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Treatable inborn errors of metabolism causing neurological symptoms in adults

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ABSTRACT

Background: The identification of inborn errors of metabolism (IEM) in adults presenting with a wide range of neurological symptoms is a relatively new field in medicine. We sought to identify which treatable IEM have been diagnosed for the first time in adults and generate a protocol for metabolic screening targeting those treatable disorders.
Methods: Medline/Pubmed searches of English language literature limited to the adult age group were performed. Diseases identified through this search were then compared to previously published lists of treatable IEM in both adults and children.
Results: 85% of the treatable conditions known to cause global developmental delay or intellectual disability in children had reports where the diagnosis of that IEM was made in one or more adult patients with neurological symptoms. Screening tests in blood, urine, CSF and MRI can detect most of these treatable conditions but the diagnostic accuracy of these screening tests in adults is not clear.
Conclusion: Treatable IEM need to be considered in the differential diagnosis of neurological symptoms in patients of any age.

1. Introduction

The presentations of inborn errors of metabolism (IEM) in children have been studied for decades to document the clinical and biochemical phenotypes of these diseases in children. However, the study of IEM presenting in adulthood is a newer field of medicine and much less is known about the phenotypes of adult onset patients. Also, as IEM are rare compared with other diseases that can cause multisystem involvement in adults (such as multiple sclerosis), neurologists are more likely to consider unusual presentations of common diseases than presentations of rare diseases. As there are hundreds of IEM which could potentially cause neurological symptoms such as encephalopathy, dementia, seizures, motor or sensory deficits, and movement disorders in adults, it is not practical to exclude them all. A targeted approach to identify those IEM which are treatable is needed in adults with neurological symptoms in whom an alternate diagnosis has not been reached. A recent comprehensive literature review [1] identified 81 treatable disorders causing global developmental delay/intellectual disability in children but a previously published list of treatable IEM causing neurological disease in adults identified far fewer disorders [2]. As global developmental delay/intellectual disability in children is a sign of brain dysfunction, we reasoned that disorders which affect the brain in children could also affect the brain in adults although the symptoms may be different.

We were interested in 3 questions:

1. Have the treatable IEM reported to cause global developmental delay/intellectual disability in children also been diagnosed in adults?
2. Would these treatable IEM come up if a treating clinician (such as a neurologist or internal medicine specialist) were quickly scanning the literature for disorders causing neurological symptoms in adults?
3. Is the phenotype of neurometabolic disorders diagnosed in adults broad enough to justify non-targeted biochemical screening?

2. Methods

A general search of Medline and Pubmed (1960–2013) was performed using the keywords "neurologic diseases, inborn errors of metabolism, adults, treatment" with the filter of "English language" in place. A disease was considered treatable if disease-specific therapy were available for any of the disease manifestations, even if the neurologic manifestations were not amenable to therapy. For example, some lysosomal diseases such as Fabry disease (OMIM 301500) would be considered treatable as there is a therapy for the somatic manifestations of the disease even though this treatment may not

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alter central nervous system complications. The list of disorders reported to cause neurologic symptoms in adults was then compared with a published systematic literature review of treatable IEM causing intellectual disability in children [1], a previous phenotypic classification of treatable neurological IEM in adults [2] and with updated information provided by an ongoing evaluation of treatable causes of intellectual disability in children [3]. Separate disease-specific searches were performed by one of the authors (SMS) for each disorder listed as causing global developmental delay/intellectual disability in children but which were not identified on the general search to see if any cases diagnosed as adults had been reported. Disorders where the diagnosis had been made in adulthood were included regardless of the age of onset of the symptoms to reflect the clinical situations faced by geneticists who routinely see both children and adults for diagnostic testing.

This paper is not intended to be an analysis of the level of evidence supporting treatment for IEM nor to be a complete review of all reported cases in the literature. The reader is referred to the systematic literature review by van Karnebeek and Stockler [1] for references on the treatment of these disorders as well as an assessment of the level of evidence and the treatment effect. Sample references supporting the utility of therapy have been provided for those disorders which have been added to the list of treatable disorders in children generated by van Karnebeek and Stockler [3] since that publication [4–6].

