HSSIEM 2009 HELLENIC SOCIETY FOR THE STUDY OF INBORN ERRORS OF METABOLISM

2nd International Symposium

Inherited Metabolic Disorders in Adult Neurology

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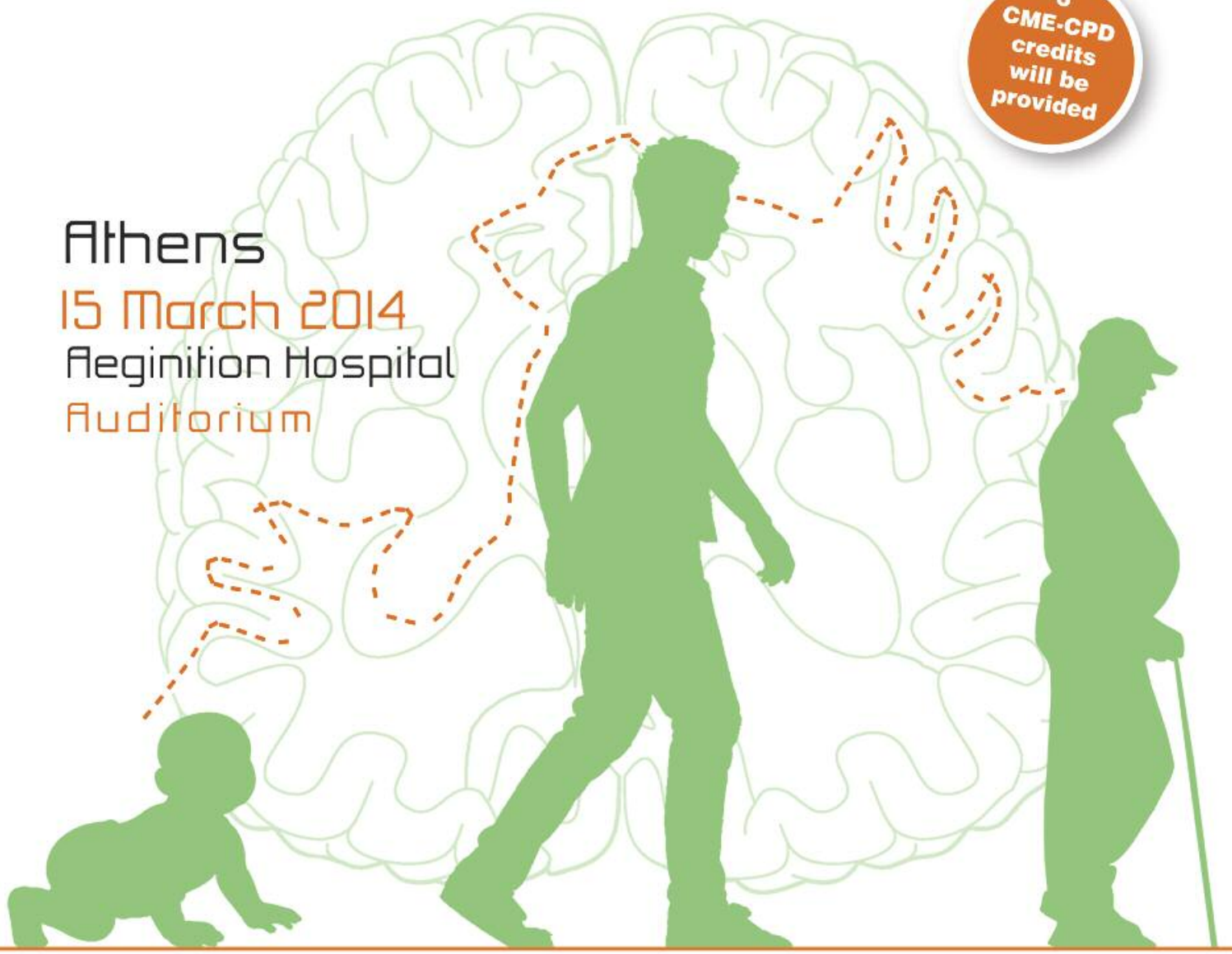

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Programme and Abstracts

NEUROMETABOLIC DISORDERS IN ADULT NEUROLOGY: AN OVERVIEW

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Neurometabolic disorders comprise a group of inherited metabolic disorders which primarily affect the nervous sytem or may show relevant neurological complications.

