Hôpitaux de Lyon

# ERNDIM DPT Schemes

## Common sample 2010

## Sialidosis type I

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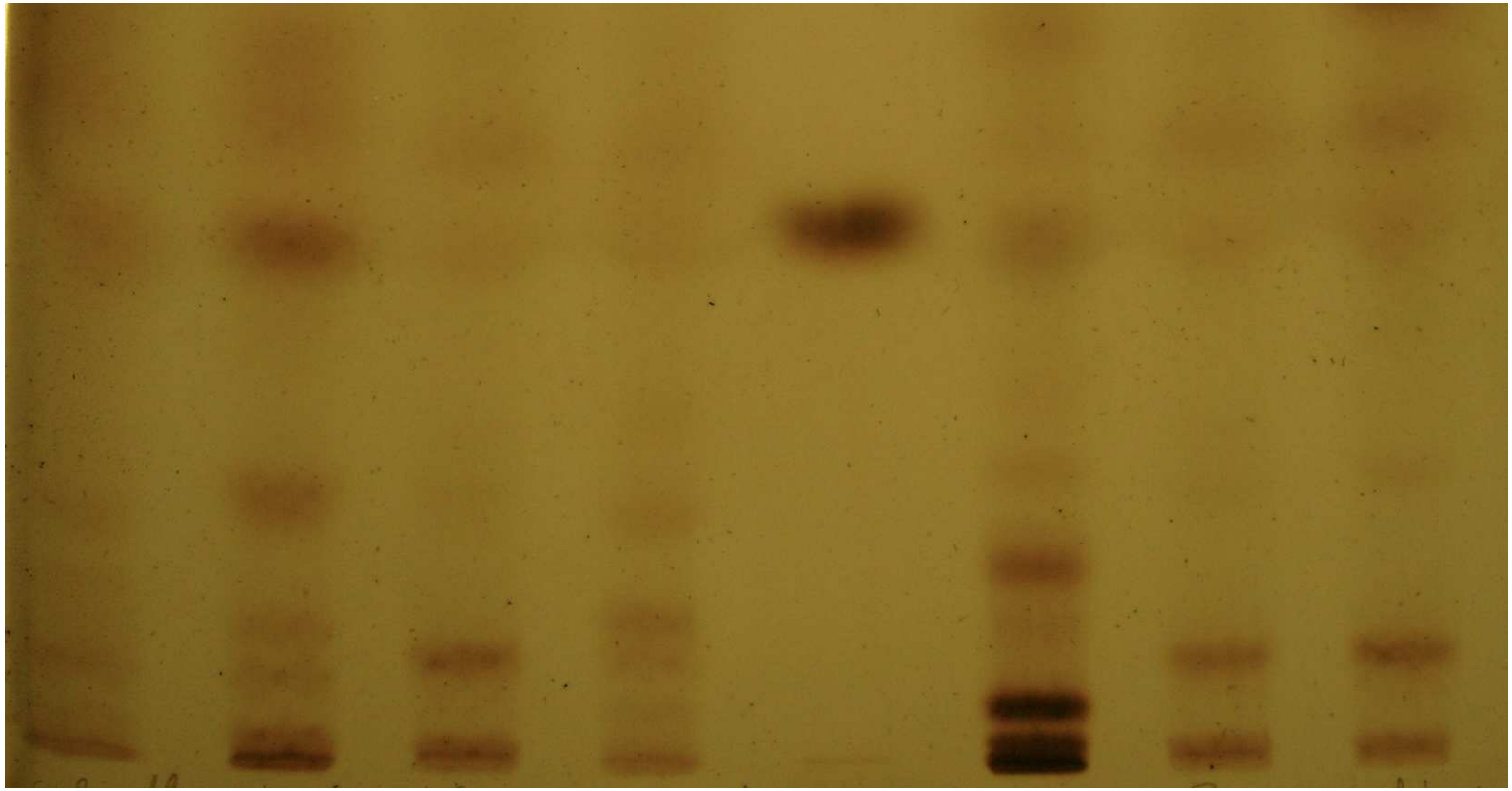
# Patient information on form at referral

