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ERNDIM
Diagnostic proficiency testing
2007
Southern Europe – Lyon Centre

ANNUAL REPORT 2007

In 2007, 22 labs participated to the Proficiency Testing Scheme Southern Europe.
Organizing Centre: Dr Christine Vianey-Saban, Dr Cécile Acquaviva-Bourdain, Service Maladies Héréditaires du Métabolisme et Dépistage Néonatal, Centre de Biologie et de Pathologie Est, Lyon.

Geographical distribution of participants

Country	Number of participants
France	9
Italy	5
Spain	4
Portugal	2
Czech Republic	1
Switzerland	1
TOTAL	**22**

Logistic of the scheme

- 2 surveys 2007-1 : patient P1, P2 and P3
  2007-2 : patient P4, P5 and P6

Origin of patients : 5 out the 6 urine samples have been kindly provided by participants

- Patient P1 : Mitochondrial acetoacetyl-CoA thiolase (MAT) – Dr E Pasquini, Meyer Hospital, Firenze
- Patient P2 : Homocystinuria (CBS deficiency) – Dr ML Cardoso, Dr MR Rodrigues, Instituto de Genetica, Porto.
- Patient P3 : Hyperlysinemia (2-aminoadipic semialdehyde synthase deficiency) – Dr J Bonham, Children's Hospital, Sheffield. This sample has been circulated to all labs participating to the DPT scheme in Europe
- Patient P4 : Aspartylglucosaminuria – Hôpital Debrousse, Lyon.

- Patient P5 : Phenylketonuria - Dr ML Cardoso, Dr MR Rodrigues, Instituto de Genetica, Porto
- Patient P6 : SCAD deficiency - Dr O Boulat, CHUV, Lausanne
- Mailing: samples were sent by DHL at room temperature.

Timetable of the schemes

- March 20 : shipment of samples of Survey 1 and Survey 2 by DHL and of the forms by e-mail
- April 13 : deadline for results submission (Survey 1)
- May 21 : analysis of samples of the second survey
- June 11 : deadline for results submission (Survey 2)
- August 11 : report of Survey 1 by e-mail
- August 22 : report of Survey 2 by e-mail
- September 4 : meeting in Hamburg
- January 22: annual report with scoring sent by e-mail

Date of receipt of samples

	Survey 1 + 2
+ 24 hours	18
+ 48 hours	2
+ 72 hours	1
+ 6 days	1

Date of reporting

All labs sent reports, but with an unacceptable delay for 3 labs for the second survey. This will not be possible within 2 years, when submission will be on the website.

	Survey 1	**Survey 2**
	(3 weeks)	(3 weeks)
Receipt of results :	22 labs	22 labs
Before deadline	19	16
+ 1 day		1
+ 2 days		1
+ 3 days	2	1
+ 5 days	1	
+ 1 month		**1**
+ 2 months		**2**
No answer	**0**	**0**

Scoring of results

The scoring system established by the International Scientific Advisory Board of ERNDIM is still the same. Three criteria are evaluated:

A	Analytical performance	Correct results of the appropriate tests	2
		Partially correct or non-standard methods	1
		Unsatisfactory of misleading	0
I	Interpretation of results	Good, diagnosis is established	2
		Helpful but incomplete	1
		Misleading / wrong diagnosis	0
R	Recommendations for further investigations	Complete	1
		Unsatisfactory of misleading	0

Since most of the laboratories in Southern Europe don't give therapeutic advices to the attending clinician, this criterion is not evaluated.

The **total score** is calculated as the sum of these 3 criteria without weighting. The maximum that can be achieved is 5 for one sample.

Meeting of participants

It took place in Hamburg on September 5 from 9.00 to 10.30, during the SSIEM Meeting.

❖ Participants

Representatives from 11 labs were present: A Ribes (Hospital Clinic, Barcelona), JA Arranz, E Riudor (Vall d'Hebron, Barcelona), S Mesli, I Redonnet-Vernhet (Bordeaux), S Funghini, E Pasquini (Florence), U Caruso, M Cassanello (Genova), O Boulat (Lausanne), I Tavares de Almeida (Lisbonne), B Merinero, C Perez-Cerda, P Ruiz-Sala (Madrid), ML Cardoso (Porto), C Rizzo (Roma), JR Alonso Fernandes, D. Castineiras, M D Boveda (Santiago de Compostella). We regret that only one French lab was represented among the 9 labs who participate to this scheme.

❖ Information from the Executive Board and the Scientific Advisory Board for next year

- Reference material provided by SKML (mix of the four 2006 samples of the scheme) is now available despite problems of storage for Gln and Asn. It should not be used as calibrant.
- Guidelines for methodology will be created or updated: organic acids, acylcarnitines, purine/pyrimidine, mucopolysaccharides.
- A website reporting system will be available in 2008 for Basel and Prague and in 2009 for the other DPT centres
- Certificate of participation for 2007 will be issued for participation and it will be additionally notified whether the participant has received an assistance letter. This assistance letter is sent out if the performance is less than 50%. Good performers are those whose performance is more than 75%.
- No assistance letter has been sent in 2006 for our centre.
- We remind you that every year, each participant must provide to the scheme organizer at least 300 ml of urine from a patient affected with an established inborn error of metabolism or a "normal" urine, together with a short clinical report. Each urine sample must be collected from a single patient (don't

send urine spiked with pathological compounds). Please don't send a pool of urines. For "normal" urine, the sample must be collected from a symptomatic patient (don't send urine from your kids !). Annex 1 gives the list of the urine samples we already sent.

A **20% discount** to the annual participation fee will be given to those labs who provide interesting urine sample. The discount would only apply once the donated samples were considered as programmed for distribution by the scheme organizer.

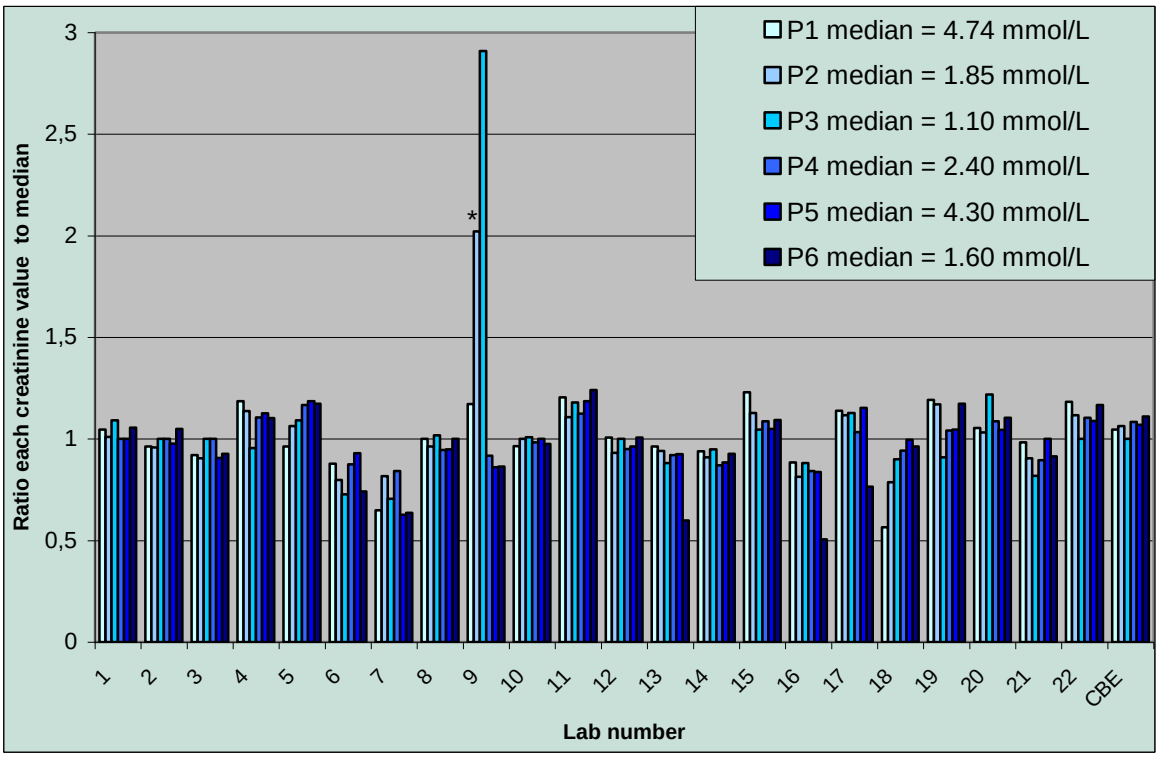
As soon as possible after collection, the urine sample must be heated at 50 °C for 20 minutes. Make sure that this temperature is achieved in the entire urine sample, not only in the water bath. Then aliquot the sample in 10 ml plastic tubes (minimum 48 tubes), add stoppers and freeze. Be careful to constantly homogenize the urine while aliquoting the sample. Send the aliquots on dry ice by rapid mail or express transport to: Dr Christine Vianey-Saban, Service Maladies Héréditaires du Métabolisme et Dépistage Néonatal, 5ième étage, Centre de Biologie et de Pathologie Est, Groupement Hospitalier Est, 59, Boulevard Pinel, 69677 Bron cedex, France. Please send me an e-mail on the day you send the samples.

