Cognitive AA pilot scheme – Circulation 2019-1 – Participants' Report

Date published: 25/07/2019
Amended versions published: 30/07/2019[1]
08/08/2019[2]

Participants were able to view the cases and submit their results using the ERNDIM Formdesk web site.

Scoring system

As for the previous circulation, each of the three aspects, analytical findings, diagnosis and further tests, were scored equally with two points each and also scoring with half points was used if appropriate.

Case 2019-1

Treated urea cycle defect, ornithine carbamoyltransferase deficiency.
Plasma amino acid concentrations together with the laboratories reference ranges were provided.

The results provided were from a 14 year old girl who exhibited multiple episodes of metabolic decompensation since the age of 8 months and has shown poor growth but is mentally normal. Current treatment comprises low protein intake plus essential amino acid mixture (equivalent to 0.8 g/kg/day), sodium benzoate, citrulline and arginine.
The diagnosis was confirmed by mutation analysis.

Correct findings / abnormalities:
Increases of plasma citrulline and arginine (1 point) and mention of the very low levels of essential amino acids were considered necessary for full points.

Correct Diagnosis:

Since it is very difficult to identify the true defect due to treatment the correct diagnosis was considered to be a urea cycle defect (2 points). Unjustified specific defects were scored with 1 point-
An example of a good evaluation is as follows:
Most likely CPS1 or OTC deficiency on supplements of citrulline or citrulline+ arginine
Alternative diagnosis of citrullinaemia with arginine supplements less likely as citrulline usually much higher in that disorder.
Low branched chain amino acids most likely secondary to sodium phenylbutyrate therapy.

Further tests:

Measurement of blood ammonia and / or urine orotic acid, the need to review the diet and appropriate genetic testing were each scored with one point to a maximum of 2 points. Regarding genetic testing it is important that mention is made of a specific gene that is appropriate to the findings and suggested diagnosis.

Comments on overall performance:
Overall proficiency was fairly satisfactory at 84%. Performance for diagnosis and further test recommendations were clearly lower than for abnormalities.

Version Number (& Date)	Amendments
[1] version 2 (30th July 2019)	• Page 4: Correction of sample numbers in table and correction of total number of points for lab 14.
[2] version 3 (8th August 2019)	• Page 5: Correction of scores for lab 24 sample 2019.01. Correction of scores assigned of "Tests" and "Total" column for sample 2019.02. Correction of the "Final Score" column scores due to corrected scoring for sample 2019.01 and 2019.02. • Page 1 and 2: overall proficiency for sample 2019.01 and 2019.02 corrected.

Case 2019-2

Pyruvate dehydrogenase deficiency

Sample details:

Plasma amino acid concentrations together with the laboratories reference ranges were provided.
The results were from a sample from a 5 day old male child with severe acidosis from soon after birth and very poor adaptation. Lactate was persistently very high and there was a very poor response to treatment. The child died and pyruvate dehydrogenase was confirmed by molecular genetic analysis

Correct findings / abnormalities:

Increased plasma alanine was the main finding scored with 1.5 points. Mention of the slightly increased level of proline was scored with an addition 0.5 points since this is a critical amino acid in the differential diagnosis of hyperlactataemia.

Correct Diagnosis
The diagnosis of pyruvate dehydrogenase deficiency or a mitochondrial disorder were each scored with 2 points. One point was scored for mention of just non-specific lactate increase.

Further tests:
Measurement of urine organic acids and lactate/pyruvate were considered to be correct, each scored with one point.

Comments on overall performance:
Overall performance was good with 85% overall proficiency. Many labs failed to mention the level of proline so that the proficiency for abnormalities and notable features was clearly lower than for interpretation.

Case 2019-3

Hyperlysinaemia

Sample details:

The sample was from an 11 year old male born at full term with normal pregnancy, birth weight and no family history. The child shows markedly delayed cognitive development, failure to thrive and exhibits tetra paresis. Restricted protein intake has been tried without obvious success.
Urine amino acid analysis showed greatly increased lysine concentration with minor increases of ornithine and arginine. Saccharopine was reported to be absent in both plasma and urine. Mutation analysis of the α-aminoadipic semialdehyde synthase gene showed compound heterozygosity for two missense mutations. [Plasma amino acid levels with reference ranges were provided.

Correct findings / abnormalities:

A marked increase of lysine was recorded by all participants and was scored with 2 points. It was important to note that methionine and phenylalanine were within the reference range since this argues against tyrosinemia type 1 and this received 1 point.

Correct Diagnosis

The diagnosis of hyperlysinuria was considered to be correct (2 points).

Further tests:

Analysis of amino acids in urine, a search for pipecolic acids and/or saccharopine and appropriate mutation analysis were each scored with one point to a maximum of two points.
Pipecolic/saccharopine 1pt

Comments on overall performance:

Overall proficiency was good at 91% although proficiency for further tests was clearly lower.
In scoring this sample we did not take into account the report of a case with NADK2 deficiency (Hum Mol Genet. **2014**;23:5009)

Comments on the whole of the fourth circulation results

As mentioned above abnormalities, diagnosis and further tests were each scored with two points and half points were used again to allow more flexibility in the evaluation.
Each of the four evaluators scored all results independently and where four or three of their scores were in agreement, this was taken as final. In cases where such agreement was missing further close evaluation based on agreed scoring criteria was used to decide on the final score.
Generally the cases were straightforward and as with previous circulations performance was much better for identification of abnormalities and notable features than for interpretative aspects.

