ERNDIM MPS Pilot Study
REPORT 2011

Scheme organisers

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1. Introduction

In 2010 the Mucopolysaccharidosis (MPS) scheme was organised for the first time by Erasmus Medical Centre (Rotterdam, NL) and SKML, the Dutch organisation for quality assurance in medical laboratories (Winterswijk, NL). The scheme continued in 2011 for a second year as a pilot study.

2. Samples

As for other qualitative schemes the MPS pilot scheme requires patient samples. Several laboratories have donated samples in 2009 and 2010, for which they are gratefully acknowledged. To be able to continue this scheme we need new patient samples. If you have one or more samples available and are willing to donate these to the scheme, please contact us at erndim-mps@erasmusmc.nl.

3. Design of the scheme and logistics

The Scheme has been designed and coordinated by Dr. George Ruijter and Dr. Jan Huijmans (scientific advisors). Dr. Cas Weykamp at SKML has prepared and shipped the samples (scheme organiser).
In 2011 the scheme consisted of 6 lyophilised urine samples as described in Table 1. Apart from the number of samples included in 2011 (2010: 8 samples) the scheme format was kept identical to 2010. Samples were distributed in February. Participants were asked to reconstitute each sample in 5 mL deionised water, determine creatinine concentration (mmol/L) and GAG concentration (mg/mmol creatinine), to qualify the GAG level according to age-matched reference values (i.e normal or increased), to analyse GAG sub fractions and qualify (i.e. normal or increased CS, HS, DS and KS) and to give the most likely diagnosis.

Table 1. 2011 samples

Survey, reporting deadline	Sample no.	Sample type
2011-1, April 30, 2011	MPS9	MPS III B (f, 19 y)
	MPS19	Normal control (m, 5 y)
	MPS11	MPS I (j, 2 y 4 m)
2011-2, June 30, 2011	MPS12	MPS II (m, 5 y)
	MPS13	MPS III A (m, 5 y)
	MPS14	MPS VII (f, 19 y)

4. Reporting

Reporting was done by completing pre-designed forms. Two reporting deadlines were chosen: April 30 and June 30. Reports were submitted by email to the scheme advisor (erndim-mps@erasmusmc.nl). In addition to results, the first reporting form (April 30, 2011) included a section to describe methods. In the second report (June 30, 2011) a question was included to assess interest in participation in the MPS scheme if it was a regular ERNDIM scheme.

5. Participants

In 2011 the MPS pilot scheme had 89 participants (2010: 88). On average 79 reports were received per sample (range 78-79). In 2010 the average number of reports was 80.

6. Methods

In the first report participants were asked to specify their methods. This question had two aims. First to make an inventory of methods in use (Table 2) and second to investigate whether relations exists between methods and diagnostic proficiency. The latter will be further studied after full analysis of the 2011 scheme.
Methods were provided by 84 laboratories.

Table 2. Methods

Method for quantitative analysis		**Standard material**		**Method for qualitative analysis**	
DMB	83 %	CS, C4S, C6S	67 %	1-D electr (limited resolution)	34 %
Alcian Blue	7 %	HS	25 %	1-D electr (discontinuous)	32 %
CPC (turbidometric)	6 %	DS	4 %	2-D electrophoresis	14 %
Uronic acid (carbazole)	4 %	Glucuronolacton	3 %	TLC	11 %
		Multiple	1 %	Other,	3 %
				Multiple	6 %

7. Results of the 2011 samples

Results are summarised in Table 3.

Variation in the quantitative results of GAG concentrations was large. Interlaboratory CVs were 24-49 % for the 6 different samples with a tendency of lower variation for higher GAG concentrations. A relatively large CV was observed for sample MPS11 (MPS I) which may be explained in part by the low creatinine concentration and the large variation in this value.

Interpretation of quantitative GAG results, i.e. labelling results as normal or increased, appeared to be very good for samples MPS11 to 13 (97 to 100 % correct; see Fig. 1). GAG concentrations apparently were clearly elevated for these 3 young MPS patients. A slightly lower level of correct interpretation was obtained for sample MPS10 of a healthy child with 89 % correct interpretation. Poorer results were obtained for samples MPS9 and MPS14 with 77 and 70 % of the laboratories interpreting their results as increased compared to their age-matched reference values. These 2 samples were from 19-year old mild MPS IIIB and MPS VII patients respectively. Apparently, it is more difficult to establish or interpret mildly elevated GAG levels for adult patients. In the case of sample MPS9 (MPS IIIB), 17 laboratories did not interpret quantitative results correctly, but 5 out of these 17 did have the correct diagnosis based on electrophoresis/TLC.