- Lab identification: after discussion during the 2006 meeting in Prague, all labs except one asked for using the ERNDIM number for an easier identification of results. However, the Scientific Advisory Board advised against the use of the ERNDIM number. Our proposal is to use the ERNDIM number for "in centre" communication and to use anonymous identification for the Annual Report on the website or other purposes. This was accepted during the meeting in Hamburg.

❖ Discussion of results

• Creatinine measurement

Results were not as good as last year.
Lab 6, 7 and 16 have systematically low values.
Lab 9 has two wrong values
If 4 wrong values are excluded, CV is around 15% for all samples (11% last year)



We discussed during the meeting the discrepancy between these results and those from other QC. One participant advised to read the two following manuscripts which give recommendations for measurement improvement (at least for plasma/serum measurement):

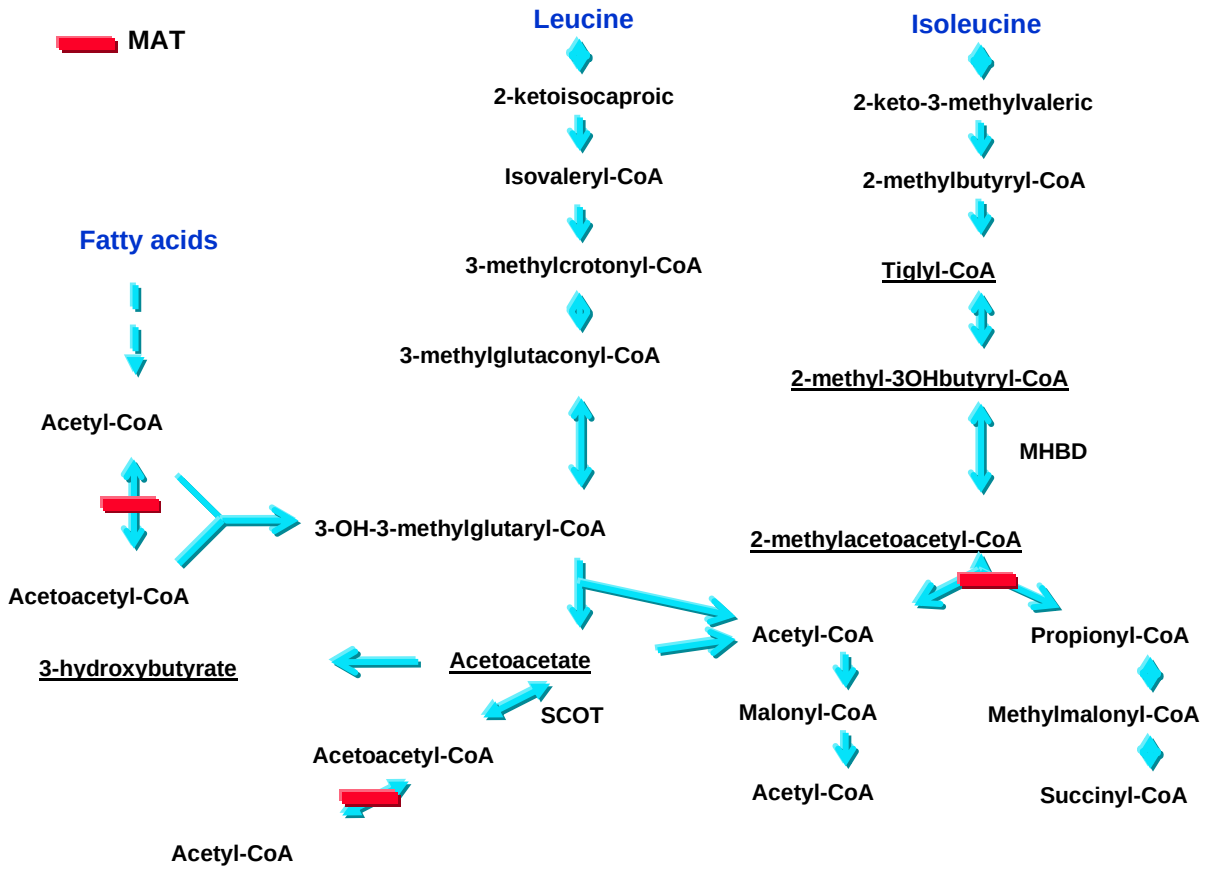
- Myers et al. Clin Chem 2006;52(1):5-18 (accessible from: http://www.clinchem.org)

- Séronie-Vivien et al, Ann Biol Clin 2004;62(2):165-75 (manuscript is in French but a summary in English is available, it is accessible from http://www.john-libbey-eurotext.fr/en/revues/bio_rech/abc)

- **Patient P1 – Mitochondrial acetoacetyl-CoA thiolase (MAT) deficiency**

The patient is a 3 year-old boy, first child of unrelated parents. Pregnancy was complicated by oligoamnios. Psychomotor development was moderately delayed. At 3 year of age, he presented a viral infection with vomiting, leading to lethargy, coma, with Kussmaul breathing, severe metabolic acidosis and ketonuria. Ammonemia and lactate were normal. The child recovered under IV glucose.
The urine sample has been collected after the acute episode. Plasma acylcarnitine profile revealed a slight elevation of C5OH (2-methyl-3-hydroxybutyrylcarnitine). MAT deficiency has been confirmed in cultured skin fibroblasts (Dr O. Sass).
The patient is now 6 year old. His neurological examination is normal; brain MRI shows a small hyperintensity signal in the right insular region (Flair sequence). Protein intake is moderately restricted with carnitine supplementation.

The following figure shows the metabolic block which involves a defect in isoleucine breakdown and a ketolysis defect.



Diagnosis

- 12 labs gave a correct diagnosis
- 3 labs gave MAT deficiency as 1st diagnosis, 2-methyl-3-hydroxybutyryl-CoA dehydrogenase (MHBD) deficiency as 2nd diagnosis
- 1 lab gave MHBD deficiency as 1st diagnosis, MAT as 2nd
- 5 labs concluded to MHBD deficiency
- 1 lab gave a wrong diagnosis

All labs, except one, performed **aminoacids** and reported a normal profile.

All labs performed **organic acids**. All except one reported an increase of 2-methyl-3-hydroxybutyric acid: 44 - 138 mmol/mol creatinine – median = 56 mmol/mol creat. Tiglylglycine was reported as slightly increased by 16 labs. Only 6 labs reported trace amounts of 2-methylacetoacetic acid, which is usually significantly increased in MAT deficiency. This probably occurred because the urine has been heat treated and 2-methylacetoacetate transformed in butanone.

Three labs performed **acylcarnitine** profiling: 2 reported an increase of C5OH and one an increase of C5:1 acylcarnitines.

Advice for further investigations was satisfying.