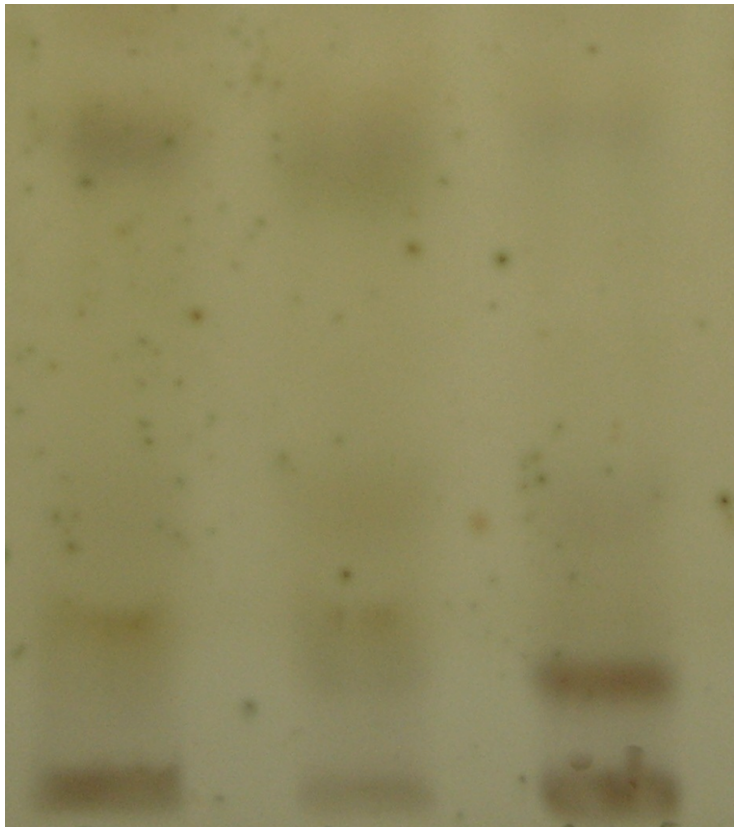
- 43 year old woman who presented progressive walking difficulties, osteoporosis, cholestasis and myoclonic epilepsy. She also had a loss of visual acuity. Opthalmoscopy revealed a cherry red spot
- Diagnosis : α-D-**neuraminidase deficiency, also called sialidosis type I or sialidase deficiency or « cherry-red spot – myoclonus » syndrome or mucolipidosis type I**
- This urine sample was provided by Dr Barth, CHU Angers, France. Diagnosis was suspected on
  - Oligosaccharides profile : abnormal bands at 4% and 16% Rf lactose
  - TLC sialic acid : sialyloligosaccharides

# Oligosaccharide TLC



| **Schindler** | Fuco sidosis | DPT | **Apartyl glucos aminuria** | **Lactose** | **GM1 gangl.** | DPT | **Sialidosis** |
|---|---|---|---|---|---|---|---|