We encourage participants to send us comments and suggestions regarding this scheme and do not hesitate to contact us if you question any of our scoring.

Date: 08.08.2019.

The Scientific evaluators:
Rachel Carling, Mary Anne Preece, Sabine Scholl-Bürgi and Brian Fowler

Lab I.D.	Sample 2019-1-Scores				Sample 2019-2-Scores				Sample 2019-3-Scores				
	Abnormal 2 pts	Diag 2 pts	Tests 2 pts	Total	Abnormal 2 pts	Diag 2 pts	Tests 2 pts	Total	Abnormal 2 pts	Diag 2 pts	Tests 2 pts	Total	Final Total
1	2	2	2	**6**	1.5	2	2	**5.5**	2	2	2	**6**	**17.5**
2	2	2	2	**6**	1.5	2	0	**3.5**	2	2	1	**5**	**14.5**
3	2	1	2	**5**	1.5	2	2	**5.5**	2	2	2	**6**	**16.5**
4	2	1	1	**4**	1.5	2	1	**4.5**	2	2	1	**5**	**13.5**
5	2	2	2	**6**	1.5	2	1	**4.5**	2	2	2	**6**	**16.5**
6	2	2	2	**6**	1.5	2	2	**5.5**	2	2	2	**6**	**17.5**
7	2	2	2	**6**	2	1	2	**5**	2	2	2	**6**	**17**
8	2	2	2	**6**	2	2	1	**5**	2	2	2	**6**	**17**
9	2	2	2	**6**	1.5	2	2	**5.5**	2	2	2	**6**	**17.5**
10	1	2	2	**5**	1.5	2	2	**5.5**	2	2	2	**6**	**16.5**
11	2	1	2	**5**	1.5	1	2	**4.5**	2	2	2	**6**	**15.5**
12	1	1	0	**2**	1.5	2	1	**4.5**	2	2	2	**6**	**12.5**
13	2	1	1	**4**	2	1	2	**5**	2	2	2	**6**	**15**
14	2	1	1	**4**	1.5	2	1	**4.5**	2	2	2	**6**	**14.5**
15	2	2	2	**6**	1.5	2	1	**4.5**	2	2	1	**5**	**15.5**
16	2	2	2	**6**	1.5	2	2	**5.5**	2	2	2	**6**	**17.5**
17	2	2	2	**6**	1.5	2	2	**5.5**	2	2	2	**6**	**17.5**
18	2	2	2	**6**	2	2	2	**6**	2	2	2	**6**	**18**
19	2	1	2	**5**	2	1	2	**5**	2	2	2	**6**	**16**
20	2	2	2	**6**	1.5	2	2	**5.5**	2	2	1	**5**	**16.5**
21	2	2	2	**6**	2	2	2	**6**	2	2	1	**5**	**17**
22	1	1	1	**3**	1.5	2	2	**5.5**	2	2	2	**6**	**14.5**
23	1	2	2	**5**	1.5	2	1	**4.5**	2	2	2	**6**	**15.5**
24	2	1	0	**3**	2	2	1	**5**	2	2	2	**6**	**14**
25	2	2	1	**5**	2	1	2	**5**	2	1	0	**3**	**13**
26	2	1	2	**5**	2	2	2	**6**	2	2	2	**6**	**17**
27	2	1	1	**4**	2	2	2	**6**	2	2	2	**6**	**16**
28	2	1	1	**4**	1	1	1	**3**	2	2	1	**5**	**12**
29	2	0	1	**3**	2	1	2	**5**	2	2	2	**6**	**14**
30	2	2	1	**5**	2	2	1	**5**	2	1	0	**3**	**13**
31	2	2	2	**6**	2	2	2	**6**	2	0	0	**2**	**14**
32	2	1	1	**4**	2	2	0	**4**	2	2	1	**5**	**13**
33	2	1	2	**5**	2	1	1	**4**	2	2	2	**6**	**15**
34	2	2	2	**6**	1.5	2	2	**5.5**	2	2	2	**6**	**17.5**
35	1	2	2	**5**	1.5	2	2	**5.5**	2	2	1	**5**	**15.5**
36	2	2	1	**5**	2	2	2	**6**	2	2	2	**6**	**17**
37	2	2	2	**6**	1.5	2	2	**5.5**	2	2	1	**5**	**16.5**
38	2	2	2	**6**	1.5	2	2	**5.5**	2	2	1	**5**	**16.5**
39	2	2	1	**5**	1.5	2	1	**4.5**	2	2	2	**6**	**15.5**
40	2	1	1	**4**	2	2	2	**6**	2	2	0	**4**	**14**
41	2	1	1	**4**	2	2	2	**6**	2	2	2	6	**16**
42	2	2	2	**6**	2	2	1	**5**	2	1	2	**5**	**16**
43	2	2	1	**5**	2	2	1	**5**	2	2	2	**6**	**16**
44	2	2	2	**6**	1.5	2	0	**3.5**	2	2	1	**5**	**14.5**
45	2	1.5	2	**5.5**	1.5	2	2	**5.5**	2	2	2	**6**	**17**
Total	85	71.5	71	227.5	77	82	70	229	90	85	71	246	
% prof.	94%	79%	79%	84%	86%	91%	78%	85%	100%	94%	79%	91%	