syed *et al*² recently reported (n = 5) that urinary CATS/METS were insignificantly increased perioperatively, a state of profound stress. However, their results cannot be extrapolated to catastrophic stresses of ICH. Currently, there is a dearth of literature on the latter.^{3,4} We confirmed that CATS/METS excess occurs temporarily after ICH, probably from an autonomic storm analogous to sympathetic dysautonomia in traumatic brain injury.⁵ As patient 1 with minimal ICH had normal CATS/METS, the degree of dysautonomia seemed to be proportional to ICH size. The temporal trajectory of increases in CATS/METS provided an evidence-based optimal PHEO screening rationale, unconfounded by ICH and allowed differentiation from PHEO. Among those with increased METS, CATS were below the PHEO diagnostic threshold in patients 2 and 4. As METS are CATS derivatives, we believe the true “CATS peak” occurred before day 7, and could be higher between days 3 and 6.

In conclusion, screening patients with ICH for PHEO is best avoided in the first week and deferred for at least a month, although a PHEO should be excluded when CATS/METS are persistently raised. This has pragmatic implications to the medical community including chemical pathologists, neurosurgeons and endocrinologists.

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Melvin Khee Shing Leow, Keh Chuan Loh

Division of Medicine, Department of Endocrinology, Tan Tock Seng Hospital, Singapore, Singapore

Tong Kiat Kwek

Division of Surgery, Department of Anaesthesia, Tan Tock Seng Hospital, Singapore, Singapore

Puay Yong Ng

Division of Surgery, Department of Neurosurgery, National Neuroscience Institute, Singapore, Singapore

Correspondence to: Dr M K S Leow, Division of Medicine, Department of Endocrinology, Tan Tock Seng Hospital

Figure 1 24 h urinary total catecholamines (CATS; ie, sum of epinephrine and norepinephrine) of five patients with intracerebral haemorrhage. Using a catecholamine cut-off of >1300 nmol/day, patients who exceeded these values would be deemed to have a positive screen for phaeochromocytoma. Pt, patient.

Hospital, 11 Jalan Tan Tock Seng, Singapore 308433, Singapore; mleowsj@massmed.org

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Lengthy appendices

It is an established fact that the appendix is attached to the caecum; however, it is a rare occurrence that the appendix matches the caecum and ascending colon in length. The most recent edition of the *Guinness Book of Records* cites the longest appendix to have been removed as measuring 23.5 cm in length¹; the previous record was 21 cm.² It may be assumed that both these aforementioned appendices were acutely inflamed. I present a case that rivals these two appendices in length. I think that the appendix in this case presented which measured at least 22 cm may be one of the longest appendices encountered, at least in recent times. It was an incidental finding at

Figure 1 One of the longest normal appendices incidentally encountered at autopsy.

autopsy in an 80-year-old who died of unrelated causes (fig 1). However, the claims to fame of these three appendices may be both premature and late. Kelly and Hurdon, in their mammoth work *The vermiform appendix and its diseases* published in 1905, cite the case of an appendix measuring 33 cm in length, presented by F Grauer to the North-Western Medical and Surgical Society in 1890.³

John D Coyne

South Manchester, Wythenshawe Manchester M20 8LR, UK; johnnycayne@doctors.org.uk

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CORRESPONDENCE

Limitations of transferability of absolute cut-points in non-standardised assays

We read the paper of Matull *et al*¹ on the biochemical markers of acute pancreatitis with much interest. We would, however, like to comment on some aspects that could be misleading.

First, absolute cut-off points as part of diagnosis or risk prediction need to be employed with great care.² This is especially true for enzyme assays such as alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase and amylase. For example, more than 200 methods of activity determination have been described for amylase.³ Amylase analytical methods vary with respect to the type of substrate and substrate concentration, use of auxiliary enzymes as well as assay conditions such as pH, temperature, incubation period and protein concentration.^{3,4}

Accordingly, reference intervals are method dependent, and it could be confusing to imply that values such as 600 or 1000 U/l have certain clinical sensitivities and specificities¹ without mentioning which analytical methods were employed, what the reference intervals were or that the figures will vary between laboratories owing to a lack in assay standardisation.^{2,4} Reference intervals for amylase range from 90–300 U/l (Phadebas, Magle AB,

Lund, Sweden) through 25–115 U/l (Dimension RxL, Dade Behring, Milton Keynes, UK) to 22–89 U/l (Olympus, Clare, Ireland). Not surprisingly, there are large differences between different assays when results from external quality assessment schemes are examined. The difference between the intermethod reference ranges is so significant that they have been flagged up as a clinical governance issue in some hospitals when changing routine clinical chemistry analysers.

The second, unrelated, aspect on which we wished to comment relates to interferences. Significant increase in serum triglyceride concentrations is a recognised interferent in some assays; however, it is unlikely to be an interferent or a competitive interferent in all 220+ amylase assays^{3–5} due to the inherent differences in assay formulation. Most modern amylase assays are not subject to such problems when the triglyceride concentration is <10 mmol/l.

It also needs to be noted that prognostic criteria such as Ranson and Glasgow are also affected by the above transferability limitations. Direct transfer without validation, especially when assays have not been standardised will lead to avoidable errors in diagnosis and assessing prognosis.

Adie Viljoen and Patrick J Twomey

Department of Clinical Biochemistry Lister Hospital
Coreys Mill Lane Stevenage, UK

Correspondence to: Dr A Viljoen, Department of Clinical Biochemistry, Lister Hospital, Coreys Mill Lane, Stevenage, SG1 4AB, UK; adie.viljoen@addenbrookes.nhs.uk

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