ERNDIM PROFICIENCY SCHEME (NORTHERN EUROPE)

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Annual Report for the Sheffield Diagnostic Proficiency Scheme for 2012

ERNDIM Proficiency Scheme Report – Samples 12.1, 12.2, 12.3, 12.4, 12.5, 12.6

Six samples were distributed in one batch to 21 participants; returns were received from 21 participants for the first batch and 20 participants for the second batch.

Patient 12.1

8 year old boy with unexplained mental retardation and metabolic acidosis
This was a patient with oxoprolinase deficiency

Findings

20/21 laboratories identified an increased excretion of 5-oxoproline (pyroglutamate)

Conclusions

20/21 laboratories concluded that this sample was from a patient with either oxoprolinase deficiency or glutathione synthase deficiency.

Further investigations

20/21 would have recommended measurement of either glutathione synthase or oxoprolinase enzyme activity. 10/21 would have also recommended measurement of red cell glutathione. 5/21 would have recommended that any siblings should be tested.

Comment

A number of respondents opted for glutathione synthase deficiency on the basis that metabolic acidosis is not usually a feature of oxoprolinase deficiency. This was a reasonable assumption and as the clinical details were fictitious the scoring will treat both alternatives equally. It is concerning that one laboratory would not have identified this prominent metabolite.

Patient 12.2

17 year old girl, epilepsy and moderate psychomotor retardation

This sample was obtained from a patient with adenylsuccinate lyase deficiency

Findings

6/21 laboratories identified an increased excretion of succinyl adenosine and/or SAICAraboside. One laboratory reported an increased excretion of dermatan and chondroitin sulphate.

Conclusions

6/21 participants concluded that adenylsuccinate lyase deficiency was the most likely diagnosis. The laboratory who identified and increased excretion of dermatan sulphate concluded that the most likely diagnosis was MPS3.

Further investigations

3/15 participants would did not identify succinyl adenosine or SAICAR would have recommended purine/pyrimidine analysis based on the clinical description.

Comment

It is a concern that despite suggestive clinical details only nine laboratories would have either identified succinyladenosine lyase deficiency or advised investigations that would have led to its discovery. It is interesting that only 7/16 UK labs in the scheme returning results would have either identified the disorder or recommended investigations that would have revealed it.

Sample 12.3

6 year old male, recurrent unexplained ataxia

This sample was from a patient with intermittent maple syrup urine disease

Findings

19/21 laboratories reported 2-hydroxyisovalerate, 2-hydoxy-3-methylvalerate or 2-hydoxy-isocaproate in some combination. 15/21 laboratories reported an increased excretion of one or more branched chain amino acids. The mean leucine excretion among those who reported it was 25 µmol/L (n=14). Interestingly, one laboratory reporting a clear increase in the excretion of BCAA's reported no abnormality of organic acid analysis.

Conclusions

19/21 laboratories concluded that the most likely diagnosis was MSUD or E3 deficiency

Further investigations

19/21 laboratories would have recommended plasma aminoacid analysis, many mentioning the need to identify allo-isoleucine. 5/21 would have recommended that any siblings should be tested.

Comment

Most labs identified the key metabolites in this sample although one laboratory failed to identify them reporting an increased citrulline excretion and concluding citrin deficiency, one laboratory reported 2-hydroxyisovalerate but concluded that PDH deficiency was the most likely cause.

Sample 12.4

4 year old with cyclical vomiting and ataxia

This sample was obtained from a patient with argininosuccinic aciduria

Findings

17/20 participants reported an increased excretion of argininosuccinate and/or its anhydrides and 10/20 also noted an increased excretion of urinary orotate. Three laboratories failed to identify an increased excretion of ASA, one reporting normal aminoacid excretion, another reporting an increased excretion of homocystine and the third did not undertake the analysis.

Notably a number of participants (11/20) also reported an increase in malonate excretion in this patient.

Conclusions

17/20 participants concluded that the most likely or possible diagnosis was argininosuccinate lyase deficiency. Two participants felt that malonyl CoA decaboxylase deficiency was the most likely diagnosis, 7/20 raised this as a possibility and three of these commented on the possibility of dual pathology..

Further investigations

15/20 participants would have recommended plasma aminoacid analysis, 14/20 would have advised blood ammonia. 6/20 would have recommended that any siblings were tested.

Comment

This was a very tricky sample and the increased malonate excretion which is a real finding is difficult to explain.

Sample 12.5

31 year old male, rhabdomyolysis following exercise

This sample was from a patient with mild multiple acyl CoA dehydrogenase deficiency

Findings

20/20 participants identified an increased excretion of acylglycines in various combinations, 6/20 also reported a dicarboxylic aciduria. 9/20 also noted the excretion isobutyryl glycine or isovaleryl glycine.

Conclusions

Based at least in part on the clinical description, 7/20 participants concluded that the most likely diagnosis was multiple acyl CoA dehydrogenase deficiency and a further 5/20 considered that this was a possible diagnosis. Despite the very unusual presentation and uncharacteristic ratio of adipate:suberate, 7/20 participants concluded that MCAD deficiency was the most likely diagnosis without raising the possibility of multiple acyl CoA dehydrogenase deficiency.

Further investigations

17/20 participants would have recommended an assessment of the acyl carnitine profile. and 6/20 laboratories would have advised that any siblings should be tested.

Comment

It is somewhat concerning that despite suggestive clinical features and some biochemical indication of disease only 12/20 participating laboratories would have raised the possibility of the potentially treatable disorder, multiple acyl CoA dehydrogenase deficiency. It may be that we have become somewhat stuck in the MCAD groove.

Sample 12.6

9 year old girl, pre-adoption medical

This sample was obtained from a normal child

Findings

20/20 participants reported essentially normal findings in this patient.

Conclusions

20/20 considered that no metabolic disorder could be identified.

Further investigations

19/20 laboratories would not have advised any additional investigations in the context of the clinical information provided and the lack of any significant findings...

Comment

It is reassuring that all labs would have reported this sample as normal and only one would have embarked upon additional investigations.

Overall comment

This was a very challenging set of samples and has raised some interesting potential points for discussion.

The clinical details accompanying the sample from patient 12.1 with oxoprolinase deficiency were potentially misleading but nevertheless most labs identified the key metabolite.

The lack of ability particularly in the UK to identify patients with suggestive clinical features who have a purine/pyrimidine disorder continues to be a concern, while rare, it suggests that these patients would be missed.

The presence of malonate in sample 12.4 misled some participants and is difficult to explain.

The concentration on MCAD deficiency in sample 12.5 despite contrary clinical details is a concern and may suggest that in the UK we have become particularly aware of this relatively common disorder to the exclusion of other possible diagnoses.

The willingness of all labs to commit to normal in the context of an EQA scheme is encouraging although the relatively benign clinical details probably provided some confidence.

Sample receipt and results return

Circulation 12.1,12.2,12.3,12.4,12.5,12.6

Nine participants received the samples on the day following dispatch; two, 2 days later; four 3 days later; two 4 days later; one, 9 days later; one, 11 days later; two participants did not record the date of sample receipt

All participants except one reported the results on time, one laboratory did not return results for the second set of samples.

Yours sincerely

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Scheme Organiser