

Cognitive AA pilot scheme – Circulation 2021-1 – Participants’ Report

Date published: 13th September 2021

Version: 1

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 a maximum of two points for each category. Where appropriate, half point scores were also used. Plasma amino acid concentrations together with the laboratories reference ranges were provided.

Case 2021-1

Mild variant citrullinaemia type 1.

The results provided were from a girl who exhibited hypoglycaemia at age of 1 day. Repeat plasma amino acids taken on 14th day of life showed citrulline 2605, arginine 22, ornithine 490, glycine 667, glutamine 584 and glutamate 300 µmol/L. Ammonia = 54 µmol/L.

Current treatment comprises low protein intake plus essential amino acid mixture, sodium benzoate and arginine. The diagnosis was confirmed by mutation analysis showing homozygosity for a likely pathogenic, novel variant (c.950T>C) in the *ASS1*-gene.

Correct findings / abnormalities

Increases of plasma citrulline (1 point), threonine and (glycine) (0.5 points) and mention of low concentration of arginine (0.5 points) were considered necessary for full points. Maximum 2 points.

Correct Diagnosis

The diagnosis of mild variant citrullinaemia type 1 was scored with 2 points. One point was scored for mention of a urea cycle disorder or citrin deficiency. Maximum 2 points.

Further tests

Genetic testing (*ASS1*-gene) and functional studies (including repeat amino acids) were scored with 1 point each.

Comments on overall performance

Overall proficiency was somewhat unsatisfactory at 66%. The diagnosis and further testing recommendations scored lower than identification of the abnormalities.

Reference

Häberle J et al (2003) Mild citrullinemia in Caucasians is an allelic variant of argininosuccinate synthetase deficiency (citrullinemia type 1) *Mol Gen Metab*

Best interpretation (scored with 2 points each)

- **Findings.** Moderately increased concentration of citrulline. Decreased concentration of arginine. Increased concentration of glycine and threonine.
- **Diagnosis.** Citrullinaemia type 1 despite no detection of orotic acid
- **Further tests.** Enzymatic activity measurement and genetic analysis of *ASS1*-gene.

Version Number (& Date)	Amendments

Case 2021-2

HHH syndrome (hyperammonemia, hyperornithinaemia, homocitrullinaemia)

Sample details

The results were from a sample from a 1.5 years old boy presenting initially with a mouth bleed. The patient has a HHH syndrome due to a mutation in the *SLC25A15*-gene.

Correct findings / abnormalities

Increased plasma glutamine (0.5), alanine (0.5), ornithine (0.5), citrulline (0.5) and methionine (0.5) were the main findings scored with maximum of 2 points. Mention of the slightly decreased concentration of threonine, cysteine and isoleucine were not scored for this case.

Correct Diagnosis

The diagnosis of HHH syndrome scored 2 points.

Further tests

Maximum 2 points were given. Measurement of ammonia, homocitrulline and/or functional testing was scored with one point, molecular genetic studies of *SLC25A15*-gene was scored with 1 point.

Comments on overall performance

Performance was good with 86% overall proficiency.

Best interpretation (scored with 2 points each)

- **Findings.** Elevations of ornithine and glutamine [depending on methodology (i.e. biochrom), homocitrulline may be co-eluting with methionine (false elevation) or high methionine is 2ndary to liver disease]
- **Diagnosis.** HHH syndrome (hyperammonemia, hyperornithinaemia, homocitrullinaemia)
- **Further tests.** Blood ammonia. Measurement of enzymatic activity (in fibroblasts) and molecular biology (*SLC25A15*-gene)

Case 2021-3

No inborn disorder of metabolism – arginine stimulation test

Sample details

The sample was from a 2.5 year old male who was hypoglycaemic on ward testing. The sample was taken during an arginine stimulation test (figure 1).

