ERNDIM PROFICIENCY SCHEME (NORTHERN EUROPE)

DEPARTMENT OF CLINICAL CHEMISTRY
Sheffield Children's NHS Foundation Trust
Western Bank
Sheffield
S10 2TH
United Kingdom

Tel: +44(0)114 271 7000
Ext: 17404
Fax: +44(0)114 276 6205

1st August 2008

Dear Colleague

Re: ERNDIM Proficiency Scheme Report – Samples 08.1, 08.2, 08.3, 08.4, 08.5, 08.6

Six samples were distributed in two batches to 21 participants, returns were received from 21 participants for samples 08.1, 08.2 & 08.3 and from 21 participants for samples 08.4, 08.5 & 08.6.

Patient 08.1

6 year old male with unexplained encephalopathy
This sample was obtained from a patient with lysinuric protein intolerance

Findings

21/21 laboratories identified an increased excretion of lysine and arginine. When reported, n=19, the quantitative excretion of lysine ranged from 561-1425 µmol/mmol cr, mean=1130 µmol/mmol cr. 18/21 also noted an increased excretion of orotate, mean = 235 µmol/mmol cr.

Conclusions

18/21 considered that the most likely diagnosis was lysinuric protein intolerance, one laboratory suggested argininaemia, one HHH syndrome and one that the findings indicated a urea cycle disorder without specifying its nature.

Further investigations

20/21 laboratories suggested that blood/plasma ammonium should be measured and 20/21 that plasma aminoacids were indicated. 8/21 would have recommended testing siblings.

Comment

It is reassuring that all laboratories identified an increased excretion of lysine. It is a little concerning that three laboratories failed to identify an increased excretion of orotate on organic acid analysis, two reporting "no abnormality" and one an increased excretion of EMA.

Patient 08.2

A 7 year old male with slowly progressing expressive dysphasia and abnormal perinatal history (umbilical strangulation). The CT revealed enlarged cisterna

magna and possibly cerebellum hypoplasia, EEG did not reveal specific epileptic grafoelements. The sample was obtained at the age of eight years, medication at the time of sample collection is unknown

This sample was obtained from a patient with Sanfillipo disease, MPS type 3

Findings and Conclusions

17/21 participants reported an increased excretion of glycosaminoglycans; mean quantitative excretion = 31 mg/mmol cr, n=15. One laboratory reported no abnormality of GAG excretion, three did not report or undertake this assay. 13/21 reported an increased excretion of heparan sulphate. On this basis of these findings 13/21 concluded that the most likely diagnosis was Sanfillipo syndrome or MPS 3.

Further investigations

15/21 participants would have advised enzyme studies to confirm an abnormality and 6/21 would have advocated testing the siblings.

Comment

It is concerning that one laboratory reported no abnormality of GAG excretion and a normal pattern and that two laboratories, despite reporting increased GAG's, reported either "a normal pattern" or "no heparan or dermatan sulphate". All 12 laboratories that identified an excretion of heparan sulphate concluded that the most likely diagnosis was Sanfillipo syndrome and this was clearly the most important diagnostic finding.

Sample 08.3

11 year old female with unexplained rickets.

This sample was obtained from a healthy child of a laboratory staff member

Findings

18/21 laboratories reported no abnormality of aminoacid excretion, three of these particularly commenting on the normal excretion of phospho-ethanolamine in the light of the clinical details. Two laboratories commented on the (increased) excretion of phospho-ethanolamine, one considering that this made hypophosphatasia a possible diagnosis and the other that this condition was the most likely diagnosis. One laboratory reported an abnormality of MPS excretion.

Conclusions

14/21 participants clearly indicated that no inherited metabolic disorder could be detected on the basis of the sample provided. 4/21 raised other possible diagnoses and 3/21 were unclear about their conclusions.

Further investigations

16/21 participants would have recommended measurement of vitamin D status, 16/21 assessment of various calcium/phosphate indices and 11/21 would have measured PTH.