# Sialic acid TLC



Free sialic acid

Sialyl oligosaccharides

Salla disease

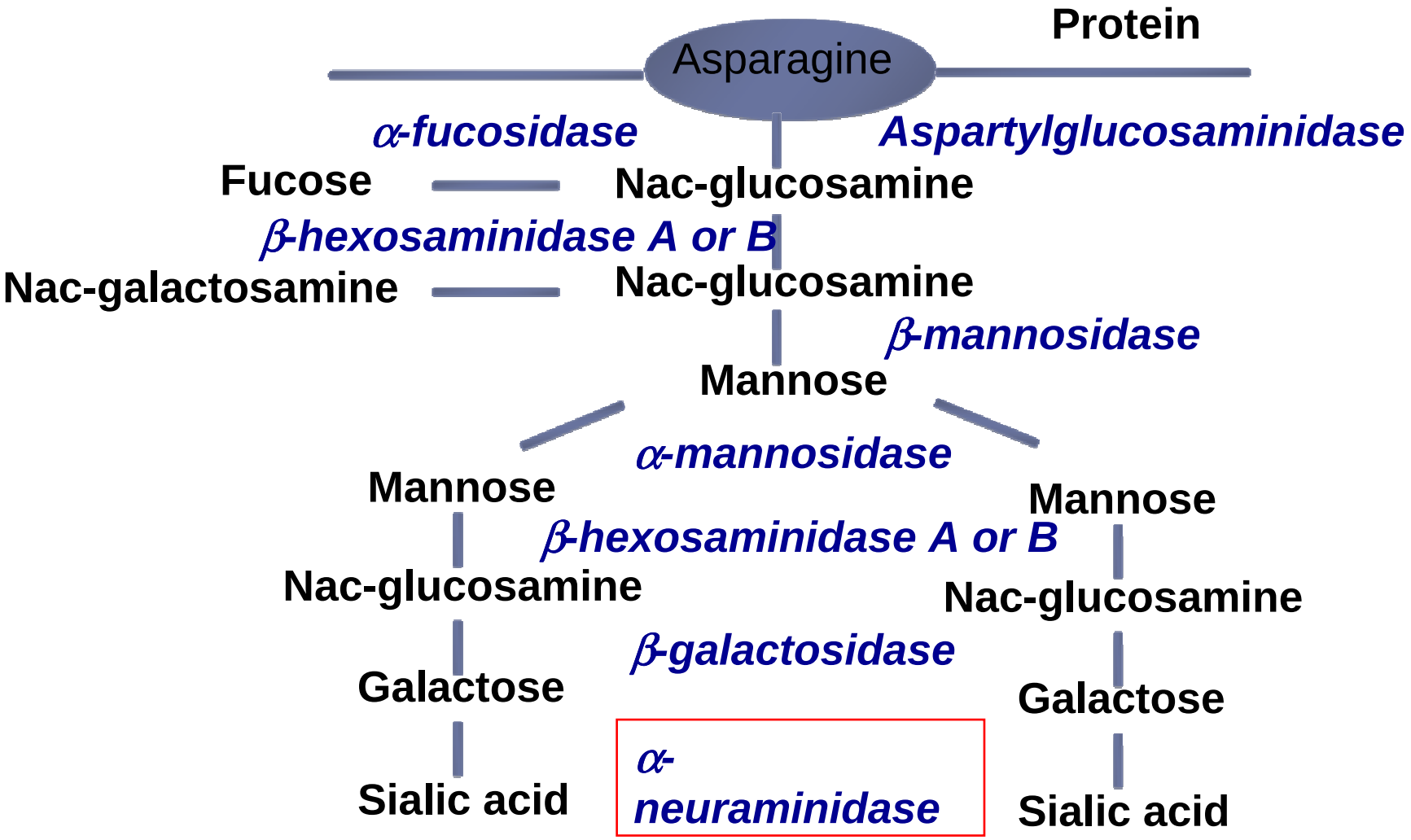
Infant

DPT

# Detailed patient information

- Born in 1967
- 18 years of age : progressive  loss of visual acuity with a cherry-red spot in the macula, leading to optic atrophy and cataract
- 32 years : myoclonic epilepsy
- 33 years : shakes, cerebellar ataxia, nystagmus, tetrapyramidal syndrome
- MRI : cortical atrophy mainly in frontal lobes
- 41 years : osteonecrosis of femoral and humeral heads (unusual in sialidosis type I)

# Degradative pathway of a glycoprotein oligosaccharide chain



# Sialidosis type I

| Clinical abnormality | Patients (%) |
|---|---|
| Cherry-red spot | 100 |
| Myoclonus | 85 |
| Visual defects | 70 |
| Ataxia | 59 |
| Hyperreflexia | 52 |
| Seizures | 48 |
| Dysarthria | 33 |
| Nystagmus | 30 |
| Hypotonia | 19 |
| Lens / corneal opacity | 15 |

Clinical features from 27 patients (Scriver)

# Confirmation of diagnosis

- Deficient α-D-neuraminidase activity
  - Leukocytes = 0.07 µkat/kg (simultaneous control : 0.41 ; controls : 0.32 – 1.70)
  - Fibroblasts = 0.7 µkat/kg (simultaneous control : 9.2 ; controls : 2.7 – 5.4)
- Normal activity in leukocytes and fibroblasts of
  - β-D-galactosidase : excluding galactosialidosis and GM1 gangliosidosis
  - total hexosaminidase and hexosaminidase A : excluding GM2 gangliosidosis
- Normal filipine test in fibroblasts : excluding Niemann-Pick type C

# DPT centres

- Amsterdam 19 labs
- Basel 21 labs
- Lyon 21 labs
- Pragues 19 labs
- Sheffield 21 labs (3 no answer)