Scoring:

- Analytical performance: increase of 2-methyl-3-hydroxybutyrate (score 2)
- Interpretation of results: MAT deficiency as first diagnosis (score 2), MHBD deficiency as first diagnosis (score 1)
- Advice for further investigations: acylcarnitines and/or MAT activity and/or mutation analysis *ACAT1* gene (score 1)

- **Patient P2 – Homocystinuria (cystathionine β-synthase deficiency)**

This 13 year old African (Guinée-Bissau) girl is born from consanguineous parents (first cousin). An elder brother died at 2 years of age in the course of a febrile illness; he had the same phenotype than the patient. She was admitted at hospital with Guillain Barré syndrome. She has a Marfan-like phenotype, arachnodactyly, ectopia lentis, generalized osteoporosis. Mental status was difficult to evaluate because she does not speak well Portuguese. She is primarily vegetarian, refusing animal proteins and this probably lead to multivitamin deficiency, including B2. She had macrocytic anemia (Hb 10.7 g/dL, VGM 111 fL), low plasma B12 (177 pg/mL - controls: 193-982) and folic acid (2.91 ng/mL - controls: 3-17) levels. Plasma homocystine level at diagnosis was 155 µmol/L, methionine 46 µmol/L and cystine 4 µmol/L. Cystathionine β synthase deficiency was confirmed in cultured skin fibroblasts : 0.04 µkat/kg prot; simultaneous control = 4.7 - controls = 1.20 – 3.40 µkat/kg prot (Dr Rolland, Lyon).
This was a challenging sample because of the spontaneous low protein diet with multivitamin deficiency.

Diagnosis

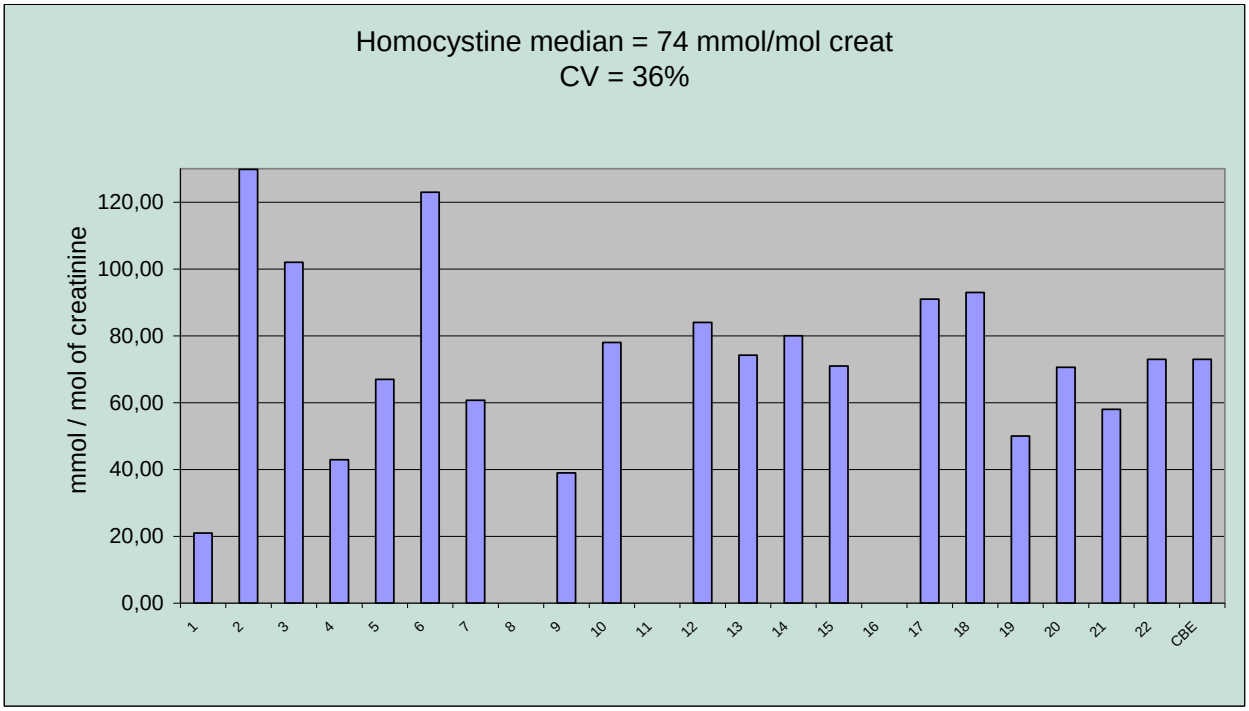
21 labs concluded to homocystinuria, with different possible aetiologies:
- 9 labs: CblE / CblG
- 7 labs: CBS deficiency
- 4 labs: homocystinuria without methylmalonic aciduria
- 3 labs: remethylation defect
- 2 labs: MTHFR deficiency
- 1 lab: possible folate malabsorption

20 labs reported an abnormal excretion of acylglycine derivatives, also with different possible aetiologies:

- 11 labs: possible or probable MAD deficiency
- 5 labs: multivitaminic deficiency
- 2 labs: riboflavine deficiency
- 1 lab: possible mild isovaleric aciduria

Amino acids

Twenty labs performed amino acids and all reported an increase of homocystine, with a high CV (36%: due to a problem of storage ?).



An increase of cysteine-homocysteine disulfide was reported by 6 labs. No increase of methionine was mentioned by 8 labs whereas 1 lab reported an increase of Met. The increase of glycine (15 labs) can be due to malnutrition.

Organic acids

All labs performed organic acids and 20 of them reported an increase of isovalerylglycine, with a great variability in the quantification: 2 to 98 mmol/mol creatinine. Standards for isovalerylglycine and its stable isotope are available from Dr Herman Ten Brink in Amsterdam (HJ.tenBrink@vumc.nl).
Other acylglycine derivatives were also detected: hexanoylglycine (18 labs), isobutyrylglycine (17 labs), suberylglycine (9 labs), 2-methylbutyrylglycine (6 labs), butyrylglycine (5 labs), valerylglycine (2 labs), phenylpropionylglycine (1 lab), and that is why 11 labs concluded to a possible MAD deficiency. However, the absence of an increase of 2-hydroxyglutaric acid which, in our hands, is systematically elevated in MAD deficiency, was against this diagnosis.

Three labs performed **acylcarnitine** profiling: 2 of them observed an increase of C4, and one of them a slight increase of C5, C6, C8, and C10.

An increase of **total homocysteine** was reported by 2 labs.

Advice for further investigations was numerous, reflecting the dilemma in the interpretation of results of this puzzling patient.

Scoring

- Analytical performance: Increase of homocystine (score 2), increase of acylglycine derivatives (score 1).
- Interpretation of results: homocystinuria (score 2), possible MAD deficiency or multivitamin deficiency (score 1).
- Advice for further investigations: plasma amino acids and/or plasma total homocysteine and/or vitamin status (score 1).

- **Patient P3 – hyperlysinuria (2-aminoadipic semialdehyde synthase deficiency)**