There are many inherited metabolic diseases (IMDs) which could potentially cause neurological symptoms. Adult neurologists are more likely to consider unusual presentation of known, common diseases than presentation of rare genetic disorders. Therefore, it is necessary to increase awareness of treatables IMDs. Nowadays, indeed, there is an increasing number of IMDs which can be treated with specific treatments.
Usually, we distinguish IMDs with onset in the pediatric age from those with onset in adulthood. This separation has been made because of the age of symptoms manifestation, but for many IMDs there is a continuum of manifestations, with different kind of expression according to the age of presentation. Furthermore, we should consider that IMDs can affect many other organs, including eye, liver, kidney, heart and muscle.

The process for diagnosing IMDs is difficult for an adult neurologist for three main reasons:
1) clinical information is based on the study of children, therefore the child phenotype may not predict the adult phenotype
2) the adult phenotype cannot be clearly predicted by the age of onset and/or the characteristic of the causative mutation (for example, we are following a 40-year-old patient with propionic acidemia and a good outcome. She presented only two episodes of metabolic decompensation in the first two years of age)
3) the range of clinical expression of a disorder may be broader in adults than in children (this is the case of Fabry disease), and can be influenced by age and other risk factors (for example, older patients can have blood hypertension which is not dependent on the genetic disease).

The diagnosis of a treatable IMD in adults should can be achieved only after a detailed biochemical work-up, with specific blood and urine tests and sometimes CSF analysis (for example, neurotransmitters measurement for Segawa dystonia).

There are many specific therapies available for IMDs and they use different approaches:
1. specific diet regimen with the aim of decreasing the concentration of a toxic compound (e.g. PKU, MSUD),
2. inhibition of the synthesis of the toxic compound (e.g. miglustat in Gaucher disease),
3. intravenous administration of the missing enzyme (e.g. Gaucher disease, Fabry disease),
4. competitive inhibition of the enzyme (e.g. in Niemann-Pick type C miglustat acts as a competitive inhibitor of the enzyme, glucosylceramide synthase, which catalyzes the first step in glycosphingolipid synthesis)
5. enzymatic enhancement with cofactors administration (e.g. homocystinuria vitamin B6-dependent),
6. increasing substrate concentration (i.e. folic acid in the methylenetetrahydrofolate reductase deficiency, MTHFR)
7. replacement of the deficient metabolic compound (e.g. serine in the case of the 3-phosphoglycerate dehydrogenase deficiency).

METABOLIC LEUKODYSTROPHIES IN ADULTS

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The term leukoencephalopathy refers to a process that involves predominantly the cerebral white matter pathologically, radiologically and in its clinical presentation. The term leukodystrophy is used to define a group of conditions that are inherited and involve the progressive destruction or loss of previously acquired myelin. The majority of these disorders have a metabolic origin. In recent years with the expansion of MRI imaging and genetic technology a number of the previously unknown underlying genetic causes have been discovered.

Whilst much is written in the paediatric literature about leukodystrophies and their diagnosis, the situation for the adult neurologist is harder, with a larger number of acquired disorders counterbalanced by a detailed table of rare disorders. Many of the leukodystrophies that present in infancy and childhood have a different clinical presentation in adulthood, making their diagnosis difficult.

In this talk I discuss:
• What are the most common acquired white matter disorders in adults (>age 16years)?
• How could an acquired from a genetic (metabolic) disorder be distinguished?
• What are the patterns of clinical presentation and MRI pattern of metabolic leukodystrophies?
• How to investigate in a rational and efficient manner?
• Particular features of some of the adult onset leukodystrophies
• New genetic insights

I will start by giving an example of an adult onset leukodystrophy case that first presented to the multiple sclerosis clinic.