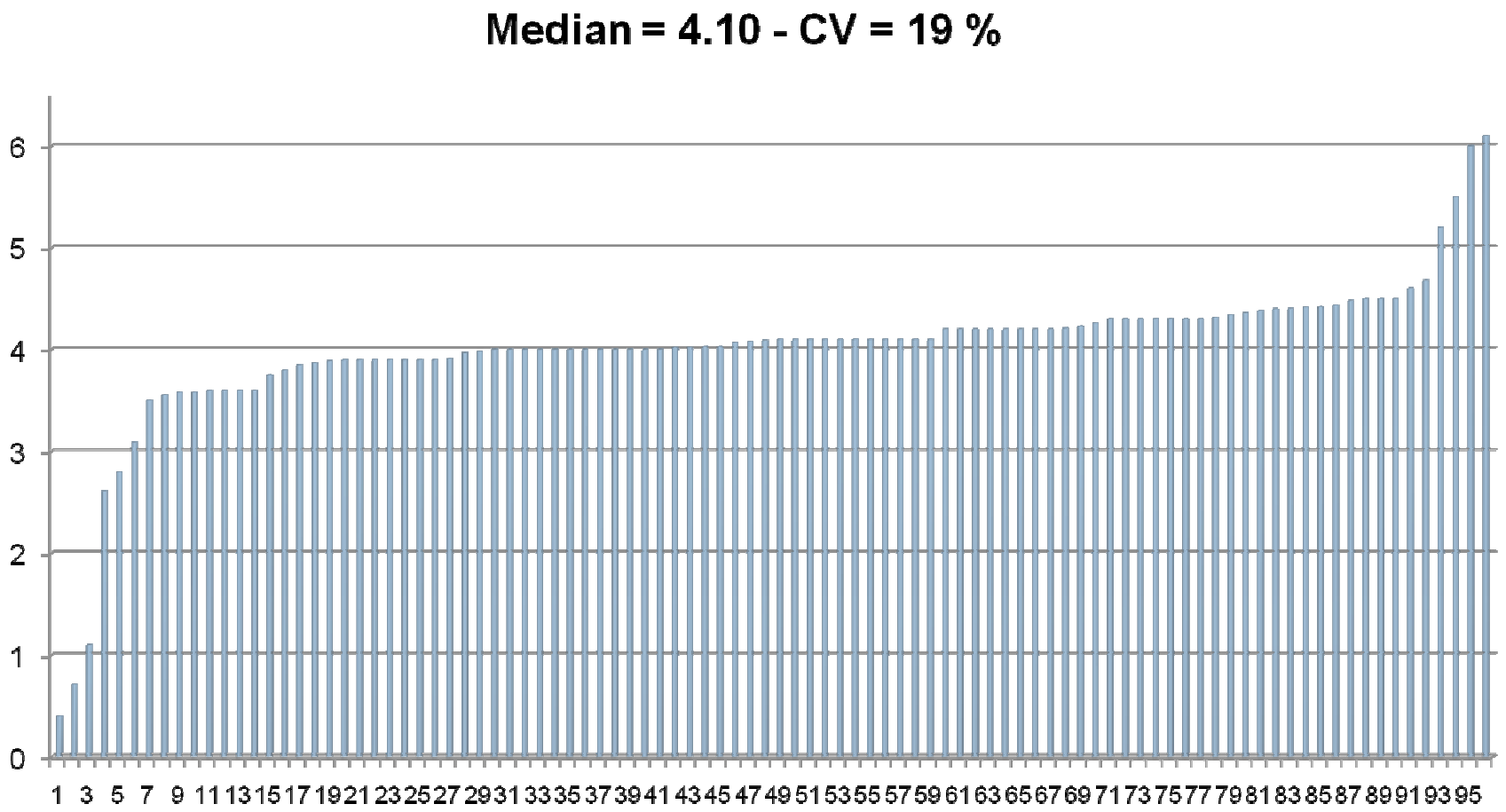
- Total 101 labs (98 responders)

# Creatinine determination

| Centre | Median | Mean | Coefficient of variation |
|---|---|---|---|
| Amsterdam | 4.20 | 4.17 | 6 % |
| Basel | 4.00 | 3.92 | 9 % |
| Lyon | 4.21 | 3.96 | 23 % |
| Pragues | 4.20 | 4.21 | 29 % |
| Sheffield | 4.00 | 3.79 | 19 % |
| All centres | 4.09 | 4.01 | 19 % |

Interlab CV 2009 Special Assay urine = 6.5 % (n = 103)
Interlab CV 2009 Quantitative organic acids = 5.8 % (n = 68)

