ERNDIM PROFICIENCY SCHEME (NORTHERN EUROPE)

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Dear Colleague

Re: ERNDIM Proficiency Scheme Report – Samples 06.1, 06.2, 06.3, 06.4, 06.5, 06.6

Six samples were distributed in two batches to 19 participants, returns were received from all 19 participants for samples 06.1, 06.2 & 06.3; returns were received from 18 participants for samples 06.4, 06.5 & 06.6.

Patient 06.1

Female, presented at the age of 24y with a history of joint pains of one years duration. Relevant clinical history included delayed motor development, fatigue on exercise during childhood and premature shedding of primary teeth. The patient was of normal stature and physical examination revealed normal muscle strength and no evidence of synovitis. The forepart of her feet and her knees were painful to pressure and there were marked crepitations of the knees. There were brisk tendon reflexes without clonus and a positive Babinski response. Several joints in her hands, knees and feet had peri- and intra-articular calcifications.

This sample was obtained from a patient with hypophosphatasia. This was the common sample distributed by all five DPT schemes

Findings

16/19 laboratories identified an increased excretion of phosphoethanolamine. The mean concentration reported by the 10 laboratories who provided a quantitative report was 122 µmol/mmol creatinine.

Conclusions

15/16 participants who identified an increased excretion of phosphoethanolamine correctly concluded that the most likely diagnosis was hypophosphatasia.

Further investigations

All 16 laboratories identifying an increased excretion of phosphoethanolamine would have recommended measurement of alkaline phosphatase activity and 8 would have advised measurement of pyridoxal 5' phosphate.

Comment

It is clearly disturbing that 3 laboratories would have missed this diagnosis when the elevation of the key metabolite was >10x ULN and the clinical details were quite suggestive.

Patient 06.2

Female, aged 13 years with joint stiffness

This sample was obtained from a patient with MPS 1 (Scheie)

Findings

16/19 participants raised the possibility of a mucopolysaccharide disorder, 15 of these reporting an increased or abnormal GAG excretion. 10 reported an increased quantitative excretion of GAGS typically around 2-3x ULN. 12 laboratories commented on an increased excretion of dermatan sulphate.

Conclusions

13 participants suggested that MPS type I,II or VI were the most likely possibilities.

Further investigations

All of those reporting an increased or abnormal GAG excretion would have advised confirmatory lysosomal enzyme assay.

Comment

It is a concern that 3 laboratories would not have suggested an MPS disorder as a possibility either because the GAG assay had provided normal results or because this investigation was not undertaken.

Sample 06.3

A female, aged 39 years, low free carnitine on routine screening

This sample was obtained from a 39 year old woman 3-methylcrotonyl-glycinuria identified following the birth of a child with low free carnitine detected by newborn screening

Findings

All 19 laboratories identified an increased excretion of 3-methylcrotonyl glycine. 9/19 commented specifically that 3-hydroxypropionate and methylcitrate excretion was not increased.

Conclusions

All 19 laboratories concluded that the most likely cause was 3-methyl crotonyl CoA carboxylase deficiency.

Further investigations

10/19 participants suggested that plasma biotinidase activity should be assessed to exclude a more generalised carboxylase deficiency. 9/19 would have advised acyl carnitine analysis.

Comment

It is encouraging that all participants identified the increased excretion of 3-methylcrotonyl glycine and suggested that this was likely to be due to isolated eficiency of 3-methyl crotonyl CoA carboxylase.

Sample 06.4

A female, aged 10 weeks, residual hypotonia following a history of seizures now ceased

This sample was obtained at 6 yrs of age from a girl with multiple acyl CoA dehydrogenase deficiency

Findings

16/18 laboratories who returned results reported an increased excretion of acylglycines (15/18 hexanoylglycine; 9/18 isovalerylglycine; 7/18

butyrylglycine). 14/18 reported an increased excretion of ethylmalonate and 12/18 increased N-acetyltyrosine.

Conclusions

16/18 laboratories who returned results indicated that a defect of fat oxidation was suggested by the findings and 13 of these felt that the most likely diagnosis was multiple acyl CoA dehydrogenase deficiency.

Further investigations

14/18 advised acyl carnitine analysis and 10 would have recommended confirmation by fat oxidation studies in fibroblasts. Only 2/18 would have suggested that plasma ammonium should be measured.

Comment

One laboratory did not identify the excretion of any metabolites associated with a defect of fat oxidation and one laboratory despite identifying an increased excretion of ethylmalonate and hexanoylglycine did not suggest that the patient may have a defect of fat oxidation or multiple acyl CoA dehydrogenase deficiency. It is a little surprising that only 2/18 laboratories would have recommended the measurement of plasma ammonium in this patient.

Sample 06.5

A female, aged 3 years with unexplained lethargy and hypotonia

This sample was obtained from a girl with ornithine carbamoyl transferase deficiency

Findings

All 18 participants returning results reported an increased excretion of orotate.

Conclusions

All 18 participants returning results suggested that the sample was obtained from a patient with a urea cycle disorder, 12/18 concluding that OCT deficiency was the most likely possibility.

Further investigations

16/18 would have recommended the measurement of plasma ammonium and 13/18 would have advised confirmation by either enzyme assay or molecular genetic analysis.

Comment

It is very reassuring that all participants identified an increased excretion of orotate and concluded that the patient was likely to have a urea cycle disorder.

Sample 06.6

A female, aged 7 years with hypoglycaemia following a period of vomiting

This sample was obtained from a normal girl of 7 yrs receiving ibuprophen

Findings

None of the participants reported any significantly abnormal findings.

Conclusions

11/18 laboratories clearly indicated that no inherited metabolic disorder could be identified while 7/18 stated no overall conclusion.

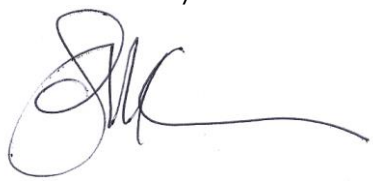
Further investigations

13/18 advised acyl carnitine analysis and 11/18 would have recommended collection of samples during any future hypoglycaemic episodes.

Comment

While only two thirds of participants came to a clearly stated conclusion in this patient this may have been influenced by a reasonable reluctance to commit to "normal" in a child whose history included unexplained hypoglycaemia.

Yours sincerely



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