METABOLIC MYOPATHIES IN ADULTS

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Metabolic myopathies usually present with exercise intolerance and acute rhabdomyolysis. An accurate diagnosis may prevent future life threatening attacks of rhabdomyolysis and improve outcome yet diagnosis is often delayed. Management strategies include exercise and diet and avoidance of activities that trigger rhabdomyolysis. The most common metabolic myopathies are McArdle disease, caused by a deficiency of the enzyme muscle glycogen phosphorylase, and disorders of fatty acid oxidation caused by mutations in the genes for CPT2 and VLCAD. Accessing genetic testing for the other rare distal glycolytic disorders is currently difficult, but likely to improve with the availability of next generation sequencing.

MOVEMENT DISORDERS AND INBORN ERRORS OF METABOLISM

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The brain and muscle are often affected by metabolic disorders, due to their complex and demanding metabolism. This is particularly true for adult forms, where the initial manifestation is often neurological or psychiatric. Within the brain, the basal ganglia and cerebellum, with high metabolic rates, are particularly prone to damage. Movement disorders (MD) are thus a common presenting feature or complication in inborn errors of metabolism (IEM). They are reported in up to 1/3 of patients, a figure likely to underestimate their true prevalence. Because MD semiology is complex and difficult, they are often not recognized or classified properly. Adequate identification and classification of MD in IEM is not just an "exciting" intellectual exercise, it helps in the aetiologic diagnosis and improves patient care.

There are two clinical scenarios where this subject may be relevant for the adult Neurologist:
- First we have those patients already diagnosed with an IEM, complicated with a MD, either from onset or during the course of the disease.
- Second we have those patients presenting with MD, due to an underlying yet undiagnosed IEM. These may include patients presenting during childhood who were never diagnosed and patients with adult-onset forms of IEM.

In both groups knowledge about MD and IEM will permit adequate symptomatic treatment, sometimes with a dramatic impact in quality of life. In the second scenario, this knowledge will also help tailoring the diagnostic strategy.

How should we approach patients with MD?
The number of IEM known is myriad (and continuously growing) and MD are likely to have been described, in one or other combination, as a manifestation of most of them. Rather than feeling appalled by this confusing picture, one should strive to be systematic. I advise the following steps:
1. Identify the type of MD (indispensable for guiding symptomatic treatment).
2. Define the mode of presentation
3. Look for associated features, both neurological and systemic.
4. Assess neuroimaging.

This process will eventually lead us towards the cause or, at least, a pathophysiologic category of IEM, thus guiding further ancillary tests. We will also be in a better position to offer symptomatic treatment and prognosis.

Suggested readings:
1. The clinical approach to movement disorders. Abdo WF, van de Warrenburg BP, Burn DJ, Quinn NP, Bloem BR. Nat Rev Neurol. 2010 Jan;6(1):29-37.
2. Clinical approach to treatable inborn metabolic diseases: an introduction. Saudubray JM, Sedel F, Walter JH. J Inherit Metab Dis. 2006 Apr-Jun;29(2-3):261-74.
3. Movement disorders and inborn errors of metabolism in adults: a diagnostic approach. Sedel F, Saudubray JM, Roze E, Agid Y, Vidailhet M. J Inherit Metab Dis. 2008 Jun;31(3):308-18.
4. The monoamine neurotransmitter disorders: an expanding range of neurological syndromes. Kurian MA, Gissen P, Smith M, Heales S Jr, Clayton PT. Lancet Neurol. 2011 Aug;10(8):721-33.
5. Neurologic Wilson's disease. Lorincz MT. Ann N Y Acad Sci. 2010 Jan;1184:173-87.
6. Parkinson's Disease and other Movement Disorders. Edwards M, Bhatia K, Quinn N. Oxford University Press. 2008

RECOGNISING AND TREATING ADULT PATIENTS WITH INHERITED METABOLIC DISEASE

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It is increasingly important for physicians from all specialities to be aware of inherited metabolic diseases. One reason for this is that, with better treatment, more patients are surviving childhood and outgrowing paediatric services. These patients need specialist adult metabolic services to continue their lifelong care. Another reason is that we are increasingly recognising forms of IMDs which can present for the first time in adulthood. This talk will concentrate on metabolic diseases which can present with acute neurological symptoms in adulthood, how they can be recognised and diagnosed, and how they should be treated.