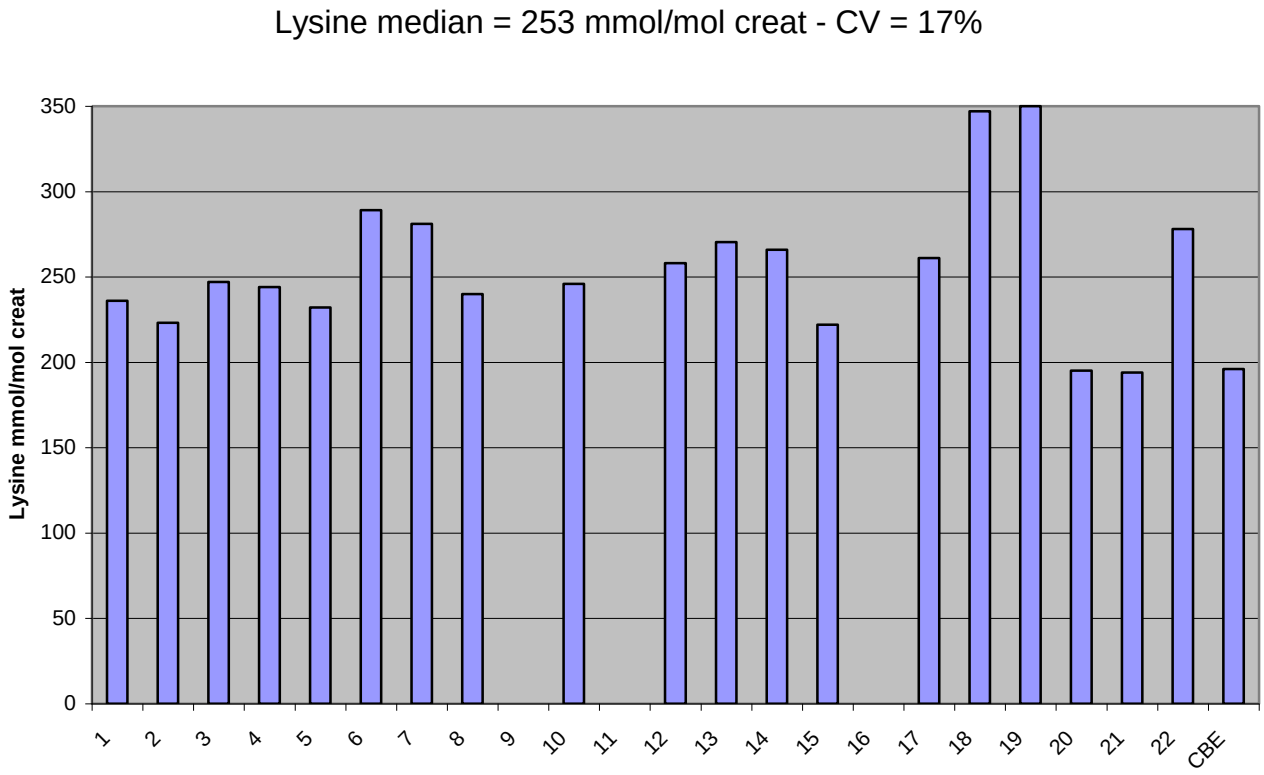
This 18 year old girl presented with learning difficulties and behavioral problems since 5 years of age. She also has short stature. No information is available concerning her plasma lysine level. The diagnosis has not been confirmed enzymatically.

This urine sample has been sent to all labs participating to QAP Proficiency Testing.

Diagnosis

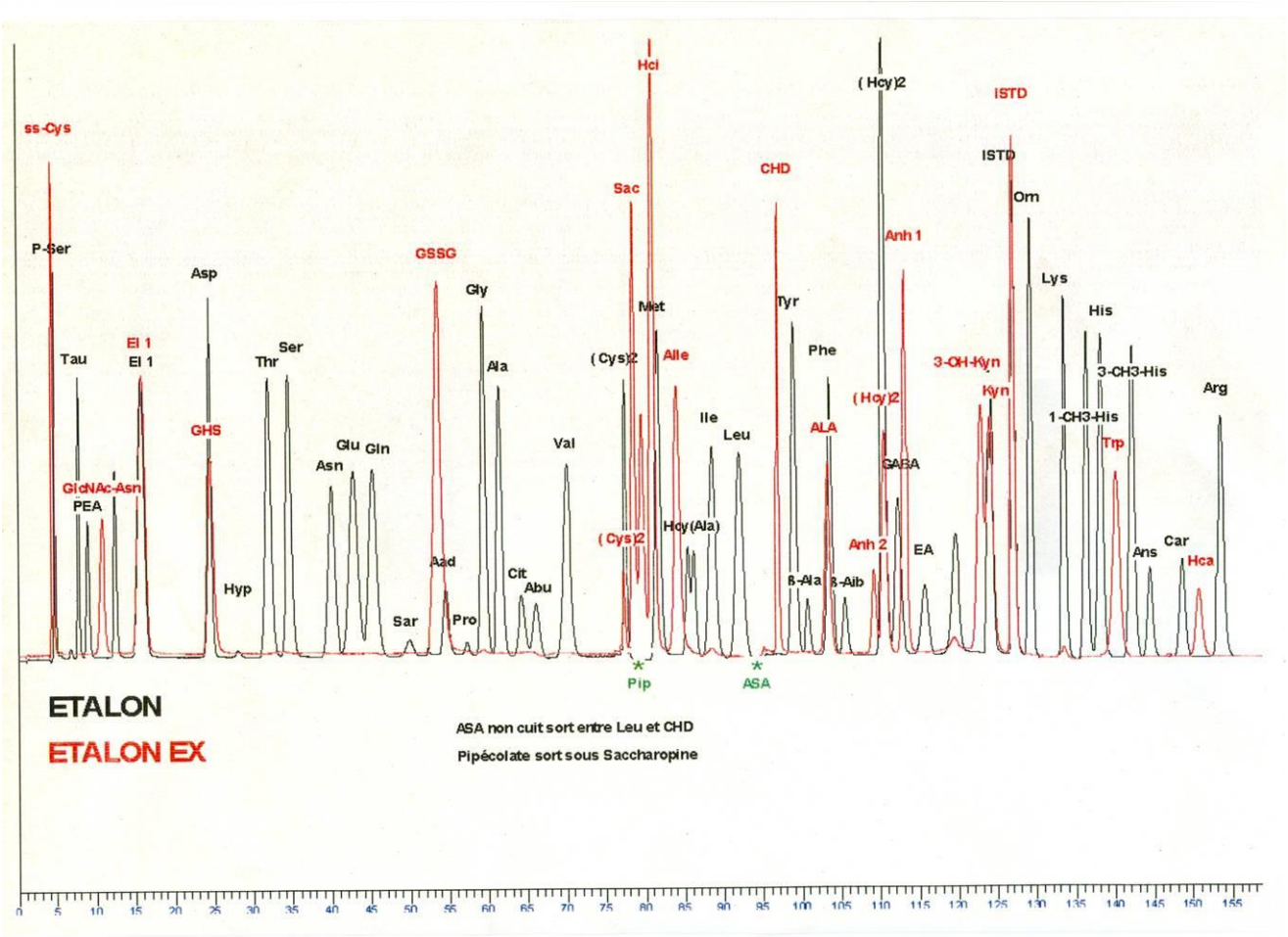
Sixteen labs concluded to hyperlysinemia, 4 labs possible LPI and 4 labs could not reach a diagnosis or gave a wrong diagnosis.

All labs performed **amino acid** analysis and 19 of them reported an increase of lysine, with a satisfying quantification.



Only 13 labs reported an increase of saccharopine (25 to 67 mmol/mol creat).
We got the following information from participants:

- Jeol analyser, saccharopine is eluted with cystine (abnormal 570 / 440 nm ratio)
- Hitachi analyser, it is eluted with isoleucine (abnormal 570 / 440 nm ratio)
- Biochrom analyser, extended program, it is well separated from cystine and methionine (see figure below)
- Using LC-MS/MS (scheme organizer), it is easy to detect



All labs performed **organic acids**. All except one reported a normal profile.

Advice for further investigations was OK for most labs.

Scoring (same for all labs participating to Proficiency Testing)

- Analytical performance: increase of lysine and saccharopine (score 2), increase of lysine, saccharopine not detected (score 1)

- Interpretation of results: hyperlysinemia (type I or II) (score 2), lysinuric protein intolerance (score 1)

- Advice for further investigations: plasma amino acids or enzymatic investigation of 2-aminoadipic semialdehyde synthase or mutation analysis (score 1).

- **Patient P4 – Aspartylglucosaminuria (aspartylglucosaminidase deficiency)**

The patient, a boy, is the first child of non consanguineous parents. Her mother had 5 miscarriages before this pregnancy. She remained in bed during the duration of this pregnancy. At birth, the patient presented with inguinal hernia and metatarsus varus. He had recurrent viral infections and diarrhea. A speech delay was noted at 2 years 1/2. Clinical examination at 4 years of age revealed slightly dysmorphic features, moderate pyramidal syndrome of lower limbs, slight leukodystrophy, hyperactivity, leading to a metabolic workup. Plasma amino acids (LC-MS/MS) allowed to detect aspartylglucosamine (32 µmol/L – controls: undetectable). Urine oligosaccharides and amino acids confirmed the diagnosis (aspartylglucosamine = 461 mmol/mol creat – controls: undetectable).
Aspartylglucosaminidase activity in leukocytes was 3.2 µkat/kg prot (simultaneous control = 67.9).
At 4 years of age, he underwent bone marrow transplantation (BMT). He subsequently presented several febrile episodes, epidermolysis, hypotension and digestive problems. He had a colonoscopy in April 2007 but a septic shock occurred leading to death 3 months after the BMT.

