ERNDIM
QUALITY ASSURANCE IN LABORATORY TESTING FOR IEM

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Qualitative Blood Spot Acylcarnitine Scheme

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1. Scheme Design

The scheme has been designed and planned by Dr Charles Turner and Prof Neil Dalton as Scientific Advisor/Scheme Organiser and deputy Scientific Advisor/Scheme Organiser, respectively, both appointed by and according to procedures laid down by the ERNDIM Board.

2. Samples

All EQA materials are 30-50µl of lithium heparin anticoagulated whole blood dried as blood spots on Whatman (Schleicher & Schuell) 903 paper. All samples are obtained following local ethical and consent guidelines.

3. Shipment

Two circulations (numbers 21 & 22) of 3 samples each were sent out to the 61 laboratories assigned to the London centre of the ERNDIM dried blood spot acylcarnitine scheme. The first was sent out in July, with a return date of 14th September 2013 and the second in November with a return date of 31st December 2013.

4. Receipt of results

Returns for circulation 21 were received from 49 (80%); all but one of these arrived by the initial due date. For circulation 22 valid returns were received from 53 (87%); all but one of these also arrived before the due date.

There were 7 laboratories who failed to make a return on either circulation. Three of these did not submit results in 2012, and a further 2 did not submit in 2011. One laboratory reported on Circulation 21 only, and five on Circulation 22 only.

5. Scoring scheme

In the process of working towards accreditation for ERNDIM there is a need for harmonization of performance assessment within the qualitative schemes (see ERNDIM 'Newsletter Spring 2013' at www.erndim.org). In 2013 we changed the scoring system from the former scale (-2, -1, 0, +1, +2) to the four point system (+1, +2, + 3, +4) which is used also in the DPT schemes. In this system a maximum of two points is given each for analytical results and interpretation, with the latter including suggestions for further testing/actions. The total score achievable for a single circulation of three samples is twelve and twenty four for the whole sample set of six samples per year. Laboratories that participate only in one circulation are treated as non-submitters.

For the 2014 scheme onwards another criterion for satisfactory performance will be the absence of any "critical error" which is defined as an error resulting from seriously misleading analytical findings and /or interpretations with serious clinical consequences for the patient.

6. Results of samples and evaluation of reporting

All submitted results are treated as confidential information and are only shared with ERNDIM approved persons for the purposes of evaluation and reporting.

Participants were asked to respond via email using a supplied report template, and to send a scan and/or table of quantitative results if possible. All laboratories responded by email.

All laboratories provided a suggested/differential diagnosis. Most suggested some form of appropriate follow-up testing to confirm a putative diagnosis. A summary of the samples sent and the number of respondents detecting the key acylcarnitine and/or suggesting the definitive diagnosis as part of their differential diagnosis is given in the table below.

Sample	Enzyme/transporter defect	Diagnostic Acylcarnitine	Respondents
21a	Multiple acyl CoA dehydrogenase deficiency (MADD, MIM 231680)	C8, C10, C12, C8/C10 ratio	48/49 ^C8 23/49 MADD
21b	Carnitine palmitoyl transferase 2 (CPT II MIM 255110)	Low C2, Raised Ratios e.g. (C16+C18:1)/C2	18/49
21c	Methylmalonyl CoA mutase deficiency (MMA MIM251000)	C3, C4DC	49/49
22a	Holocarboxylase Synthase deficiency (HLCS MIM 253270)	C5OH, C3	53/53 ^C5OH 36/53 HLCS
22b	Medium chain acyl CoA dehydrogenase deficiency (MCADD, MIM 201450)	C8, C6, C10:1	46/53
22c	Vitamin B12 responsive methylmalonic acidaemia CblA (MIM 251100)	C3, C4DC	40/53 ^C3 36/53 MMA/PA

The profiles from patients with MCADD (22b) and Methylmalonyl CoA mutase deficiency (21c) were very characteristic of the disorders and were correctly characterized by almost all laboratories despite the fact that the MMA (21c) showed elevations of some other acylcarnitines (C5OH, C5DC, C5:1) due to renal failure. Most laboratories correctly identified the elevated C8 carnitine in the spot from the patient with MADD (21a) however many laboratories suggested this could be MCADD despite the low C8/C10 and C10:1/C10 ratios.

The sample from the patient with MMA/CblA provided difficulties for a few laboratories due to the high free carnitine concentration, secondary to supplementation not referred to in the clinical details given, which was clearly distracting for a minority of respondents. Likewise, biotin treatment and clinical details which could be interpreted as indicating a benign condition, made interpretation of the raised C5OH in the holocarboxylase synthase deficiency patient (22a) problematic.

Sample 21b proved particularly difficult to interpret, despite being not atypical of the underlying disorder, carnitine palmitoyl transferase II deficiency (CPT II). The clinical details given should have aroused suspicion, as muscle pain and raised CK are frequently seen in the late onset form of

the disease. The increases in long chain acylcarnitines together with low free and C2 are relatively subtle, and long chain acylcarnitines are normally higher in whole blood which mean that discrimination is better in plasma or serum. Nevertheless 12 laboratories were able to be highly confident of the diagnosis. All 12 described the use of long chain/C2 or long chain/free carnitine ratios. Since so many participants in the scheme failed to recognise the abnormality and make the correct diagnosis this sample was classified as an educational sample and was not included in scoring.

Proficiency per sample

Sample	No of returns	A (%)	I (%)	Total (%)
21a	48	100%	76%	88%
21c	49	100%	96%	98%
22a	53	100%	83%	92%
22b	46	100%	100%	100%
22c	49	90%	77%	83%

n.b. Sample 21b was classed as an educational sample

Cumulative Scores

The maximum score achievable was 20 points as sample 22b was classed as an educational sample and not included in the scoring.

Total Score	No of labs (who submitted results for both rounds)
20	14
19	11
18	8
17	3
16	4
15	3
14	1
13	0
12	3
11	0
10	0
9	0
8	0
7	0
6	0
5	0
4	0
3	0
2	0
1	0
0	0

7. Donation of samples

Once again, we are extremely grateful to the centres that have provided informative material for circulation. If any participants can provide samples in the future it would enormously facilitate this scheme, providing, as it does, genuine clinically derived samples for assay and interpretation. 3-4ml of lithium heparin anticoagulated whole blood or 65-70 30-50µl blood spots on Whatman (Schleicher & Schuell) 903 or Perkin Elmer/Ahlstrom 226 paper would provide sufficient material for one circulation. Samples for use in the scheme should be accompanied by a short clinical history and confirmation that informed consent/local ethical approval (as required in the referring centre) for use of the sample has been obtained.

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