The possibility of a late presentation of an IMD should always be considered for patients presenting with encephalopathy (which can be a psychiatric presentation in adults), rhabdomyolysis, disturbances of acid-base balance, or atypical stroke particularly if these episodes are recurrent and there is no obvious underlying cause. Typically acute decompensation can be triggered by metabolic 'stress' (fasting, intercurrent infection, major surgery, gastrointestinal illness, excessive alcohol or exercise) but a precise underlying precipitant is not always identified. Hypoglycaemia is a fairly unusual initial presentation of IMD in adulthood: due to their mature glycogen stores adults can maintain their blood glucose levels despite significant metabolic disturbance.

Acute encephalopathy, a rapid decrease in conscious level (over hours or days), not secondary to ictal nor syncopal episodes, is the commonest presentation. Initial symptoms are often psychiatric, with reduced cognition / concentration, a change in personality and agitated or aggressive behaviour. There may be neurological findings such as abnormal posturing, abnormal gait and poor coordination. The most common metabolic cause of encephalopathy is hyperammonaemia and if this is not to be missed, all adults who present with acute or acute-on-chronic encephalopathy should have a plasma ammonia level measured promptly. Over 95% of cases of hyperammonemic encephalopathy in adults will be secondary to decompensated hepatic disease. If this can be excluded as a cause then consideration should be given to other causes, and primary defects of the urea cycle are important amongst these. Regardless of the underlying cause, it is essential to start treatment immediately in order to avoid death or long-term neurological damage. The treatment of hyperammonaemia aims to reduce catabolism and ammonia production and to lower plasma ammonia before cerebral oedema develops.

The most common metabolic causes of exercise-induced rhabdomyolysis in adulthood include disorders of glycogen metabolism (eg. glycogen storage disease (GSD) types V or VII) and the fatty acid oxidation disorders (eg. carnitine palmitoyltransferase 2 (CPT2) and very long chain acyl-CoA dehydrogenase (VLCAD) deficiencies). Acute severe rhabdomyolysis should be treated with prompt fluid (saline) replacement, intravenous dextrose and renal support as required.

Stroke or stroke-like events can occur in a number of metabolic disorders including Fabry disease, homocystinuria, mitochondrial disorders, organic acidemias and urea cycle defects. A number of these conditions are treatable so it is important to consider these rare causes of stroke.

In order not to miss an inherited metabolic disease it is important to collect plasma and urine in the acute phase. Tests such as urine organic acids, plasma amino acids and plasma acyl carnitine profiles will need to be sent to specialist labs and further tests may then be required for definitive diagnosis.

LABORATORY INVESTIGATION OF ADULT PARTIENTS WITH INHERITED METABOLIC DISORDERS

Prof. Simon Heales
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Patients with inherited metabolic diseases may not be identified until the adult period due to a number of factors that include failure to diagnose in childhood or a late clinical presentation. Traditionally, specialised metabolic laboratories receive a significant proportion of their workload from paediatric patients. However, an increasing number of samples are now being received from adult patients for diagnostic testing and evaluation of treatment efficacy. In this presentation, I will provide examples from adult patients that reflect the specialist expertise of the laboratories that I work with. These include the inherited disorders of neurotransmitter, mitochondrial and lysosomal metabolism.

Concerning the disorders of dopamine and serotonin metabolism, patients with a pterin related disorder can be identified by a newborn screening programme (hyperphenylalaninaemia). However, sepiapterin reductase deficiency and the autosomal dominant form of GTP cyclohydrolase deficiency are not associated with hyperphenylalaninaemia and so may not be diagnosed until later in life. For such patients, a strong index of suspicion should be pursued as the response to treatment, e.g. monoamine replacement (L-dopa) can be positive. This group of patients can be identified by undertaking a phenylalanine loading test. A positive result from this investigation should be followed by confirmatory mutation analysis. Other disorders of monoamine metabolism such as tyrosine hydroxylase deficiency may be identified by cerebrospinal fluid (CSF) analysis and measurement of the dopamine and serotonin metabolites, homovanillic acid and 5-hydroxyindoleacetic acid respectively

For mitochondrial disorders, it is very well documented that such patients can present over a wide age range. Investigations such as peripheral lactate, lactate pyruvate ratios, urine organic acids can be informative but may also be unremarkable. If a mitochondrial disorder is still suspected then further investigations should include assessment of respiratory chain enzymes and complex V activities in a tissue (muscle) biopsy. Patients with mitochondrial disorders are also at risk of developing a cerebral folate deficiency. Assessment of CSF 5-methyltetrahydrofolate status should therefore be considered.

