Co- funded by the Health Programme of the European Union

Benefits of the Inherited NeuroMetabolic Diseases Network (InNerMeD) in biomarkers development

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on behalf of all InNerMeD partners

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INTRODUCTION

Inherited neurometabolic diseases (INMD) are characterized by metabolic disorders that adversely affect the brain development and/or function. Early pre-symptomatic or even prenatal diagnosis and new-born screening are crucial for application of the appropriate therapy as early as possible, with the aim to prevent, or at least minimize, the impairment of brain function. Searching for novel biomarkers applicable in diagnosis, treatment and monitoring of diseases is continuous process.

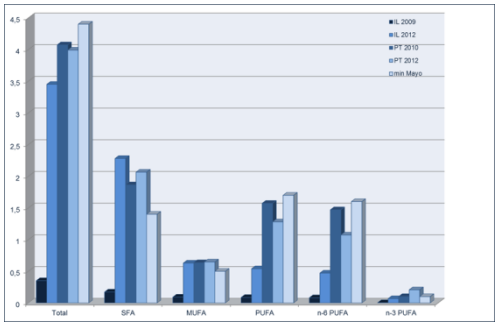
Long chain fatty acid oxidation disorders, like 3-OH-acyl-CoA-dehydrogenase (LCHAD) deficiency and three-functional protein (TFP) deficiency, is a group of inherited metabolic disorders in which treatment and treatment monitoring is still matter of debate, particularly the extent of dietary fat restriction. Due to a restricted, low fat diet therapy, these patients are at high risk from the essential fatty acids deficiency.

Here, we present the method of monitoring the fat restricted diet in this group of patients, in order to increase awareness on INMD, the potential biomarkers development, and benefits of Inherited NeuroMetabolic Disease (InNerMeD) Information Network.

METHODS

Total lipids were extracted from serum with a mixture of isopropanol/chlorophorm (1.5:1 *v/v*). Fatty acids were trans-esterified to methyl esters with 1 M HCl in methanol. Fatty acid methyl esters were extracted twice with petrol-ether and analysed by gas chromatography.

Figure 1



Fatty acid composition in serum of patients at the onset of the disease and after applied diet therapy. For comparison, min values for children of the same age referenced by Mayo Clinic are shown.

SFA - saturated fatty acids; MUFA - monounsaturated fatty acids; PUFA - polyunsaturated fatty acids.

CONCLUSION

During the long-term monitoring of patients with metabolic diseases numerous data are collected that can serve as a source for the selection of new biomarkers. The analysis of fatty acid composition provides an opportunity for more efficient disease monitoring and more individualized therapy control in patients with fatty acids oxidation disorders.

International network InNerMeD (Inherited Neurometabolic Diseases Information Network) ensures the availability of data for a large number of patients from other countries, which is especially important when it comes to rare diseases and the small number of patients.

The expected benefit from the InNerMeD network is to increase validated knowledge on INMD and to expand activities with networks of excellence focused on genetic CNS diseases.

SUBJECTS

The subjects were patients at the Department of Pediatrics, University Hospital Centre, Zagreb, Croatia. Serum samples were collected during regular controls at the department. Two patients were chosen to present: PT, (TFP deficiency, born in 2010), and IL, (born in 2009, LCHAD deficiency). Patient IL developed a metabolic crisis on the second day of life, manifested by hypoglycemia, hypotonia, cyanosis and circulatory collapse. Patient PT was presented for the first time at the age of 5.5 months when, after acute respiratory infection, he developed hypoglycemia, hypotonia, bradycardia, and disturbance of consciousness followed by respiratory failure. In both children, upon diagnosis, specific dietary regimen that includes regular meals, adequate energy intake and limited fat intake with additional reduction of long chain fatty acid fats was applied.

RESULTS

Inherited metabolic disorders in patients resulted in changes in the composition of fatty acids (Figure 1). Fatty acid composition in serum of subjects suffering from impaired β-oxidation of long chain fatty acids shows a significant deviation from the expected values. Implementation of a diet therapy, involving administration of MCT oil (medium chain triglycerides, fatty acids contain 8-12 C atoms) while also limiting the fats with long-chain fatty acids, is reflected in the increased concentration of medium chain fatty acids in the serum. Supplementation with docosahexaenoic acid (DHA, C 22:6n-3) allows normalization of essential polyunsaturated fatty acids.

InNerMeD

Inherited NeuroMetabolic Disease (InNerMeD) Information Network (www.innermed.eu) is the first European Network on INMD funded by the Directorate-General for Health and Consumers within the Second Health Programme of the European Commission (Grant Agreement No. 201212121 - Collaborative Project) organized through Work packages (Figure 2). The main objectives of the Network are: i) acquisition of critical mass of knowledge encompassing multi-specialist competences, ii) a further boost to research and technological innovation; iii) creation of repository containing standardized data spanning research, clinical features, available therapies and off-label application, biomarkers and genetic data; iv) dissemination of knowledge among physicians, patients and general stakeholders to anticipate diagnosis and supply an adequate therapy.

Figure 2