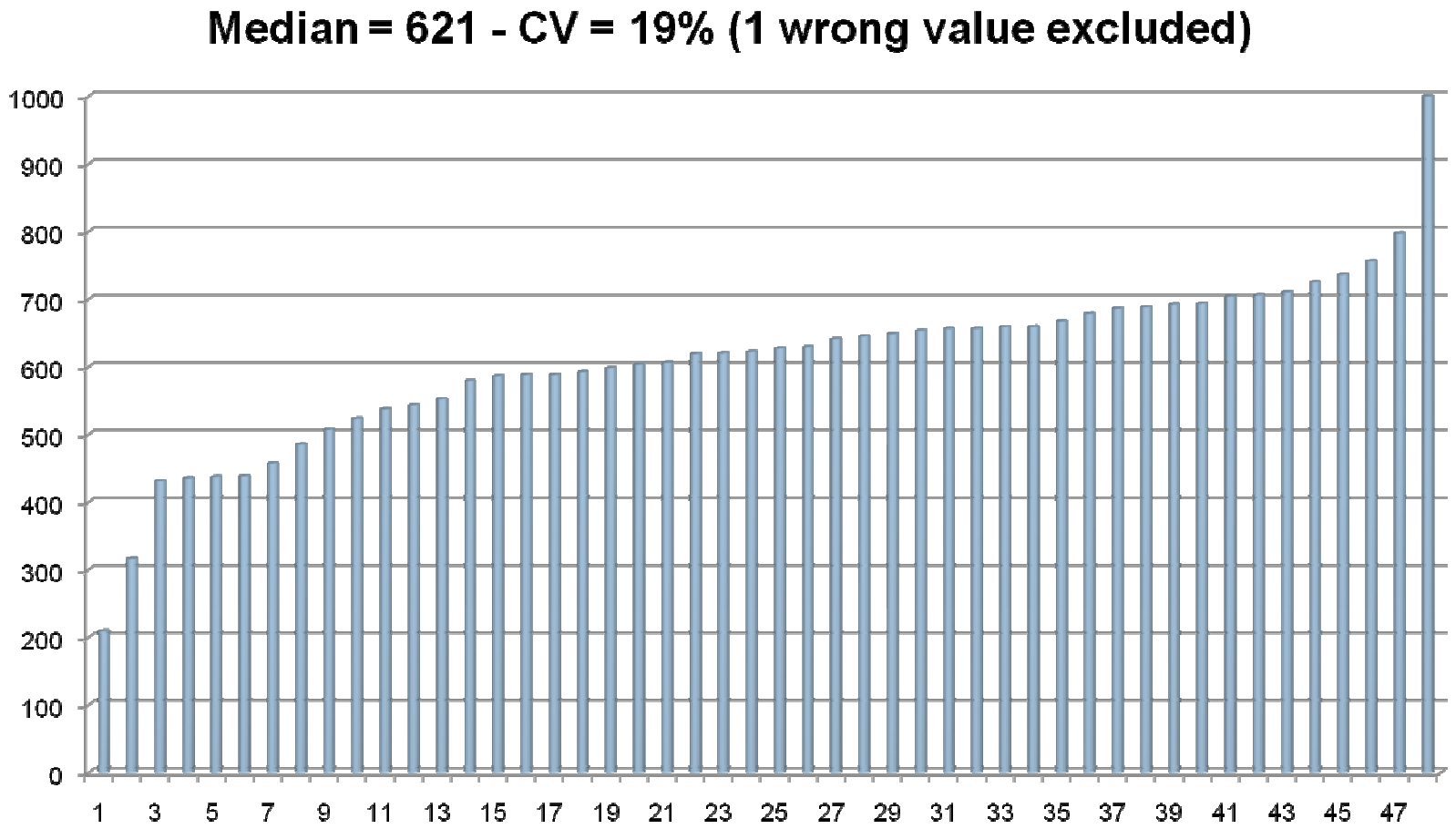
# Creatinine determination (mmol/mol creat)



# Lab findings

- Organic acids : 70 / 98 labs
  - Valproate (Depakine) metabolites 51 labs
  - Levotiracetam (Keppra) metabolites 26 labs
  - Slight increase of lactic acid 14 labs
  - No significant abnormality 13 labs
  - Other comments : 10 labs
- Amino acids : 77 / 98 labs
  - Increase of glycine secondary to valproate therapy 50 labs
  - No significant abnormality 23 labs
  - Low serine, high glutamic acid , probably due to a problem of storage of the urine sample 5 labs