The urine sample has been collected at the time of the diagnosis.

Diagnosis

Only 9 labs concluded to aspartyglucosaminuria, and 3 labs to oligosaccharidosis. Three labs concluded to a wrong oligosaccharidosis and 7 labs to a wrong or no diagnosis.

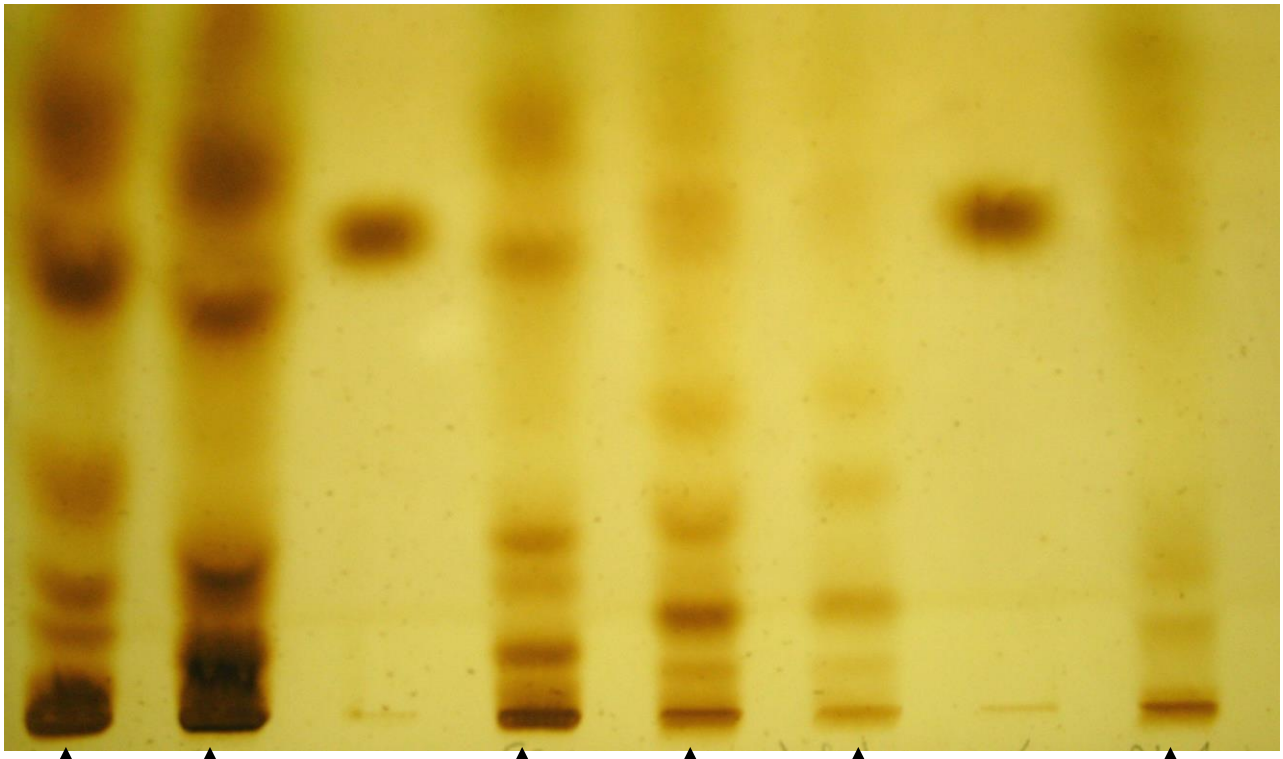
Aminoacid analysis was performed by all labs except one. Only 9 of them (# 40%) detected the abnormal presence of aspartylglucosamine. Aspartylglucosamine was separated from Tau and urea on Beckman analyser.

We got the following information from participants:
- Jeol analyser, aspartylglucosamine is eluted with urea, but abnormal ratio 570 nm / 440 nm
    - Urea : 570 / 440 nm ratio = 12
    - Patient P4 : 570 / 440 nm ratio = 9
    - P4 after hydrolysis of urine : 570 / 440 nm ratio = 12
- Hitachi analyser, it is eluted before or with urea (abnormal 570 / 440 nm ratio in the last case)
- Biochrom analyser, it is separated from urea (see above)
- LC-MS/MS (scheme organizer), it is easy to detect

Standard for aspartylglucosamine [2-acetamido-1-N(β-L-aspartyl)-2-deoxy-β-D-glucopyranosylamine or 2-acetamido-1-β-(L-aspartamido)-1,2-dideoxy-D-glucose or β-D-GlcNac] is available from Sigma (Ref A6661) http://www.sigmaaldrich.com.

Eighteen labs performed **oligosaccharide** analysis and only 9 of them reported a profile consistent with aspartylglucosaminuria (one lab confirmed this hypothesis using ninhydrine detection). Five labs reported an abnormal profile but did not conclude, whereas 3 labs concluded to a wrong diagnosis, and 4 labs did not detect any abnormality.

The following figure illustrates the oligosaccharide profile we obtained for patient P4, in comparison with fucosidosis, GM1 gangliosidosis and sialidosis.



Advice for further investigations was satisfying for those who reached a correct diagnosis, but was misleading for those who concluded to a wrong oligosaccharidosis or to a mucopolysaccharidosis.

Scoring

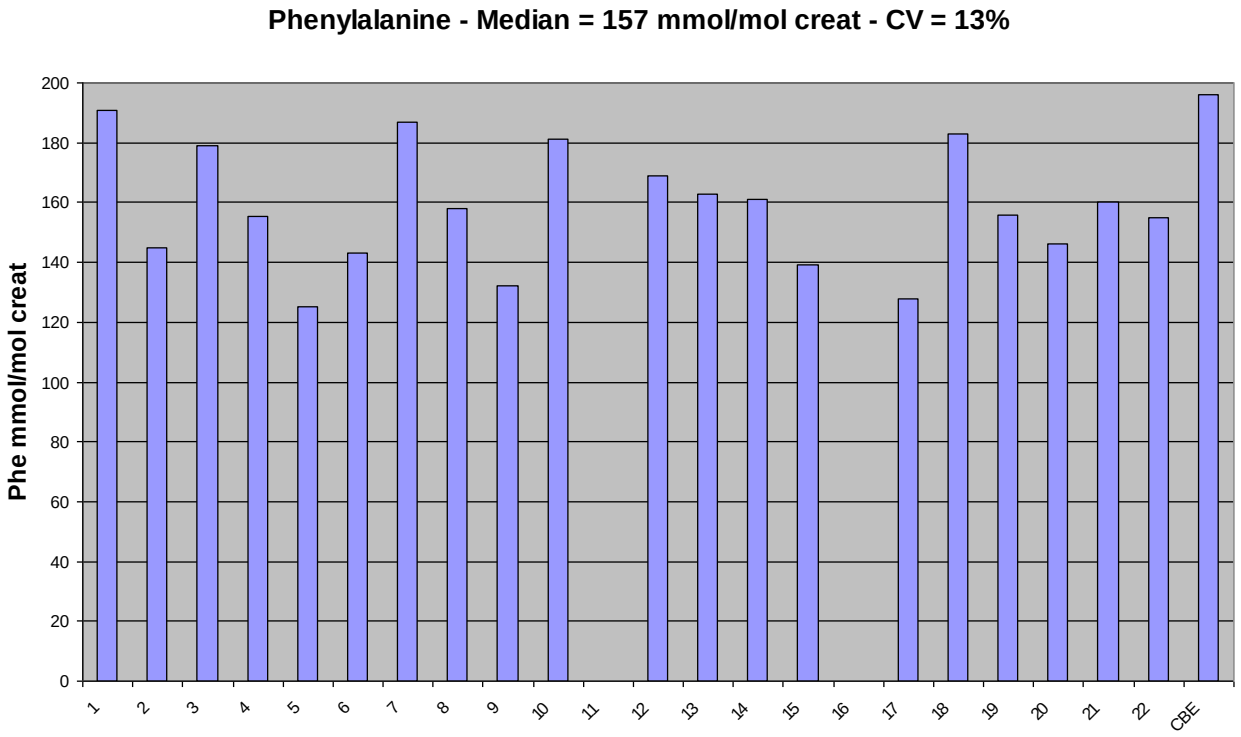
- Analytical performance: identification of aspartylglucosamine (score 2), abnormal oligosaccharide profile (score 1)
- Interpretation of results: aspartylglucosaminuria (score 2), oligosaccharidosis (score 1)
- Advice for further investigations: aspartylglucosaminidase activity or mutation analysis *AGU* gene or refer urine sample to a specialized lab or repeat oligosaccharides/mucopolysaccharides on a new urine sample (score 1)