3. Results

A total of 311 English language references were reviewed and from these, 34 different individual or groups of IEM were identified as potentially being associated with neurologic symptoms in adult patients and for which therapy for some or all of the disease manifestations is available (Table 1). A broad range of phenotypic presentations of some disorders in adults was apparent and examples of these are included in the Discussion. Three disorders (Krabbe disease (OMIM 245200), abetalipoproteinemia (OMIM 200100) and acute intermittent porphyria (OMIM 176000) were identified from the literature search as a treatable cause of neurologic disease in adults but not identified as a cause of global developmental delay/intellectual disability in children [1]. An additional 3 disorders (Fabry disease, ataxia with vitamin E deficiency (OMIM 277460), and the group of fatty acid beta oxidation defects) causing neurological symptoms in adults were not identified through the literature search but by review of a previous publication [2] and are included in Table 1. Forty-four other disorders were identified as causes of intellectual disability in children [1] which did not arise in the general search for disorders causing neurological symptoms in adults (Table 1). However, when separate disease-specific searches for these 44 disorders were performed, 32 of these disorders had one or more cases in the literature where the diagnosis was made in adulthood although the symptoms may have begun in childhood. All but 3 [Smith–Lemli–Opitz syndrome (OMIM 270400), SC4MOL deficiency (OMIM 607545), and VMAT deficiency (OMIM 193001)] of the 12 disorders for which no published cases of diagnoses made in adulthood may be picked up by the screening tests recommended here (Table 2).

4. Discussion

4.1. Outcomes of the literature review

Our literature search has demonstrated 3 points of interest:

1. Almost all of the treatable disorders which cause global developmental delay/intellectual disability in children have been first diagnosed in adult patients.
2. We chose simple key search words that we felt a clinician (such as a neurologist or an internal medicine specialist) might use if they were doing a quick search of the literature for diagnostic possibilities and yet more than half of the treatable diseases which can present in adulthood were identified only through searches specific to the disease. This is likely related to the deliberately vague search terms we chose but does illustrate that lower levels of awareness of these rare disorders amongst adult physicians may result in under-diagnosis of these treatable diseases.
3. The list of treatable IEM diagnosed in adults has expanded greatly in only a few years [2].

4.2. Screening protocol for treatable disorders

A list of tests designed to screen for treatable IEM causing neurological symptoms in adults is shown in Table 2.

Our protocol is not based on specific clinical phenotype. A comprehensive list of treatable disorders organized by phenotype has previously been published [2]. Obviously, in patients with a recognizable clinical phenotype, targeted investigations to confirm the clinical diagnosis should be performed. For example, in a patient presenting with migraine headaches and stroke like episodes, "screening bloodwork" is not appropriate and the clinician may choose to go straight to the appropriate diagnostic test such as mitochondrial DNA analysis to look for MELAS (OMIM 540000) mutations.

In many adults with neurological symptoms, clinical evaluation using history and physical examination may not suggest a specific diagnosis or the diagnostic tests based on the clinical evaluation may be negative. In those cases only, we suggest that a broader spectrum of investigations to ensure that treatable IEM causing neurological diseases are ruled out (Table 2), regardless of the phenotype, for several reasons:

a. Information on disease phenotype derived from the study of children may not predict phenotype in adults. For example, pyruvate dehydrogenase deficiency due to a mutation in PDHA1 (OMIM 312170; a cause of the neurologically devastating condition known as Leigh disease in infants) has been reported in a cognitively normal adult [7].
b. Phenotype in adults can not be predicted by age of onset or characteristics of the mutation. For example, Wortmann et al. demonstrated the same mutation in patients ages 1 and 52 presenting with leukoencephalopathy due to 3-methylglutaconic aciduria (OMIM 250950) [8]. Similarly, two severe mutations (one involving a stop codon) in methylene tetrahydrofolate reductase (OMIM 236250) were demonstrated in a 56 year old woman with severe hyperhomocysteinemia (total homocysteine 170 μmol/L) whose first symptoms did not begin until the age of 51 [9].
c. The range of clinical expression of a condition may be broader in adults than in children — cerebrotendinous xanthomatosis (OMIM 213700; CTX), for example, has been diagnosed in adults presenting with epilepsy only [10], as a movement disorder with or without cognitive impairment [11], and even as atypical Parkinsonism [12].

These examples demonstrate that the treatable IEM in adults cannot be ruled out based on the age of disease onset or the specific type of neurological features so consideration of all treatable diseases should be performed in adults where no diagnosis has been reached.

We have divided the screening tests into those that should be performed in all patients and those which can be used more selectively. We feel that the commonly available tests in blood and urine should be performed in all adults in whom a diagnosis has not been reached and there should be a low threshold for CSF analysis. For the tests that are not readily available or where no screening test is appropriate, clinical judgment should play a role in decision-making. For example, testing for Fabry disease is appropriate in a patient presenting with stroke but may not be appropriate in a patient presenting with an acute encephalopathy who has no extra-neurologic features of the disease and no relevant family history, particularly as it is primarily the