Patients with Lysosomal storage disorders (LSDs) can also present as paediatric or adult cases. Currently, we are developing robust assays, including those that can work with dried blood spots, in order to screen high risk populations for LSDs such as Pompe and Fabry disease. Additionally, we are increasing our repertoire of plasma/urine biomarkers that will support an enzymatic diagnosis and provide information with regards to the efficacy of treatments such as enzyme replacement therapy.

HISTOLOGICAL STUDIES IN MUSCLE

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The inborn errors of energy metabolism are rare inherited diseases caused by alterations in the catalytic activity of a specific enzyme, activator or transport protein that interfere with the process of metabolism. They may present at any age from neonatal period through adolescence. Since any organ can be affected, they are characterized by the occurrence of a constellation of symptoms and manifestations varying from an acute life-threatening illness to a slowly progressive degenerative disorder.

Skeletal muscle is subject to high metabolic demands and intact metabolic pathways are required for normal muscle function. A large number of genetic defects are known to be related with glycogen and lipid metabolism or mitochondrial function. These disorders, irrespective of the site of the metabolic block, are mainly manifested with exercise intolerance and chronic progressive weakness. Muscle histology is helpful in some of these metabolic diseases and may be therefore included in the diagnostic work-up among the plethora of other tests.

The disorders of glycogen metabolism are the result of abnormal glycogen synthesis or breakdown within muscles or other tissues. Glycogenoses are classified into different types and new entities have been recently described. Muscle biopsy may show excessive deposition of glycogen or only minimal changes. Type II glycogenosis, also known as Pompe disease, involves lysosomal storage of glycogen with intact cytoplasmic glycogen metabolism and pathological changes can vary from a striking vacuolar myopathy in the infantile form, to a fairly normal pattern in some late-onset patients. Phosphorylase (type V) and phosphofructokinase (type VII) deficiency can be easily recognized by the histochemical absence of the respective enzymes. Polyglucosan bodies which are abnormal aggregates consisting of amylopectin-like material in addition to normal glycogen particles may be revealed in branching enzyme deficiency (type IV) and phosphofructokinase deficiency (type VII). Glycogen storage diseases are now expanded to include type 0 and XV caused by defects of glycogen synthesis, also known as “aglycogenoses”, which are histologically characterized by the absence of glycogen.

Muscle lipid disorders are due to lipid dysmetabolism involving defects of intramitochondrial fatty acid transport or β-oxidation and the lipid storage myopathies. Carnitine palmitoyltransferase II deficiency, the most common cause of recurrent rhabdomyolysis in adults, is characterized by nonspecific changes in muscle biopsy without increased lipid droplets. Similarly, very-long-chain acyl-coenzyme A dehydrogenase deficiency may have a fairly normal histological appearance, but immunohistochemistry may be useful in the detection of the enzymatic deficiency. On the contrary, muscle biopsy in primary carnitine deficiency, multiple acyl-coenzyme A dehydrogenase deficiency and neutral lipid storage disease with ichthyosis or myopathy may show striking accumulation of lipid droplets affecting especially type 1 muscle fibers.

Mitochondria are ubiquitously found and their dysfunction can affect multiple tissues and especially those with increased metabolic needs, such as muscle. Mitochondrial myopathy, a well recognized entity, is mainly characterized by easy fatigability and fixed muscle weakness. The histopathological hallmarks in muscle biopsy include the ragged red fibers due to diseased mitochondrial aggregates and the cytochrome oxidase negative fibers.

In conclusion, metabolic myopathies represent a group of heterogeneous disorders which may be a perplexing diagnostic challenge. Although, the development of more conclusive biochemical studies and the advent of molecular analysis have modified the diagnostic strategy in many of these diseases, muscle biopsy remains an essential element in the assessment of patients with suspected metabolic myopathy and may considerably narrow down the spectrum of alternative diagnoses.