ERNDIM PROFICIENCY SCHEME (SCANDINAVIA & UK)

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August 2005

Dear Colleague

Re: ERNDIM Proficiency Scheme Report – Samples 05.1, 05.2 and 05.3

Three samples were distributed and returns were received from all 26 participants.

Patient 05.1

A 20 year old patient, who was born to non-consanguineous parents. He is slightly retarded (stopped school at 12) but is working as a gardener. From 17 years old, he presented with opthalmalogical symptoms ascribed to allergy and from 18, palmer keratosis ascribed to verucca.

This sample was obtained from a patient with tyrosinaemia type 2

Findings

All 26 participants noted an increased excretion of tyrosine. 16/26 quantitated the excretion, mean tyrosine 87 μmol/mmolcr, SD 8.0 μmol/mmolcr. Similarly all participants commented on an increased excretion of tyrosine related metabolites on urinary organic analysis. 16/26 participants reported that succinyl acetone was either "not detected" or was below the lower limit of clinical significance.

Conclusions

25/26 laboratories concluded that the findings together with the clinical information provided indicated a likely diagnosis of tyrosinaemia type 2. 1/26 felt that their findings may reflect liver dysfunction and did not refer to tyrosinaemia type 2.

Further investigations

25/26 laboratories recommended quantitative plasma amino acid analysis. 9/26 would have recommended mutation analysis to help confirm tyrosinaemia type 2. Only 3/26 would have advised enzyme assay on liver biopsy material with a number 13/26 suggesting that liver biopsy and enzyme assay, while possible may not be indicated.

Comment

It seems likely that all participants would have eventually established a diagnosis in this patient although it probably was an omission for one laboratory not to mention the possibility of tyrosinaemia type 2 given the characteristic clinical picture.

Patient 05.2

A male aged 3 years, unexplained recurrent hypoglycaemia.

This sample was from a healthy child of one of the laboratory staff

Findings

All 26 participants reported normal analytical findings in this sample.

Conclusions

22/26 laboratories clearly reported "No abnormality detected" or a similar overall conclusion.

Given the history of recurrent hypoglycaemia 25/26 indicated that further laboratory or clinical investigation was warranted.

Further investigations

20/26 participants would have advocated a blood/plasma acyl carnitine profile with 9/26 indicating the need to obtain a urine sample for organic acid analysis during or shortly following a period of documented hypoglycaemia. 14/26 advised endocrine investigations and 5/26 brave laboratories would have recommended a controlled fast.

Comment

It is a little surprising that only around one third of laboratories would have recommended obtaining samples during a period of hypoglycaemia although a number commented that they would investigate the patient using the agreed "hypoglycaemia protocol" which may have contained such advice.

I was surprised that 20% of laboratories would have recommended a controlled fast, although I guess in practice this may be an end point in a sequential process.

Sample 05.3

Male aged 6 years, rickets, ? cause.

This sample was obtained from a patient with tyrosinaemia type 1

Findings

24/26 laboratories commented specifically on an increased excretion of tyrosine, the remaining 2/26 reporting a generalised amino aciduria. 15/26 documented a quantitative tyrosine result, mean 331 μmol/mmolcr, SD 65 μmol/mmolcr. All participants noted an increased excretion of tyrosine related metabolites on urinary organic acid analysis. 23/26 commented on a significant excretion of succinyl acetone or one its derivatives e.g. di-hydroxyheptanoate. 3/26 either did not comment on the presence of these key metabolites or specifically indicates that succinyl acetone was "not detected" (1 laboratory).

Conclusions

23/26 laboratories concluded that the patient suffered from tyrosinaemia type 1. All of the remaining 3 had failed to identify succinyl acetone or its metabolites, two of these felt that tyrosinaemia type 1 was possible, presumably on the basis of the prominent tyrosine excretion and the clinical features.

