Laboratory Diagnosis of FXIII deficiency: Data from a UK NEQAS (Blood Coagulation) Exercise

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Background:

FXIII deficiency is a rare coagulation bleeding disorder, with characteristic symptoms including delayed bleeding and intracranial haemorrhage. Traditionally, laboratory diagnosis has been carried out using clot solubility tests. However, we have previously demonstrated poor sensitivity of these tests to anything other than severe deficiency. Furthermore, a recent ISTH Scientific Subcommittee communication *(Kohler et al, JTH 2011)* has recommended that the first line test in the diagnosis of FXIII deficiency should be a quantitative FXIII activity assay. We report here data from a proficiency testing exercise carried out in 2011, and compare data with results from previous EQA exercises carried out by our organisation.

UK NEQAS FXIII Screeing Exercises 2002-11:

2002 Exercise

Survey		S02:01	S02:02
Clot solubility: interpretation			
	Normal	48	119
	Borderline	19	2
	Abnormal	58	3
FXIII assay (u/dl)	median	10.1	100.6
(n=30)	range	0-55	20-136

2003 Exercise

Survey		S03:01	S03:02
Clot solubility: interpretation			
	Normal	114	4
	Borderline	1	0
	Abnormal	2	109
FXIII assay (u/dl)	median	86.0	3.5
(n=39)	range	67-154	0-131

2008 Exercise

Survey		S08:01	S08:02
Clot solubility: interpretation			
	Normal	80	2
	Borderline	0	0
	Abnormal	0	78
FXIII assay (u/dl)	median	93.0	4.7
(n=48)	range	5-146	0-75

2011 Exercise

Survey		S11:01	S11:02
Clot solubility: interpretation			
	Normal	1	52
	Borderline	0	6
	Abnormal	58	1
FXIII assay (u/dl)	median	3.7	76.2
(n=63)	range	0.5-17	34.9-101.5

Errors in interpretation:

The rate of false normal interpretations for clot solubility screens when the FXIII level is less than 5u/dl has fallen from 3.5% in 2003 to less than 2% in 2011. However, a higher incidence of false positive or borderline screens with normal plasma was observed in this latest exercise. In each case, a possible technical error in laboratory methodology could be identified that could have contributed to the error in diagnosis.

Increasing use of assays:

The number of centres employing specific FXIII assays has increased from under 20% of centres investigating FXIII deficiency in 2003 to over 50% of centres in 2011. Many of these centres have ceased to employ clot solubility tests, in keeping with the recent ISTH/SSC recommendations.
Assay results for all participants in the 2011 exercise are shown in figs 1 and 2. The most widely employed methods are the Siemens Berichrom photometric assay and the HemosIL FXIII latex immunoassay. There was a significant difference in results obtained with these two most widely used methods (n=39, median 5.0u/dl, and n=19, median 2.0u/dl respectively, $p<0.001$). Despite this, precision was improved compared with the results from the previous exercise (from 177% to 82.1% for the deficient sample, and 21.6% to 14.8% for the normal sample).

Fig 1
FXIII deficient sample

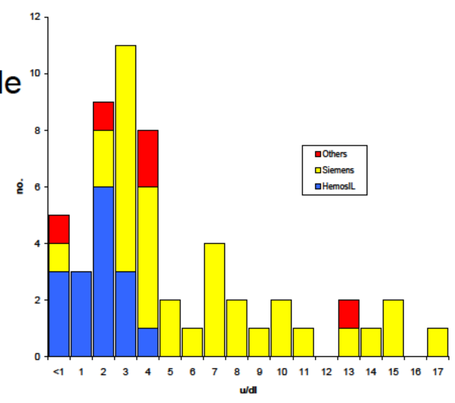
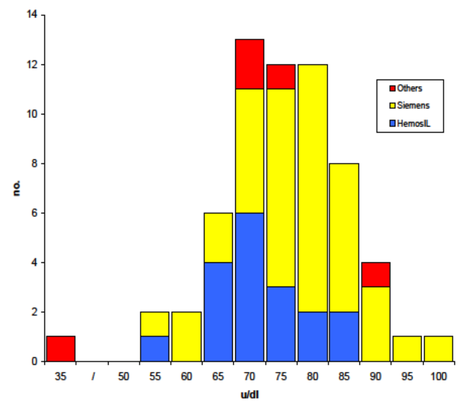


Fig 2
Normal sample



Conclusions:

Perhaps because of the ease and cost of performing a solubility test, these tests continue to be used. Our data show that this can be successful in some centres, depending on the sensitivity of the method in use. Where FXIII assays are employed to investigate suspicion of FXIII deficiency or to confirm abnormal screening test results, further standardisation of these assays is required.

DOI: 10.3252/pso.eu.WFH2012.2012