# Glycine determination (mmol/mol creat)

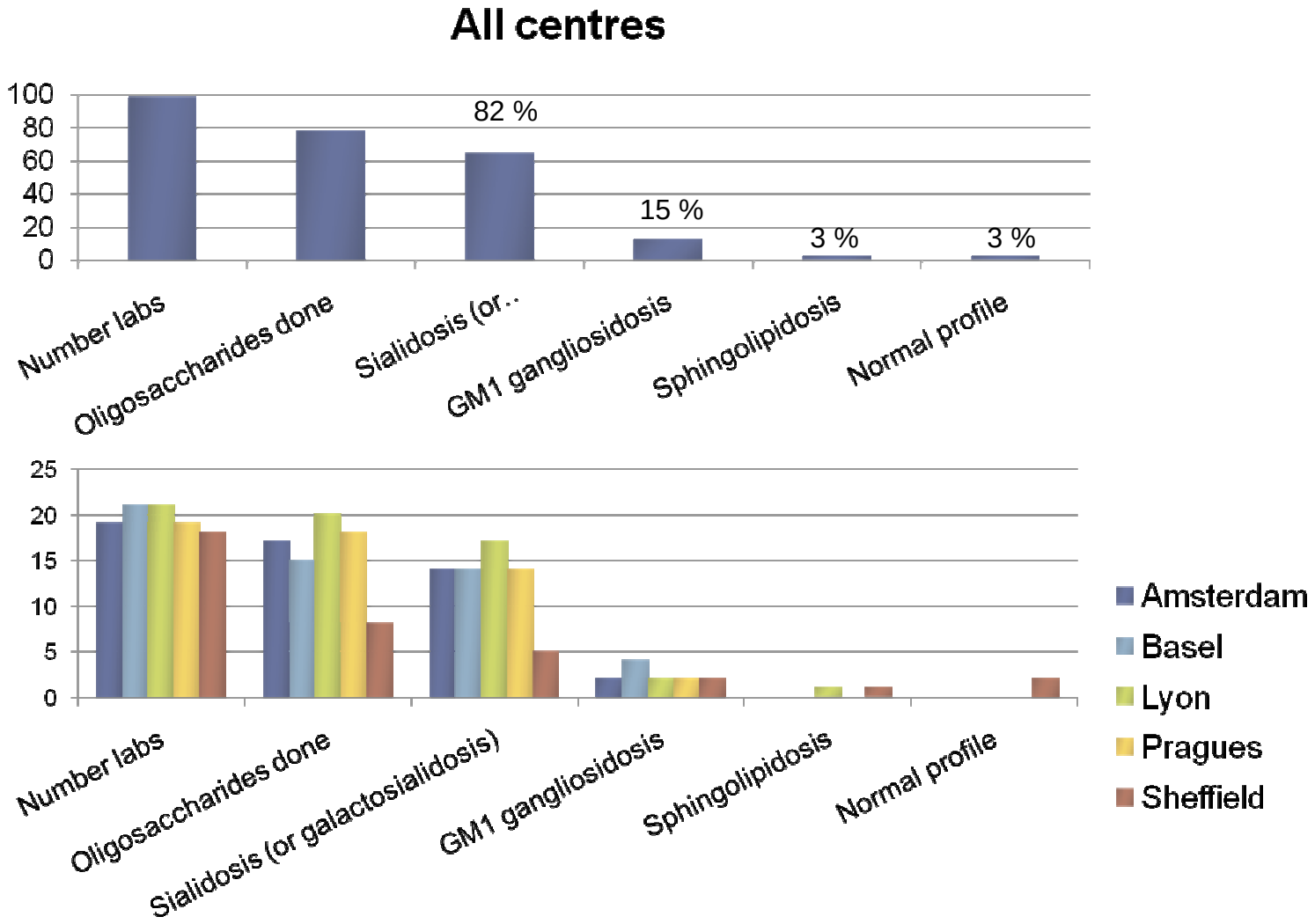



Interlab CV 2009 Plasma amino acids = 10.8 %

# Oligosaccharides determination

| DPT centre | Number of labs | Test performed | % |
|---|---|---|---|
| Amsterdam | 19 | 17 | 89 % |
| Basel | 21 | 15 | 71 % |
| Lyon | 21 | 20 | 95 % |
| Pragues | 19 | 18 | 95 % |
| Sheffield | 18 | 8 | 44 % |
| **Total** | **98** | **78** | **80 %** |

