ERNDIM QC scheme for CDG screening

Nijmegen, 21-07-2010

Dear colleagues,

Please find enclosed the results of the QC scheme 2010 for CDG screening, for the first time run as an official scheme under ERNDIM. The current scheme included 51 participants from many countries around the world.

One of the main concerns for future rounds of this QC scheme will be the access to patient material (about 2 ml plasma/serum per patient), since we have almost run out of stock. We would like to ask you if you could provide material for future rounds of this QC scheme. Please, send samples (2-2.5 ml) to my address below, including information about age, sex, and a brief clinical description on first visit of the patient.

In case of any questions, please do not hesitate to contact me.

With kind regards, also on behalf of Cas Weykamp,

Dr. Dirk J. Lefeber
Clinical Biochemical Geneticist
Department of Laboratory Medicine
830- Laboratory of Genetic, Endocrine and Metabolic Disease
Radboud University Nijmegen Medical Centre
Geert Grooteplein 10
6525 GA Nijmegen
The Netherlands
tel: +31 24 3614428 / 3953
fax: +31 24 3618900
D.Lefeber@neuro.umcn.nl

ERNDIM QC scheme for CDG screening 2010

General comments

We have received 44 report forms, seven centres were unable to respond. In total 318 plasma/serum samples were shipped after lyophilisation in the presence of a cryoprotectant. We had to resend a few samples due to shipment or handling problems. No sample degradation was reported, and no interference was reported of the lyophilisation procedure in any of the methods used. Isofocusing was employed most often (27), followed by CE (7) and HPLC (7), Mass spectrometry (2) and Western Blotting (1). The presence of EDTA in plasma samples CDG005 and CDG009 caused strong signals at the asialotransferrin position in HPLC analysis, which complicated interpretation in a few cases.

Results

Six samples were selected for shipment, the clinical information is representative for the patients.

	Clinical information	Patient data	Final diagnosis
ERNDIMCDG005	Floppy infant, thrombocytopenia, skeletal abnormalities, abnormal facial features	M, 2 weeks	CDG-Ic
ERNDIMCDG006	Abnormal fat distribution, mental retardation	F, 6 years	No CDG
ERNDIMCDG007	Mental and motor retardation, cerebellar hypoplasia	M, 12 years	CDG-Ia
ERNDIMCDG008	Myopia, cutis laxa, mental retardation	F, 10 years	CDG-II(ATP6V0A2)
ERNDIMCDG009	Hypoglycemia	F, 2 years	No CDG
ERNDIMCDG010	Proteinuria, coagulopathy	M, 11 years	No CDG

In the graph, the overall score is shown for all centres. The abnormal profiles were found by most centres and interpreted correctly as either type I or type II (96% average score), while a 81% score was obtained for the suggestions for further diagnostics. These results are slightly higher than for the 2009 scheme.

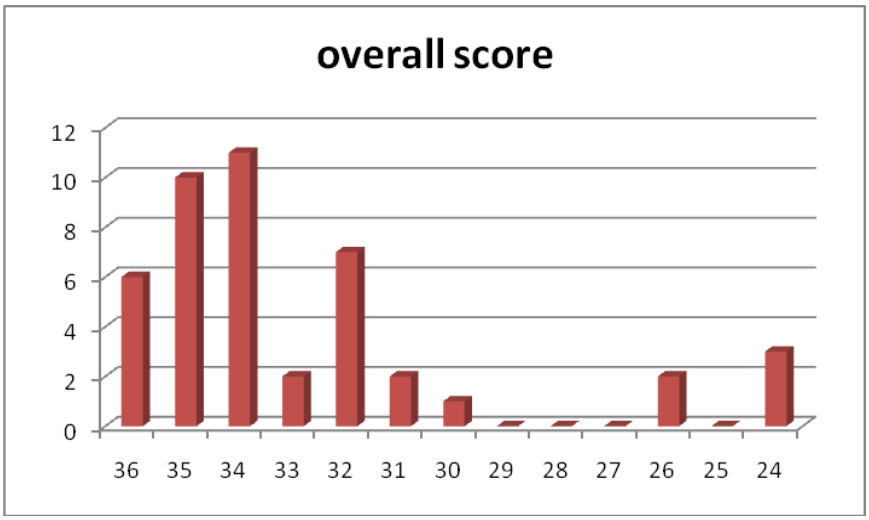

Figure: Overall results. *x*-axis: score, *y*-axis: number of centres

The scoring system was similar to previous years (per sample: 4 points for correct identification and assignment of the profile type, and 2 points for proper suggestions for further diagnostics). According to the wish of ERNDIM we expect that the participants act as a counsellor with advice to the clinician for further work-up. We tried to keep the scoring as objective as possible, although this was quite difficult in some cases. The individual scores will be send to you by email.

ERNDIMCDG005

In the screening of metabolic patients, a clear CDG type I profile was obtained in this patient. A polymorphism was excluded (profile is not very suggestive) and the clinical phenotype is not highly suggestive of either galactosemia or fructosemia as secondary causes of CDG type I. Enzyme analysis (phosphomannomutase and phosphomannose isomerase) was normal. Subsequent analysis of lipid-linked oligosaccharides showed accumulation of Dol-PP-$GlcNAc_2Man_9$, and molecular genetic analysis (*ALG6* gene) led to the diagnosis of CDG-Ic.

Almost all centres correctly assigned this as an abnormal profile corresponding to a CDG type I and most centres suggested appropriate work-up for reaching the final diagnosis. Some centres requested a repeat sample due to young age. Very young children can sometimes present with a very mild type II profile. In case of a type I profile, further CDG diagnostics should be considered. Although skeletal abnormalities have been described for CDG-Ig, they can be found in other subtypes as well.

ERNDIMCDG006

A normal profile was identified by almost all centres.

ERNDIMCDG007

This sample is from a patient with a relatively mild form of CDG-Ia. At younger age, a clearly abnormal profile was observed that normalized completely with age. In this recent sample, the profile was again abnormal. Slightly abnormal profiles are well known for CDG-Ia patients with cerebellar hypoplasia as main presenting symptom.

Almost all centres correctly assigned this as an abnormal profile corresponding to a CDG type I and almost all centres suggested appropriate work-up for reaching the final diagnosis. Liver pathology as secondary cause for abnormal glycosylation results in type II profiles and is not correlated with type I profiles.

ERNDIMCDG008

During the screening of patients with a suspected metabolic disorder, a type II profile was observed with increased disialo- and trisialotransferrin. Secondary causes were excluded. Abnormal ApoCIII isofocusing lead to the suspicion of a combined N- and O-glycosylation defect. The clinical phenotype of cutis laxa is known in ATP6V0A2 deficiency.

Almost all centres reported an abnormal profile suggestive for CDG type II. Glycan analysis and ApoCIII isofocusing were often suggested as further diagnostics, not always was ATP6V0A2 analysis indicated. Several centres suggested CDG-IIa, but both clinical symptoms and type of profile are not suggestive. It should be noted that the transferrin glycosylation can be normal in ATP6V0A2-CDG until 6 months of age (ApoCIII already abnormal). In some cases the O-glycosylation abnormality is very mild and the patient can present with a more or less isolated N-glycosylation deficiency.

ERNDIMCDG009

A normal profile was identified by almost all centres.

ERNDIMCDG010

A normal profile was identified by all centres.