- **Patient P5 - Phenylketonuria**

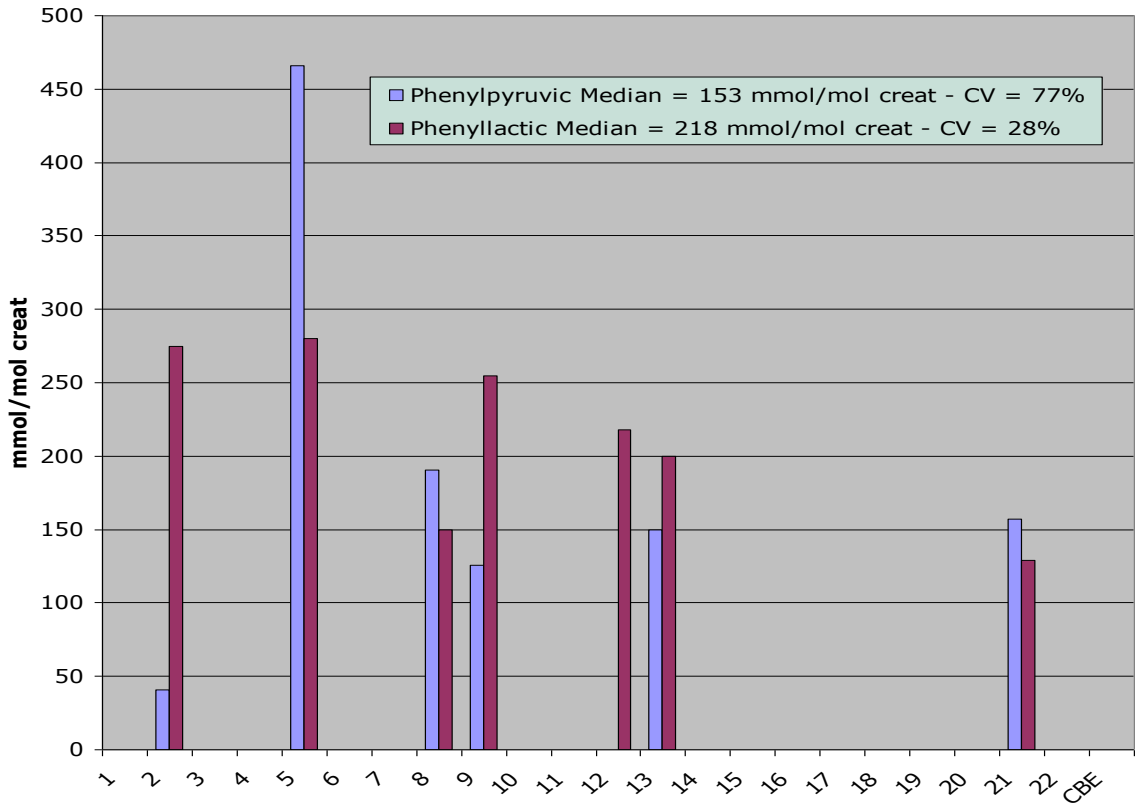
This urine sample was collected from an 8-year-old boy. Phenylketonuria (PAH deficiency) was diagnosed at birth by neonatal screening. The parents did not follow the low protein diet (poor socioeconomic familial background). He has a mild mental retardation, tremor and behavioral problems. The urine sample was collected at 8 years of age.

Diagnosis: All labs concluded to hyperphenylalaninemia.

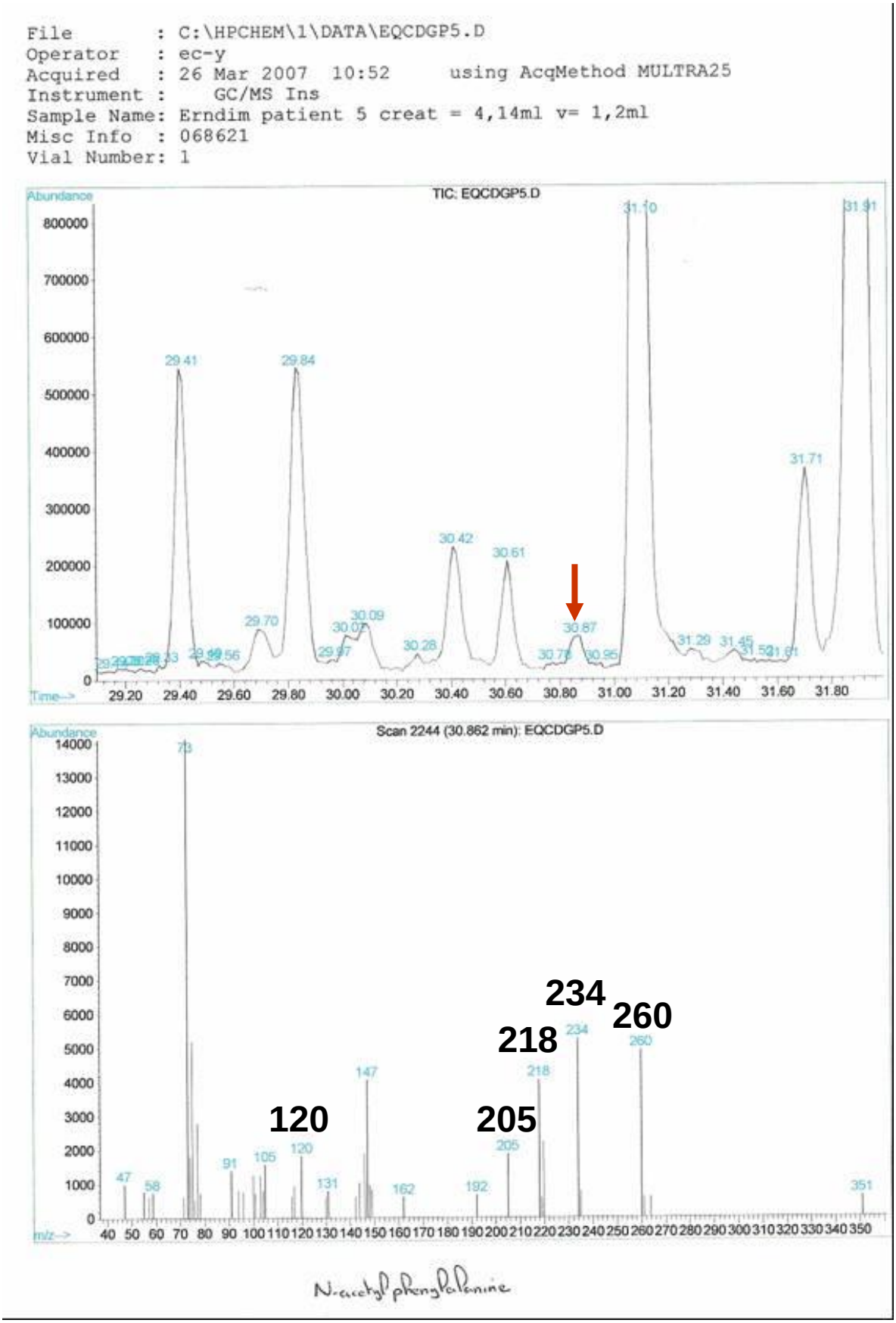
All labs performed **aminoacids** and all, except one, reported an increase of phenylalanine. Quantification was satisfactory.