Table 3. Results for samples MPS9 to MPS14

Sample ID	MPS9	MPS10	MPS11	MPS12	MPS13	MPS14
Diagnosis **Age of patient**	MPS III 19 y	Normal 5 y	MPS I 2 y 4 m	MPS II 5 y	MPS III 5 y	MPS VII 19 y
No. of reports	78	78	78	79	79	79
Creatinine (mmol/L) **Average** **SD**	 2.21 0.31	 6.05 0.56	 1.09 0.35	 3.14 0.31	 1.66 0.22	 3.95 0.48
GAG (mg/mmol) **Average** **SD**	 9.4 4.6	 10.0 4.1	 130 50	 54.4 13.2	 51.9 15.9	 10.9 5.1
Quantitative GAG **Increased (%)** **Normal (%)**	 77 23	 11 89	 100 0	 100 0	 97 3	 70 30
Diagnosis **Correct (%)** **Part. correct (%)** **Not correct (%)** **No diagnosis %)**	 49 0 28 23	 78 9 6 6	 24 41 27 8	 39 39 13 9	 79 0 13 9	 5 9 73 13

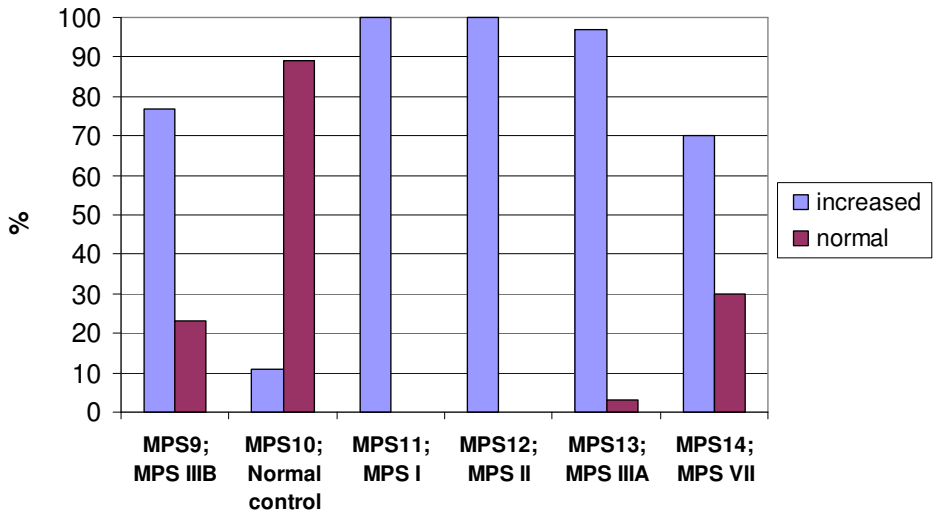

Figure 1. Interpretation of quantitative GAG results. For each sample the percentage of laboratories scoring the GAG level as 'increased' or 'normal' is indicated.

Diagnostic proficiency was scored with the following criteria. The MPS III samples (MPS9 and MPS 13) were correctly interpreted with only the diagnosis 'MPS III'. For the normal sample MPS10 'normal' was considered correct, while 'normal/MPS IV' was scored as partially correct. The MPS I and II samples (MPS11 and MPS12) were correct with the diagnosis 'MPS I/II' or 'MPSI/II/VII' and partially correct with 'MPS I/II/VI'or 'MPS I/II/VI/VII'. Finally, the MPS VII sample was scored as correct with the diagnosis 'MPS VII' and partially correct with combinations of different MPS disorders and normal as long as MPS VII was among the possible diagnoses mentioned.

On average 11 % of the laboratories did not report a diagnosis (range 6-23). This was mainly due to the fact that these laboratories did not perform qualitative analysis of GAG. An exception was sample MPS9 for which 23 % of the laboratories did not suggest a diagnosis. With this sample many laboratories reported the absence of bands or the presence of faint bands upon qualitative analysis, which precluded a diagnosis.

Diagnostic proficiency for MPS9, the mild MPS III sample, was only 49 %, while it was 79 % for MPS13, the second MPS III sample in this year's scheme. With regard to sample MPS9, the majority of the laboratories (18/22) that did not come to the right diagnosis scored this sample as normal. Clearly, classic MPS III patients are much easier diagnosed than mild variants.

The MPS I and MPS II samples were diagnosed (partially) correct by 65 and 78 % of the laboratories. Many laboratories (24 %) diagnosed the MPS I sample as MPS VI. Apparently, the dermatansulfate fraction was predominant in this sample, which masked heparansulfate.

Sample MPS14 from a mild MPS VII patient was included as an educational sample and indeed proved to be rather difficult. Only 4 laboratories gave MPS VII as the only possibility, while 7 others mentioned MPS VII among the possible diagnoses. Of the 11 labs with MPS VII among the possible diagnoses, 5 reported elevated CS, suggesting that this might be an important clue here. From the laboratories not mentioning MPS VII, 33 labeled this sample as normal (although many did in fact interpret the quantitative results as 'elevated'). Another 12 labs gave MPS IV as the possible diagnosis. This may be related to the inability to separate chondroitinsulfate and keratansulfate in the electrophoretic system used.

8. Scoring of results

In the pilot phase of the scheme scoring of results of individual laboratories will not be performed.

9. Preview of the scheme in 2012

In 2012 the MPS scheme will be a full ERNDIM scheme. The format of the MPS 2012 scheme will be similar to 2011.

10. Questions, Comments and Suggestions

If you have any questions, comments or suggestions, please address to the scientific advisor of the scheme, Dr. George Ruijter (erndim-mps@erasmusmc.nl) and/or the scheme organiser Dr. Cas Weykamp (c.w.weykamp@skbwinterswijk.nl).