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Movement disorders

Neurometabolic disorders are treatable causes of dystonia

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ABSTRACT

A broad range of rare inherited metabolic disorders can present with dystonia. For clinicians, it is important to recognize dystonic features, but it can be complicated by the mixed and complex clinical picture seen in many neurometabolic patients. Careful phenotyping is the first step towards the diagnosis of the underlying condition and subsequent targeted treatment, further supported by imaging, biochemical diagnostics and the availability of modern diagnostic techniques such as next generation sequencing. As several neurometabolic disorders are treatable causes of dystonia, these should have priority in the diagnostic process. In the symptomatic treatment of dystonia, several therapeutic options are available. Awareness for the occurrence and optimal treatment of dystonia and other movement disorders in neurometabolic conditions is important because these symptoms can have a substantial impact on the quality of life and daily functioning; this effect is not only exerted by the dystonia itself, but also by the frequently associated non-motor features. In this paper, the highlights and key concepts of neurometabolic forms of dystonia are discussed, with a focus on phenomenology, the diagnostic approach, the most important neurometabolic aetiologies, co-occurring non-motor features and therapeutic options.

1. Introduction

Dystonia is one of the most well-known hyperkinetic movement disorders and is defined by "sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures or both. Dystonic movements are typically patterned, twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation" [1].

Dystonia can be a presenting symptom in numerous conditions; the differential diagnosis of dystonia consists of a large number of both acquired and inherited disorders. Examples of acquired causes are drug-induced dystonia and dystonia due to perinatal asphyxia, infections or traumatic and structural brain lesions. However, the list with inherited

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conditions that can cause dystonia largely outnumbers the list with acquired causes. There are many genetic forms of dystonia, these are further divided in primary inherited dystonias, where there are no other systemic or neurological symptoms; and metabolic/degenerative disorders, often presenting with a more complex phenotype. The latter group comprises the largest number of inherited disorders associated with dystonia.

The exact pathophysiology of dystonia is not completely understood. Already in early days, an important role of the basal ganglia was acknowledged; with lesions in these structures leading to dystonia. More recent insights from imaging and neurobiological studies have led to the hypothesis that dystonia is rather a circuit disorder; stating that not only the basal ganglia, but also thalamocortical connections, the brain stem and cerebellum seem to be involved in the pathophysiology of dystonia. It is now thought that dysfunction in any part of this network can give rise to dystonia [2].

The true prevalence of all different types of dystonia is unknown, but it surely is one of the most prevalent hyperkinetic movement disorders. The reported European prevalence for only the primary isolated dystonias amongst adults is 15.2/100,000 [3], which is likely an underestimation and does not include the dystonic patients below 18 years. When focusing on the group of neurometabolic disorders, dystonia is the most prevalent movement disorder in these patients.

In the academic field of movement disorders, the primary inherited disorders, with DYT1 or Oppenheim's dystonia as a flagship, have historically gotten most of the attention both in terms of pathophysiological and therapeutic studies. However, there is growing awareness for the importance of more insight in movement disorders in patients with neurometabolic disorders. Although movement disorders are often not the sole symptom in patients with an inborn error of metabolism (IEM), they are increasingly recognized as having a substantial impact on quality of life and daily functioning, together with the co-occurring non-motor features [4].

In this paper, we will focus on neurometabolic disorders as causes of dystonia in both children and adults, with special attention for the treatable causes. We will discuss the phenomenology, diagnostic approaches including biochemical testing, brain imaging and next generation sequencing (NGS) of dystonia in IEM and give a brief overview of several important neurometabolic aetiologies. We will further touch on the co-occurring non-motor features and discuss therapeutic strategies for neurometabolic dystonia.

2. Phenomenology of neurometabolic dystonia

There are two main routes through which a clinician can encounter neurometabolic forms of dystonia. Either because a patient presents with a movement disorder of an unknown cause, or because a patient with a known metabolic disorder develops a movement disorder. In both situations, correct and timely recognition and classification of the movement disorder is of utmost importance. In patients with an unknown aetiology, a detailed description of the movement disorder phenotype may guide the clinician in the right direction to obtain a diagnosis, of course with due consideration of other clinical and demographic features like age of onset and accompanying signs and symptoms. In patients with a known metabolic disorder, awareness for dystonia and other movement disorders will enable optimal treatment and support [4].

Box 1. Clinical characteristics that might suggest IEM as a cause of dystonia

- Mixed movement disorder phenotype: other movement disorder besides dystonia :
  - e.g. ataxia, parkinsonism, myoclonus, chorea or tremor.
- Other accompanying (non)-neurological signs :
  - e.g. psychomotor retardation or cognitive decline, seizures, eye (movement) abnormalities, organomegaly, skin abnormalities and deafness.
- Most often generalised distribution.
- Usually young age of onset.
- Often acute onset after metabolic decompensation leading to basal ganglia damage, although a more insidious and progressive course can be seen as well.
- In most cases continuous temporal pattern, but can also very well be paroxysmal or influenced by intercurrent illnesses, fatigue, exercise, or eating/fasting.

Thus, careful description of the motor features is essential. Guidance for a good phenomenological description has been provided in the consensus paper on the classification of dystonia, in which five clinical characteristics of dystonia are described: age at onset, body distribution, temporal pattern, coexistence of other movement disorders, and other neurological manifestations [1] (Box 1).

Especially in the case of neurometabolic disorders, detangling the movement disorder phenotype can be challenging. One of the reasons for this complexity is that patients with a metabolic disorder not rarely present with a mixed movement disorder rather than one subtype [5]. So, in patients with a neurometabolic disorder dystonia can be present together with parkinsonism, ataxia, myoclonus, tremor and less often chorea. When dealing with young children, an additional challenge is the distinction between ''involuntary'' movements arising from immaturity of the central nervous system and the presence of a real movement disorder [6].

In addition to mixed movement disorders, the clinical picture of neurometabolic disorders is often complicated by additional neurological and systemic symptoms, such as seizures or psychomotor retardation. It is important to note that the presence of multiple additional symptoms might guide the clinician in the direction of a neurometabolic condition. The most significant clinical clues include eye movement abnormalities, parkinsonian features, dementia, muscle weakness, neuropathy, organomegaly, ophthalmological or skin abnormalities and deafness [7,8].

Characteristics of the dystonia itself that are more frequently associated with a metabolic aetiology include a generalised distribution, usually an early and (sub) acute onset, and mostly a more or less continuous temporal pattern