All labs performed **organic acids**. All of them, except one reported an increase of phenyllactic acid and 20 of them an increase of phenylpyruvic acid, with a great variability of results for this organic acid (due to problem of storage?).



An increase of 2-hydroxyphenyllactic, 4-hydroxyphenyllactic, 4-hydroxyphenylpyruvic, mandelic, and 4-hydroxyphenylacetic acids was also reported. One lab reported the abnormal presence of N-acetylphenylalanine, which is eluted between azelaic and hippuric diTMS derivatives.



Pterin analysis performed by one lab discarded a defect in the biosynthesis or regeneration of BH4 cofactor.

Advice for further investigations was satisfying.

Scoring

- Analytical performance: increase of phenylalanine (score 1), increase of phenolic acids (score 1)
- Interpretation of results: hyperphenylalaninemia (PAH deficiency or PKU or disorder of biopterin metabolism) (score 2)
- Advice for further investigations: Plasma/blood amino acids or plasma/blood Phe or pterin profile in urine (score 1)

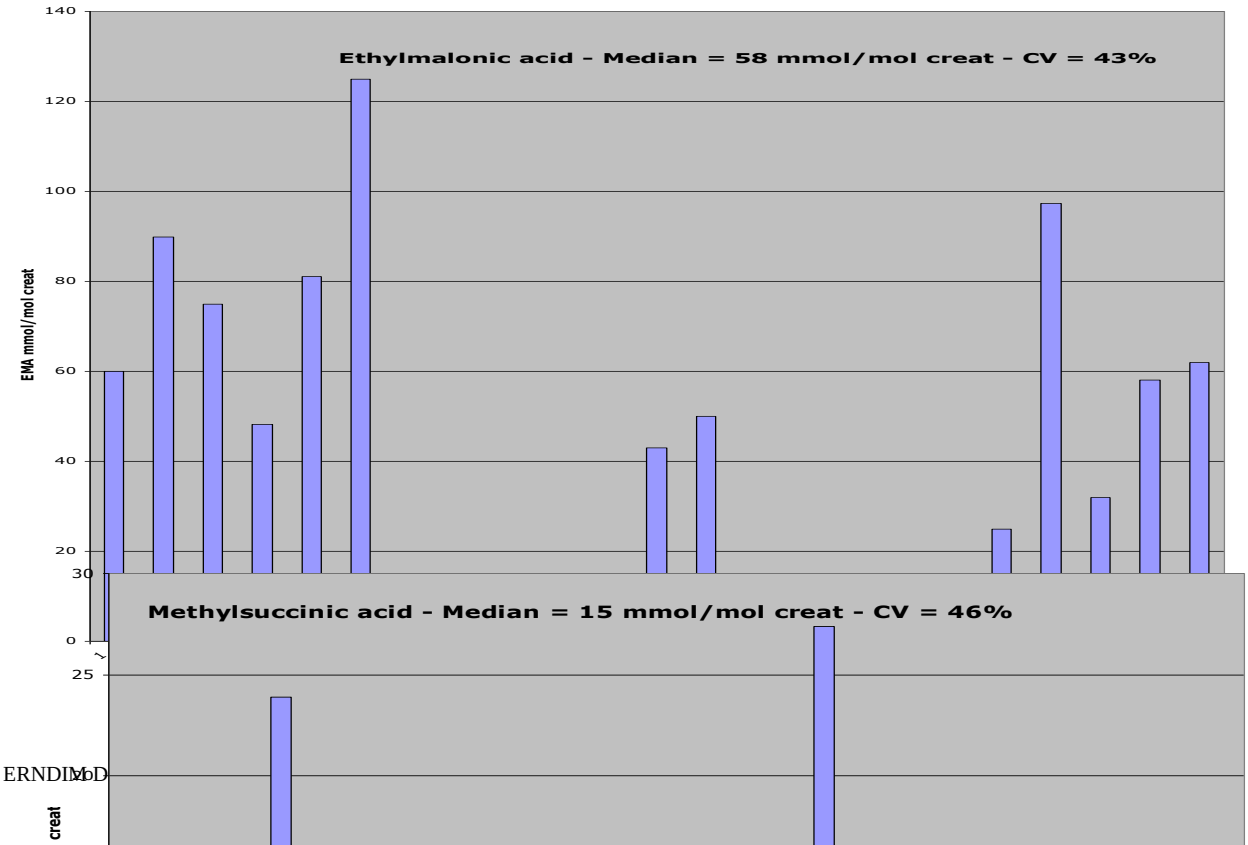
- **Patient P6 - Short-chain acyl-CoA dehydrogenase (SCAD) deficiency**

Patient 6 is a 7-year-old girl. No information about family was available: adopted girl originating from India. She was already followed for severe dilated cardiomyopathy of unknown origin. She was hospitalized in intensive care unit, with severe cardiac decompensation in the course of a viral infection. Plasma acylcarnitine profile revealed a high increase of butyrylcarnitine (C4) = 4.2 µmol/L (controls <0.8). Mutation analysis of *ACADS* gene showed she was homozygous for both variations c.625G>A and c.730G>A. However a large deletion of the gene cannot be excluded. The question of a cardiac transplantation was raised but could not be performed because of worsening of the cardiac function, despite symptomatic treatment. The child died from cardiac failure with secondary severe liver dysfunction. It is not clear whether cardiomyopathy was due to SCAD deficiency, but biochemical and molecular investigation were indicative of SCAD deficiency.

Diagnosis

Sixteen labs concluded to SCAD deficiency as first diagnosis, 4 labs concluded to either a fatty acid oxidation (FAO) defect, or multiple acyl-CoA dehydrogenase (MAD) deficiency, or systemic carnitine deficiency or isobutyryl-CoA dehydrogenase (IBDH) deficiency as first diagnosis. Two labs did not give a diagnosis.

All labs performed **organic acid** profile. An increase of ethylmalonic acid was reported by 19 of them, and an increase of methylsuccinic acid by 14, with a high CV in quantification of both metabolites.



Two labs reported an increase of butyrylglycine or isobutyrylglycine, whereas 7 labs reported that no acylglycine derivatives were detected. Metabolite of aspirine (2-hydroxyhippuric acid) was mentioned by 7 labs.

Seven labs performed **acylcarnitine** profile: 3 reported an increase of butyrylcarnitine (C4), 4 reported a normal profile.

Advice for further investigations was correct. In our experience, measurement of SCAD activity in fibroblasts can be unreliable, especially in patients with c.625G>A and/or c.730G>A variations. The residual enzyme activity probably depends of cell culture conditions. Measurement of SCAD activity in muscle tissue is more informative, but is too invasive. We would recommend first to perform mutation analysis of *ACADS* gene, and second eventually to measure SCAD activity.

Scoring

- Analytical performance: increase of ethylmalonic acid (score 1), increase of methylsuccinic acid (score 1)

- Interpretation of results: SCAD deficiency as first diagnosis (score 2), other FAO defect or IBDH deficiency as first diagnosis (score 1)

- Advice for further investigations: plasma/blood acylcarnitines or mutation analysis *ACADS* gene or SCAD activity (score 1)