# Interpretation of oligosaccharide profile



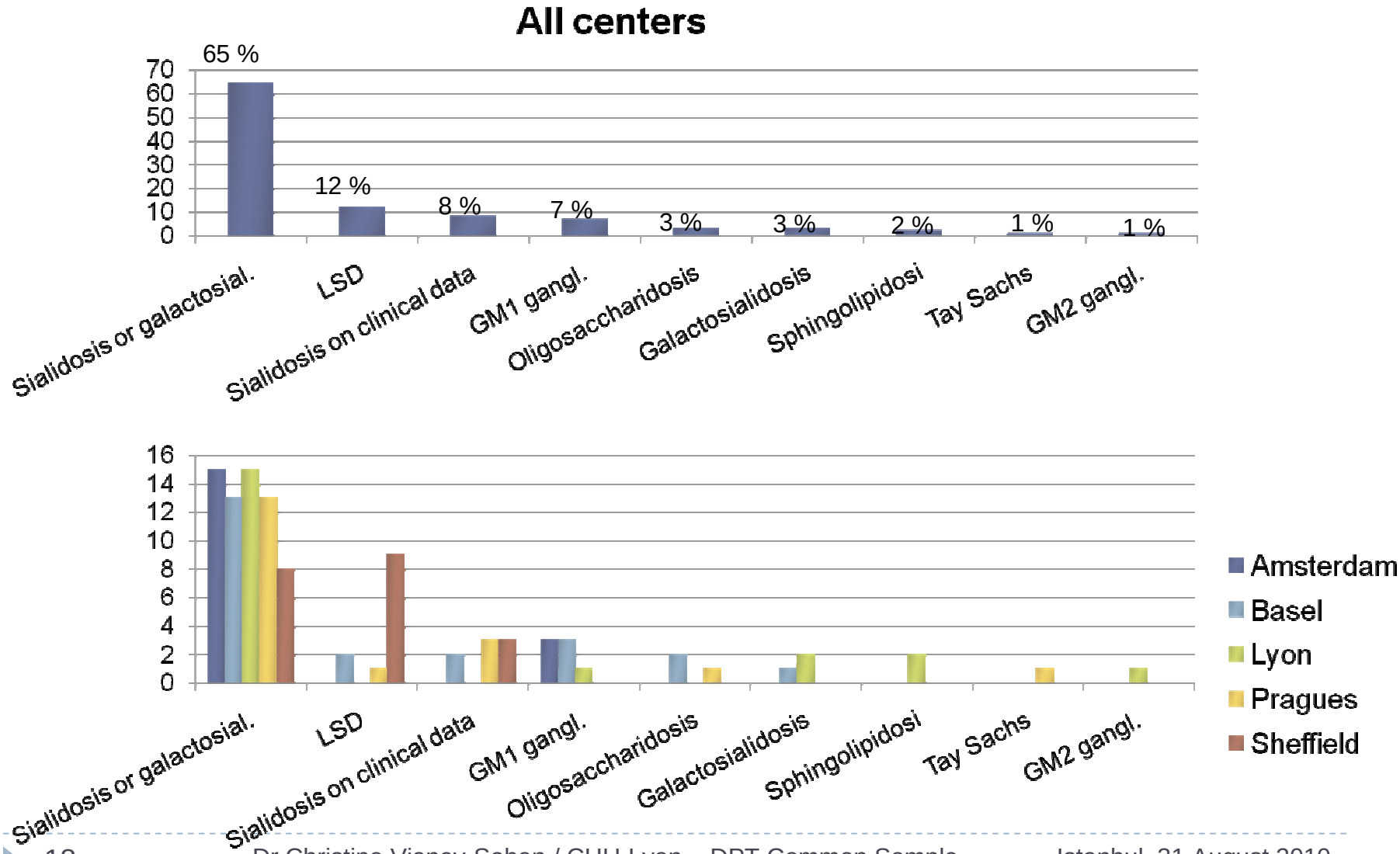
# Other assays

- Sialic acid TLC (10 labs)
  - Increase of sialyloligosaccharides 8 labs
  - Normal profile 2 labs
- Free sialic acid quantification (6 labs)
  - Normal results 6 labs
- Bound sialic acid quantification (6 labs)
  - Increase of bound sialic acid 6 labs