Comment

Given the clinical details it is not surprising that a number of participants advised other investigations or were a little guarded about their conclusions. However, it is a little disturbing that two laboratories felt that they could identify excretion of phospho-ethanolamine in sufficient concentration to warrant raising hypophosphatasia as a possible or likely diagnosis.

Sample 08.4

5 year old male with seizures and macrocephaly

This sample was obtained from a healthy child of a laboratory staff member

Findings

Only one participant, noting the presence of 2-hydroxyglutarate, reported any significant findings in this sample.

Conclusions

18/21 participants clearly indicated that no inherited metabolic disorder could be detected on the basis of the sample provided. Two laboratories failed to state a clear conclusion and one laboratory concluded that L-2-hydroxyglutaric aciduria was the most likely diagnosis.

Further investigations

6/21 participants would have advised blood/plasma acyl carnitine analysis and 4/21 would have raised the possibility of measuring glutaryl CoA dehydrogenase activity in fibroblasts.

Comment

It is reassuring that all but three laboratories would have clearly concluded that no metabolic disorder was indicated from these investigations.

Sample 08.5

3 year old male investigated for speech delay. He was born from a risk pregnancy. Speech delay but otherwise developmentally normal.

This sample was obtained from boy with isovaleric aciduria

Findings

20/21 participants identified an increased excretion of isovalerylglycine, 5 reported that this was also accompanied by an increased excretion of 3-hydroxyisovalerate.

Conclusions

On this basis 20/21 considered that the findings made isovaleric acidaermia the most likely diagnosis with two of these adding the possibility of multiple acyl CoA dehydrogenase deficiency.

Further investigations

16/21 participants would have recommended analysis for blood/plasma acyl carnitines and 17 would have advised enzyme confirmation of isovalerylCoA dehydrogenase deficiency 8/21 would have recommended testing the siblings.

Comment

It is rather concerning that one laboratory failed to identify an increased excretion of isovaleryl glycine or other relevant metabolites.

Sample 08.6

A 9 year old male with atypical chondroplasia, younger brother with same habitus, small stature, macrocephaly.

This sample was obtained from a boy with Morquio disease, MPS type 4

Findings

16/21 participants identified an increased excretion of glycosaminoglycans. Where this was quantitated the mean excretion was 31.3 mg/mmol cr. 16/21 laboratories identified an increased excretion of the key metabolite keratan sulphate, accompanied by chondroitin sulphate in seven labs.

Conclusions

17/21 participants concluded that Morquio disease was the most likely diagnosis in this patient. This included all laboratories who identified an increased excretion of keratan sulphate and one laboratory who failed to do so but reported an increase in dermatan and chondroitin sulphate.

Further investigations

19/21 participants recommended enzyme confirmation and 7/21 would have arranged testing in siblings.

Comment

It is concerning that three participants who undertook the analysis failed to identify excretion of keratan sulphate, this was clearly the key metabolite and in two of these labs it prevented them being clearer about the nature of the MPS disorder.

This seemed a relatively straightforward set of samples and it is a little surprising that some laboratories could not achieve a clearer diagnosis in some cases. As an interesting observation only around one third of laboratories would seem to routinely advise that the siblings of the index case are investigated to exclude the disorder. It is difficult to determine whether this reflects real practice but it would be concerning if it did. The scores are attached.

Sample receipt and results return

Circulation 8.1,8.2,8.3

Eleven participants received the samples on the day following dispatch; three, 2 days later; two, 3 days later; one, 8 days later; one 10 days later; one 17 days later and two did not report.

Twenty reported on time, one was 3 days late.

Circulation 8.4,8.5,8.6

Thirteen participants received the samples on the day following dispatch; two, 2 days later; one, 7 days later; one 8 days later; one 9 days later and three did not report.

Twenty reported on time, one was 3 days late.

Yours sincerely

Dr J R Bonham
Scheme Organiser