Further investigations

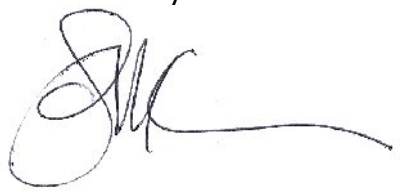
22/26 participants recommend quantitative plasma amino acid analysis. 12/26 mutation analysis, 13/26 enzyme assay. 12/26 laboratories would have suggested α-fetoprotein analysis because of the risk of hepatic malignancy in this condition.

Comment

It is a little disappointing that 3 laboratories failed to detect succinyl acetone or its metabolites. It is a guess, but unfamiliarity with the spectrum of di-hydroxyheptanoate and related compounds may have contributed here.

The scores assigned to individual laboratories will be available when the next circulation 05.4, 05.5 and 05.6 is analysed.

Yours sincerely



Dr J R Bonham
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Dear Colleague

Re: ERNDIM Proficiency Scheme Report – Samples 05.4, 05.5 and 05.6

Three samples were distributed and returns were received from all 26 participants.

Patient 05.4

A male. Aged 13 year with dorsal kyphosis.

This sample was obtained from a patient with MPS type IV aged 13 years.

Findings

All 14 laboratories who made a quantitative measurement of MPS excretion showed an elevated excretion. Only 9 participants specifically identified an increased excretion of keratan sulphate.

Conclusions

24/26 participants concluded, on the basis of laboratory findings or the clinical description, that an MPS disorder was likely or possible with 13 of these specifically indicating that MPS type IV was likely or possible.

Further investigations

16/26 laboratories would have recommended enzyme measurement to help confirm the diagnosis.

Comment

It is somewhat concerning that only 9/13 of the laboratory undertaking qualitative MPS analysis were able to identify excretion of keratan sulphate. 4/13 reported a normal pattern and 1/13 an unidentified band.

It is encouraging that quantitative MPS assay gave abnormal results in all laboratories who undertook the investigation.

Patient 05.5

A female, aged 27 years with osteoarthritis.

This sample was obtained from a patient with alkaptonuria.

Findings

All 26 participants returning results reported an increased excretion of homogentisic acid. All six participants who reported a quantitative result for MPS analysis reported a clearly evaluated value, possibly due to interference with the method. 10/26 reported some generalised increase of amino acid excretion.

Conclusions

All participants concluded that the patient suffered from alkaptonuria.

Further investigations

5/26 participants recommended that other family members should be treated.

Comment

It is encouraging that all participants identified an increased excretion of homogentisic acid and made an appropriate interpretation.

Sample 05.6

A female, aged 30 years, severe osteoporosis.

This sample was obtained from a 30 year old woman with classical homocystinuria.

Findings

25/26 laboratories identified an increased excretion of homocystine. (Mean concentration 59 μmol/mmolcr). 8/26 laboratories commented specifically on the normal excretion of methylmalonate in this patient.

Conclusions

All laboratories who identified the excretion of homocystine concluded that this was most likely due to cystathionine β-synthesis deficiency. A number also outlining other possible causes.

Further investigations

24/25 participants who identified an increased excretion of homocystine would have asked for plasma amino acid analysis and 20/25 would have requested a sample for total plasma homocysteine measurement. Only 9/25 commented directly or indirectly on the need to determine methylmalonate excretion in this patient. 16/25 participants suggested a therapeutic trial with pyridoxine.

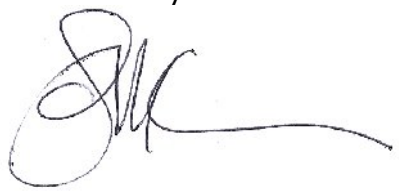
Comment

It is a little disturbing that even one laboratory should miss such an important diagnosis, but this is better than the response to previous similar circulations.

It is surprising that not many more than one third of laboratories would have either commented directly upon the presence of methylmalonate or advised its subsequent analysis and similarly surprising that fewer than two thirds would have suggested a therapeutic trials with pyridoxine.

The scores assigned to individual laboratories are shown in the table attached.

Yours sincerely



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