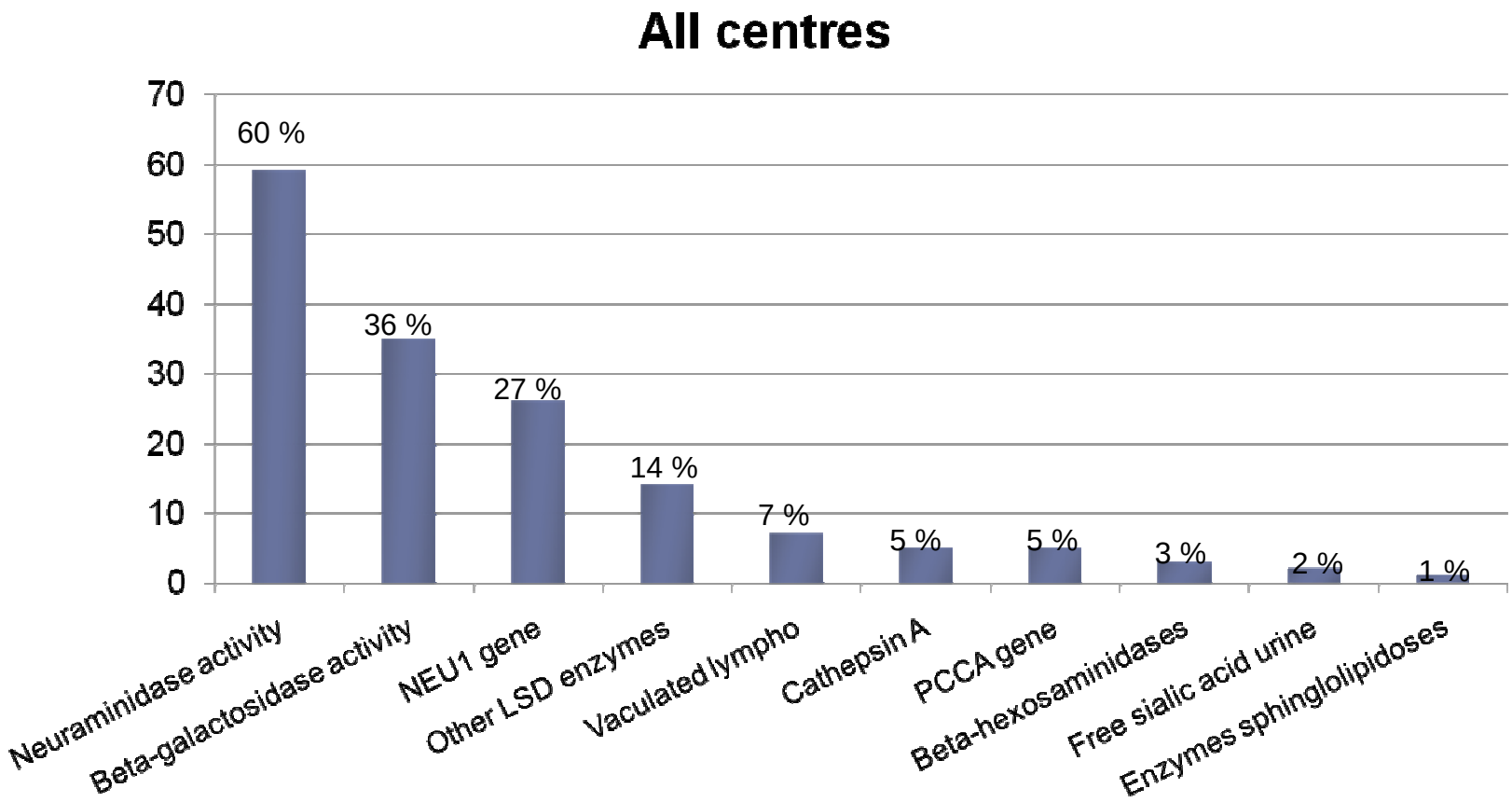
# Other assays

- Mucopolysaccharides 74 / 98 labs
  - Normal excretion 62 labs
  - Increased excretion 11 labs
  - Normal pattern 24 labs
- Purines and pyrimidines 27 / 98 labs
  - Normal results 25 labs
  - Increase of succinyladenosine 2 labs
- Bile acids 3 / 98 labs
  - Normal results 3 labs

# Interpretation of results



# Advice for further investigations



# Scoring

- Analytical performance
  - Oligosaccharide profile suggestive of sialidosis or galactosialidosis, and/or increase of silalyloligosaccharides, and/or increase of conjugated sialic acid 2
  - Abnormal oligosaccharide profile 1
- Interpretation of results
  - Sialidosis or galactosialidosis 2
  - Oligosaccharidosis, or diagnosis of sialidosis based on clinical data, or “sialidosis or GM1gangliosidosis” 1
  - GM1 or GM2 gangliosidosis, sphingolipidosis 0
- Advice for further investigations
  - α-neuraminidase activity (leukocytes, or fibroblasts) and / or mutation analysis *NEU1* gene 1

# Scoring

| DPT Centre | Analytical (%) | Interpretation (%) | Advice further invest (%) | Total (%) |
|---|---|---|---|---|
| Amsterdam | 74 % | **82 %** | 84 % | 79 % |
| Basel | 71 % | 69 % | 81 % | 72 % |
| Lyon | **88 %** | 81 % | **90 %** | **86 %** |
| Pragues | 71 % | 71 % | 89 % | 75 % |
| Sheffield | 44 % | 78 % | 67 % | 62 % |
| **All centres** | **70 %** | **76 %** | **83 %** | **75 %** |

# Conclusions

- Oligosaccharide assay should be more widely available
- When an abnormal oligosaccharide profile is observed, the assay has to be repeated with urine samples from patients with known disorder(s) on the same plate. Scheme organizers can provide urine samples of such patients
- The ERNDIM QAP for mucopolysaccharides should be extended to oligosaccharides