ERNDIM PROFICIENCY SCHEME (NORTHERN EUROPE)

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Dear Colleague

Re: ERNDIM Proficiency Scheme Report – Samples 10.1, 10.2, 10.3, 10.4, 10.5, 10.6

Six samples were distributed in one batch to 21 participants, returns were received from 20 participants for samples 10.1, 10.2 & 10.3 and from 18 participants for samples 10.4, 10.5 & 10.6.

Patient 10.1

5 year old male, unexplained developmental delay and dystonia
This sample was obtained from a patient with malonyl CoA decarboxylase deficiency

Findings

20/20 laboratories identified an increased excretion of malonate and 18/20 commented on an accompanying excretion of methylmalonate.

Conclusions

20/20 laboratories correctly concluded that this sample was from a patient with malonyl CoA decarboxylase deficiency.

Further investigations

20/20 would have recommended measurement of enzyme activity and 9/20 would have suggested mutation analysis. 12/20 would have suggested acylcarnitine analysis and 7/20 laboratories recommended that any siblings should be tested.

Comment

It is reassuring that all laboratories identified an increased excretion of malonate.

Patient 10.2

6 year old boy with several unexplained seizures

This sample was obtained from a normal child

Findings

19/20 laboratories reported no significant findings, one laboratory commenting on a mildly increased excretion of keratan sulphate

Conclusions

19/20 participants reported no abnormality detected, one suggesting the possibility of MPS4 or GM1 gangliosidosis.

Further investigations

17/20 participants would not have recommended any immediate further metabolic investigations, 3/20 would have advised a variety of additional targeted tests.

Comment

It is reassuring that almost all participants reported no abnormalities in this normal sample. As always a number of laboratories would have advised additional testing, although whether this would have been done in practice is less clear as participants typically take a cautious approach when dealing with EQA samples leading some to advise additional tests.

Sample 10.3

Adult female with insomnia and slurred speech

This sample was obtained from a patient with citrullinaemia

Findings

20/20 laboratories noted an increased excretion of citrulline (mean 4250 µmol/mmol cr, range 1278-6380 mmol/mmol cr). A number also commented on an increased excretion of arginine, threonine and lysine.

14/20 laboratories reported the excretion of benzoate or hippurate and 14/20 commented on a modestly increased excretion of orotate, 3/20 also reporting excretion of uracil. 3/20 reported orotate excretion as normal or not increased.

Conclusions

19 of the 20 laboratories reporting an increased excretion of citrulline considered that citrullinaemia type 1 or 2 was a probable diagnosis. The remaining laboratory did not specifically raise this possibility but suggested a urea cycle disorder or sulfite oxidase deficiency.

A number of participants commented on the benzoate excretion as an indication that this may be a patient on treatment.

Further investigations

18/20 participants would have recommended plasma aminoacid analysis and 8/20 enzyme assay. 9/20 would have suggested mutation testing. 13/20 would have recommended checking blood ammonium and 2/20 would have advised that siblings should be tested.

Comment

It is encouraging that all laboratories identified the increased excretion of citrulline. It is perhaps surprising that only13/20 would have checked blood ammonium.

Sample 10.4

3 year old male, short stature, rickets

This sample was obtained from a 3 year old boy with cystinosis

Findings

17/18 participants reported a generalised aminoaciduria or increased excretion of a number of aminoacids.

10/18 commented on an increased excretion of pyroglutamate and 12/18 on ketonuria

Conclusions

8/18 participants concluded that this sample could indicate cystinosis with a further 6/18 laboratories reporting the findings consistent with Fanconi syndrome or generalised aminoaciduria without speculating about the possible cause. Of the remaining four, two considered that PDH deficiency or mitochondrial disease was the most likely cause without mentioning cystinosis, one that the findings were consistent with pyroglutamic aciduria and one reported no specific abnormality.

Further investigations

10/18 participants would have recommended measurement of white cell cystine and 6/18 plasma aminoacids.

Comment

The aminoaciduria in this sample was comparatively mild and found in combination with pyroglutamic aciduria and ketosis may have misled some laboratories. The association of cystinosis with pyroglutamic aciduria and ketosis is described as some participants pointed out in their report: *JIMD 1999 22: 224-26. Pyroglutamic aciduria and nephropathic cystinosis. C Rizzo et al*

It is perhaps a little surprising that only one third of laboratories reporting an increased excretion of aminoacids would have recommended measurement of plasma aminoacids and that only 8/18 raised the possibility of cystinosis.

Sample 10.5

43 year old woman, progressive walking difficulties, osteoporosis, cholestasis and myoclonic epilepsy. Loss of visual acuity, opthalmoscopy revealed a cherry-red spot.

This sample was the common sample from a patient with neuraminidase deficiency or sialidosis type I

Findings

8/18 participants identified findings consistent with an increased excretion of sialyloligosaccharides. 15/18 commented on the excretion of valproate metabolites and 11/18 on the, probably linked, increased excretion of glycine.

Conclusions

The clinical description in this case was very suggestive and many participants based their conclusions and recommendations for further testing on this alone without supporting laboratory results. Consequently, 11/18 laboratories indicated that sialidosis or galactosidosis was possible or probable. Six of the remaining seven considered that a lysosomal storage disorder was possible and only one that no abnormality was present.

Further investigations

5/18 participants suggested the possibility of vacuolated lymphocytes should be excluded and 11/18 recommended measurement of neurominidase or ß-galactosidase activity with 9/18 advising the measurement of other lysosomal enzymes.

Comment

This was a difficult sample for the UK participants many of whom do not undertake oligosacchardide analysis. 1/9 participants who undertook the appropriate investigations reported a normal oligosaccharide pattern and a normal excretion of sialic acid.

Sample 10.6

1 year old male, unusual smell and family history of unexplained early infant deaths
This sample was obtained from a normal child

Findings

11/18 participants reported no significant findings. 5/18 identified an increased excretion of glycine and 2/18 (clustered) a peak migrating to the position of succinyladenosine.

Conclusions

17/18 laboratories reported no abnormality detected. One laboratory raising the possibility of mild succinate lyase deficiency.

Further investigations

13/18 participants would have recommended acylcarnitine analysis on the basis of the family history. 13/18 advised a range of other specific metabolic tests.

Comment

It is reassuring that 17/18 labs would have reported this as normal but again there is an understandable tendency to advise additional investigations, partly prompted by the family history and partly due to the caution attributed to all EQA samples.

Overall comment

This was a difficult but interesting sample set with a mild generalised aminoaciduria due to cystinosis and a common sample that posed problems for those laboratories not undertaking oligosaccharide analysis. The samples with more striking findings created little difficulty for most participants.

There was an understandable reluctance to commit to normal in the normal cases. I suspect that this over investigation does not happen in practice, at least I hope not.

The scores are attached.

Sample receipt and results return

Circulation 10.1,10.2,10.3,10.4,10.5,10.6

Nine participants received the samples on the day following dispatch; one, 2 days later; one, 2 days later; one, 3 days later; two 8 days later; 7 laboratories did not report the date of receipt.

For samples 10.1,10.2,10.3 18 reported on time, one was 2 weeks late, one was 2 months late one did not return results.

For samples 10.4,10.5,10.6 14 reported on time, one was 1 day late, one was 3 days late, one was 7 days late and one was 14 days late. Three did not return results.

Yours sincerely

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Scheme Organiser