Scores of participants

- **Survey 2007-1**

Lab n°	Patient P1 MAT deficiency				Patient P2 CBS deficiency				Patient P3 Hyperlysinemia			
	A	**I**	**R**	**Total**	**A**	**I**	**R**	**Total**	**A**	**I**	**R**	**Total**
1	2	2	1	**5**	2	2	1	**5**	2	2	1	**5**
2	2	1	1	**4**	2	2	0	**4**	1	0	0	**1**
3	2	2	1	**5**	2	2	1	**5**	1	1	1	**3**
4	2	1	1	**4**	2	2	1	**5**	1	2	1	**4**
5	2	2	1	**5**	2	2	1	**5**	2	2	1	**5**
6	2	1	1	**4**	2	2	1	**5**	2	2	1	**5**
7	0	0	1	**1**	2	2	1	**5**	2	2	1	**5**
8	2	2	1	**5**	2	1	1	**4**	1	2	1	**4**
9	2	2	1	**5**	2	2	1	**5**	0	0	0	**0**
10	2	2	1	**5**	2	2	1	**5**	2	2	1	**5**
11	2	1	1	**4**	1	1	0	**2**	0	0	1	**1**
12	2	2	1	**5**	2	2	1	**5**	1	1	1	**3**
13	2	2	1	**5**	2	2	1	**5**	2	2	1	**5**
14	2	1	1	**4**	2	2	1	**5**	2	2	1	**5**
15	2	2	1	**5**	2	2	0	**4**	2	2	1	**5**
16	2	2	1	**5**	1	1	0	**2**	0	0	0	**0**
17	2	2	1	**5**	2	2	1	**5**	1	2	1	**4**
18	2	2	1	**5**	2	2	1	**5**	2	2	1	**5**
19	2	1	0	**3**	2	2	1	**5**	2	2	1	**5**
20	2	2	1	**5**	2	2	1	**5**	2	2	1	**5**
21	2	2	1	**5**	2	2	1	**5**	2	2	1	**5**
22	2	2	1	**5**	2	2	1	**5**	2	2	1	**5**

❖ **Survey 2007-2**

Lab n°	Patient P4 Aspartylglucosaminuria				Patient P5 Hyperphenylalaninemia				Patient P6 SCAD deficiency			
	A	**I**	**R**	**Total**	**A**	**I**	**R**	**Total**	**A**	**I**	**R**	**Total**
1	2	2	1	**5**	2	2	1	**5**	2	2	1	**5**
2	2	2	1	**5**	2	2	1	**5**	2	2	1	**5**
3	1	1	1	**3**	2	2	1	**5**	2	2	1	**5**
4	2	2	1	**5**	2	2	1	**5**	2	2	1	**5**
5	2	2	1	**5**	2	2	1	**5**	2	2	1	**5**
6	1	1	0	**2**	2	2	1	**5**	1	1	1	**3**
7	0	0	0	**0**	2	2	1	**5**	1	2	1	**4**
8	1	1	0	**2**	2	2	1	**5**	2	1	1	**4**
9	0	0	0	**0**	2	2	0	**4**	0	0	1	**1**
10	1	1	1	**3**	2	2	1	**5**	1	2	1	**4**
11	0	0	0	**0**	1	2	1	**4**	1	2	1	**4**
12	1	1	0	**2**	2	2	1	**5**	2	2	1	**5**
13	2	2	1	**5**	2	2	1	**5**	1	2	1	**4**
14	1	1	1	**3**	2	2	1	**5**	2	2	1	**5**
15	0	0	0	**0**	2	2	1	**5**	1	0	0	**1**
16	0	0	0	**0**	2	2	1	**5**	2	2	1	**5**
17	0	0	0	**0**	2	2	1	**5**	1	2	1	**4**
18	2	2	1	**5**	2	2	1	**5**	2	2	1	**5**
19	2	2	1	**5**	2	2	1	**5**	2	2	1	**5**
20	0	0	0	**0**	2	2	1	**5**	2	2	1	**5**
21	2	2	1	**5**	2	2	1	**5**	1	1	1	**3**
22	2	2	1	**5**	2	2	1	**5**	2	1	1	**4**

- **Total scores**

Lab n°	Survey 2007-1	Survey 2007-2	Cumulative score	Cumulative score (%)
1	15	15	**30**	**100 %**
2	9	15	**24**	**80 %**
3	13	13	**26**	**87 %**
4	13	15	**28**	**93 %**
5	15	15	**30**	**100 %**
6	14	10	**24**	**80 %**
7	11	9	**19**	**63 %**
8	13	11	**24**	**80 %**
9	10	5	**15**	**50 %**
10	15	12	**27**	**90 %**
11	7	8	**15**	**50 %**
12	13	12	**25**	**83 %**
13	15	14	**29**	**97 %**
14	14	13	**27**	**90 %**
15	14	6	**20**	**67 %**
16	7	10	**17**	**57 %**
17	14	9	**23**	**77 %**
18	15	15	**30**	**100 %**
19	13	15	**28**	**93 %**
20	15	10	**25**	**83 %**
21	15	13	**28**	**93 %**
22	15	14	**29**	**97 %**

Performance

	Number of labs	% total labs
Excellent performers (100 % of good responses)	**3**	**14 %**
Good performers (> 75 % good responses)	**17**	**77 %**
Poor performers (< 50 % good responses)	**0**	**0 %**

❖ **Summary of scores**

Sample	Diagnosis	Analytical (%)	Interpretation (%)	Recommen-dations (%)	Total (%)
Patient P1	MAT deficiency	95	82	85	**90**
Patient P2	CBS deficiency	95	93	82	**92**
Patient P3	Hyperlysinemia	73	77	86	**77**
Patient P4	Aspartylglucosaminuria	55	55	55	**55**
Patient P5	Hyperphenylalaninemia	98	100	95	**98**
Patient P6	SCAD deficiency	77	82	95	**83**

DPT-scheme in 2008

Same “rules” as in 2007:

- Two surveys of 3 urines, including “normal” patients
- Results have to be sent within 3 weeks by e-mail, mail or fax
- Scoring will be analyzed for all centres
- Poor performers: those who don’t reply to both surveys or those who received an assistance letter (score < 50 %)
- Good performers: those who reached a score > 75 %

We remind you that to participate to the DPT-scheme, you must perform at least:

- Amino acids
- Organic acids
- Oligosaccharides
- Mucopolysaccharides

If you are not performing one of these assays, you can send the samples to another lab (cluster lab) but you are responsible for the results.

Please send quantitative data for amino acids and, if possible, for organic acids.

Meeting in 2008

The next meeting for the DPT-scheme Southern Europe will take place during the 44th Symposium of SSIEM in Lisbon, on Tuesday September 2nd probably from 9.00 to 10.30. Further information will be sent as soon as we get more details.

We remind you that attending this meeting is an important part of the proficiency testing. The goal of the program is to **improve** the competence of the participating laboratories which includes the critical review of all results with a discussion about improvements.

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ANNEX 1

PROFICIENCY TESTING – SOUTHERN EUROPE
URINE SAMPLES ALREADY SENT

• **1998 : 1**	**A**	**OCT**
	B	**Propionic**
• **1999 : 1**	**C**	**MPS I or II**
	E	**Cystinuria**
• **1999 : 2**	**D**	**CblC**
	F	**HMG-CoA lyase**
• **2000 : 1**	**G**	**Iminodipeptiduria**
	H	**Glutathion synthetase**
• **2001 : 1**	**P1**	**Mevalonate kinase**
	P2	**L-2-OH glutaric**
• **2001 : 2**	**P3**	**Methylmalonic**
	P4	**MPS IIIA San Fillippo**
• **2002 : 1**	**P1**	**LCHAD**
	P2	**Sulphite oxidase**

• **2002 : 2**	**P3**	**Biotinidase**
	P4	**MPS I**
• **2003:1**	**P1**	**Tyrosinemia type I**
	P2	**SC-BCAD deficiency**
	P3	**Argininosuccinic aciduria**
• **2003:2**	**P4**	**MCC deficiency**
	P5	**Sialidosis (common sample)**
	P6	**MSUD**
• **2004:1**	**P1**	**Tyrosinemia type I, treated patient**
	P2	**Propionic acidemia**
	P3	**Non metabolic disease, septic shock**
• **2004:2**	**P4**	**Mevalonic aciduria (common sample)**
	P5	**Fucosidosis**
	P6	**Alkaptonuria**
• **2005:1**	**P1**	**Isovaleric acidemia**
	P2	**Tyrosinemia type II (common sample)**
	P3	**Disorder of peroxysome biogenesis**
• **2005:2**	**P4**	**Multiple acyl-CoA dehydrogenase deficiency**
	P5	**Alpha-mannosidosis**
	P6	**4-hydroxybutyric aciduria**
• **2006:1**	**P1**	**Aromatic amino acid decarboxylase deficiency**
	P2	**Hyperoxaluria type I**
	P3	**Mucopolysaccharidosis type VI**
• **2006:2**	**P4**	**Hypophosphatasia (common sample)**
	P5	**Lysinuric protein intolerance**
	P6	**MCAD deficiency**