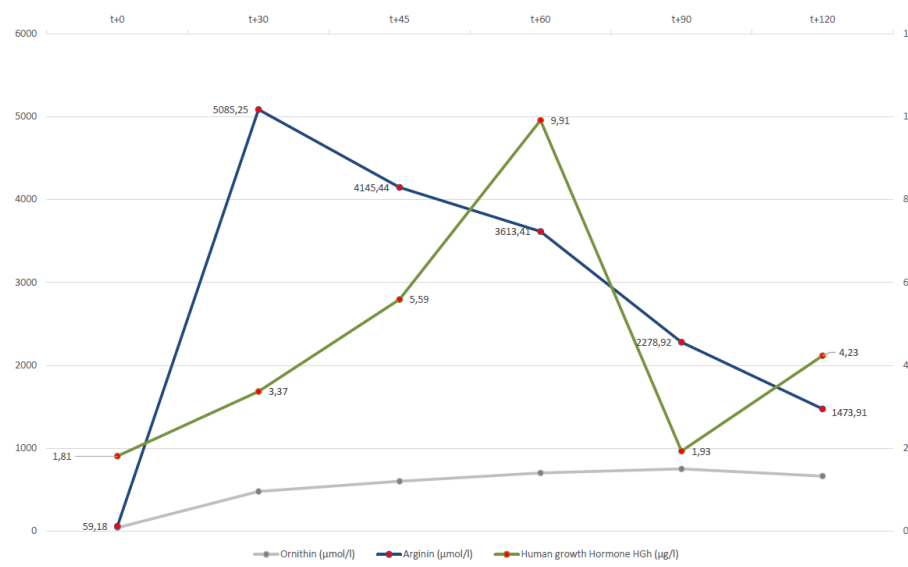


Figure 1: Arginine, ornithine and HGH concentrations during an arginine stimulation test.

Correct findings / abnormalities

A marked increase of arginine and ornithine was recorded by all participants and was scored 1.5 points. Additionally, a decrease of alanine or threonine or isoleucine or cystine was scored 0.5 points.

Correct Diagnosis

Arginine infusion during testing for growth hormone deficiency (2 points). Mentioning arginine or ornithine supplementation was scored with 1 point. Maximum 2 points.

Further tests

Repeat amino acids in plasma was scored with 1.0 point. Measurement of ammonia in blood and organic acids/orotic acid in urine was scored with 0.5 points each. Past medical history asking for arginine/ornithine supplementation was scored with 1 point. Maximum 2 points.

Comments on overall performance

Overall proficiency was low at 63% although proficiency for further tests was clearly lower.

Best interpretation (scored with 2 points each)

- **Findings.** High increase of ornithine and arginine with normal glutamine. Decrease in alanine and threonine, isoleucine, phenylalanine.
- **Diagnosis.** Exogenous arginine administration (patient undergoing arginine stimulation test for suspected growth hormone deficiency)
- **Further tests.** Review patient's medical record/information to confirm/exclude exogenous arginine administration. Repeat plasma amino acids to review.

Comments on the whole of the first circulation results 2021

- As mentioned above abnormalities, diagnosis and further tests were each scored with 2 points and 0.5 points were used again to allow more flexibility in the evaluation if necessary.
- Each of the four evaluators scored all results independently and where three or four of their scores were in agreement, this was taken as final. In cases where the scores were not in agreement, further close evaluation based on agreed scoring criteria was used to determine on the final score.

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: 13.09.2021

The scientific evaluators

Sabine Scholl-Bürgi, Rachel Carling, Mary Anne Preece and Brian Fowler

Part. No.	2021.01 abnormalities	2021.01 diagnosis	2021.01 recommendations	2021.01 Sum	2021.02 abnormalities	2021.02 diagnosis	2021.02 recommendations	2021.02 Sum	2021.03 abnormalities	2021.03 diagnosis	2021.03 recommendations	2021.03 Sum	Sum 2021.01-2021.03
1	2,0	2,0	1,0	5,0	2,0	2,0	2,0	6,0	2,0	1,0	2,0	5,0	16,0
2	1,5	2,0	1,0	4,5	2,0	2,0	2,0	6,0	2,0	0,0	0,0	2,0	12,5
3	2,0	1,0	0,0	3,0	2,0	2,0	2,0	6,0	2,0	0,0	1,0	3,0	12,0
4	1,0	2,0	1,0	4,0	2,0	2,0	1,0	5,0	1,5	0,0	2,0	3,5	12,5
5	2,0	2,0	1,5	5,5	2,0	2,0	2,0	6,0	2,0	1,0	2,0	5,0	16,5
6	2,0	2,0	2,0	6,0	2,0	2,0	2,0	6,0	2,0	0,0	1,0	3,0	15,0
7	2,0	1,0	1,0	4,0	2,0	2,0	2,0	6,0	2,0	1,0	2,0	5,0	15,0
8	2,0	1,0	1,0	4,0	2,0	2,0	2,0	6,0	1,5	2,0	2,0	5,5	15,5
9	1,5	0,0	1,0	2,5	2,0	2,0	2,0	6,0	2,0	0,0	1,0	3,0	11,5
10	1,5	2,0	0,5	4,0	2,0	2,0	1,0	5,0	2,0	0,0	1,0	3,0	12,0
11	2,0	1,0	1,0	4,0	2,0	2,0	2,0	6,0	2,0	0,0	1,0	3,0	13,0
12	2,0	1,0	0,5	3,5	2,0	2,0	2,0	6,0	2,0	0,0	0,5	2,5	12,0
13	2,0	0,0	1,0	3,0	2,0	2,0	2,0	6,0	2,0	0,0	1,0	3,0	12,0
14	2,0	2,0	1,0	5,0	2,0	2,0	2,0	6,0	2,0	2,0	1,1	5,1	16,1
15	2,0	2,0	2,0	6,0	2,0	2,0	2,0	6,0	2,0	0,0	0,0	2,0	14,0
16	2,0	2,0	1,0	5,0	1,0	2,0	1,0	4,0	2,0	0,0	2,0	4,0	13,0
17	1,5	0,0	1,0	2,5	1,0	2,0	2,0	5,0	1,5	2,0	2,0	5,5	13,0
18	2,0	1,0	2,0	5,0	2,0	2,0	2,0	6,0	2,0	0,0	0,5	2,5	13,5
19	1,5	2,0	2,0	5,5	1,0	2,0	2,0	5,0	1,5	0,0	2,0	3,5	14,0
20	2,0	2,0	2,0	6,0	2,0	2,0	2,0	6,0	2,0	2,0	2,0	6,0	18,0
21	2,0	2,0	0,5	4,5	2,0	2,0	1,0	5,0	2,0	2,0	2,0	6,0	15,5
22	1,0	2,0	1,0	4,0	1,5	2,0	2,0	5,5	2,0	0,0	2,0	4,0	13,5
23	2,0	1,0	1,0	4,0	2,0	2,0	2,0	6,0	2,0	2,0	2,0	6,0	16,0
24	2,0	2,0	2,0	6,0	2,0	2,0	2,0	6,0	2,0	2,0	1,0	5,0	17,0
25	2,0	2,0	2,0	6,0	1,5	2,0	2,0	5,5	1,5	2,0	2,0	5,5	17,0
26	2,0	2,0	2,0	6,0	2,0	2,0	2,0	6,0	2,0	1,0	2,0	5,0	17,0
27	1,5	1,0	0,5	3,0	2,0	2,0	1,0	5,0	2,0	0,0	1,5	3,5	11,5
28	1,5	2,0	2,0	5,5	2,0	2,0	2,0	6,0	2,0	2,0	2,0	6,0	17,5
29	1,0	1,0	0,0	2,0	2,0	2,0	2,0	6,0	2,0	2,0	2,0	6,0	14,0
30	1,0	2,0	1,0	4,0	1,0	2,0	2,0	5,0	1,5	0,0	0,5	2,0	11,0
31	2,0	1,0	0,0	3,0	1,5	2,0	2,0	5,5	2,0	0,0	1,0	3,0	11,5
32	1,5	2,0	1,0	4,5	2,0	2,0	2,0	6,0	2,0	0,0	1,5	3,5	14,0
33	1,5	1,0	0,0	2,5	2,0	2,0	2,0	6,0	2,0	2,0	0,0	4,0	12,5
34	1,0	2,0	1,0	4,0	2,0	2,0	2,0	6,0	2,0	2,0	2,0	6,0	16,0
35	2,0	2,0	2,0	6,0	1,0	0,0	0,0	1,0	2,0	0,0	0,5	2,5	9,5
36	2,0	0,0	1,0	3,0	2,0	2,0	2,0	6,0	2,0	0,0	0,0	2,0	11,0
37	1,0	2,0	1,0	4,0	2,0	2,0	2,0	6,0	2,0	0,0	2,0	4,0	14,0
38	1,5	2,0	2,0	5,5	1,5	2,0	2,0	5,5	1,5	2,0	2,0	5,5	16,5
39	1,0	1,0	0,0	2,0	1,0	2,0	2,0	5,0	2,0	0,0	1,0	3,0	10,0
40	1,0	2,0	1,0	4,0	1,5	2,0	1,0	4,5	2,0	2,0	2,0	6,0	14,5
41	2,0	1,0	0,0	3,0	2,0	2,0	2,0	6,0	2,0	2,0	2,0	6,0	15,0
42	2,0	1,0	1,0	4,0	2,0	2,0	1,0	5,0	2,0	0,0	1,0	3,0	12,0
43	2,0	1,0	0,0	3,0	2,0	2,0	1,0	5,0	2,0	0,0	0,0	2,0	10,0
44	1,0	1,0	1,0	3,0	2,0	2,0	1,0	5,0	2,0	0,0	1,0	3,0	11,0
45	2,0	2,0	1,0	5,0	2,0	2,0	1,0	5,0	2,0	0,0	1,0	3,0	13,0
46	2,0	1,0	1,0	4,0	2,0	2,0	2,0	6,0	2,0	0,0	1,0	3,0	13,0
47	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0
48	2,0	0,8	1,0	3,8	2,0	0,0	1,0	3,0	2,0	0,0	0,5	2,5	9,3
49	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0
50	1,0	1,0	0,0	2,0	1,0	0,0	1,0	2,0	1,5	0,0	0,0	1,5	5,5
total	81	69	50	199	87	90	82	259	92	34	62	188	645
% prof.	81%	69%	50%	66%	87%	90%	82%	86%	92%	34%	62%	63%	72%

