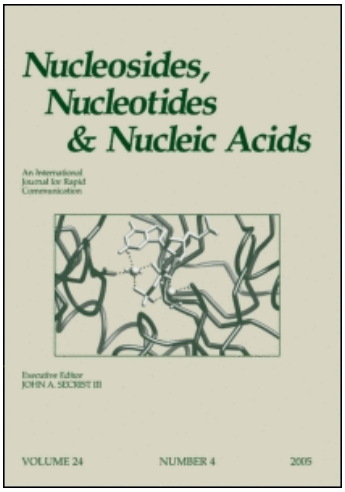

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The Motor Disorder of Classic Lesch-Nyhan Disease

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ABSTRACT

Reports describing the neurological features of Lesch-Nyhan disease (LND) vary widely, thereby implying the involvement of different neurological substrates. The movement abnormalities in 20 patients with LND were investigated. Dystonia was the most frequent and severe movement disorder. At rest, hypotonia was more frequent than hypertonia. These findings are compatible with basal ganglia dysfunction in LND.

Key Words: Dystonia; Choreoathetosis; Ballismus and rigidity.

INTRODUCTION

LND is a neurogenetic disorder caused by congenital deficiency of the purine salvage enzyme hypoxanthine-guanine phosphoribosyltransferase (HPRT). The condition is associated with hyperuricemia and a characteristic neurobehavioral phenotype

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that includes self-injurious behavior, cognitive dysfunction, and motor disability.[1,2] The genetic, metabolic, and behavioral features of the disease have been the focus of a number of detailed studies. However, the nature of the motor disorder has received less attention. While many reports describe LND as choreoathetosis with spasticity, others reports describe dystonia with hypotonia, thereby implying the involvement of different neurological substrates in the pathophysiological process. To define the neurological substrates involved in LND more clearly, a prospective evaluation of the motor disorder was conducted for 20 patients.

MATERIAL AND METHODS

A total of 20 patients with LND was identified by the characteristic clinical phenotype including hyperuricemia, self-injurious behavior, and motor disability. The diagnosis was confirmed by demonstrating residual HPRT enzyme levels of less than 1% in cultured fibroblasts or blood. A neurological examination was performed, with specific attention to the motor features. Dystonia, chorea, ballismus and ataxia were rated on a 0–3-point severity scale (Table 1). The prevalence of hypotonia and hypertonia was also recorded.

RESULTS

The most prominent feature of the motor syndrome in all 20 cases was generalized dystonia, affecting essentially all portions of the body, including face, neck, trunk, and limbs (Fig. 1). Abnormal movements were typically absent at rest; but became obvious with stress, excitement, anticipation, or voluntary movement. Other extrapyramidal signs were also evident, including chorea (13 cases, 65%), and ballismic movements (7 cases, 35%). These rapid flinging movements were most common in the arms, occasionally triggered by the presence of an object near enough to be hit such as the examiner. The following were completely absent: cerebellar ataxia, tremor, and myoclonus.

Resting muscle tone varied considerably in individual cases with time and muscle group evaluated (Fig. 1). Stress or excitement increased muscle tone; but when fully relaxed, hypotonia was present in 17 cases. Increased resting tone was present only in 7 cases, characterized by either rigidity (3 cases) and/or spasticity (5 cases). Spasticity of

Table 1. Rating scale for movement abnormalities in LND.

Score	Description
0	Absent; motor feature not detected
1	Mild; abnormality present but it does not significantly interfere with voluntary acts.
2	Moderate; abnormality significantly interferes with activity, but activity can still be completed with great effort.
3	Severe; abnormality is incompatible with any meaningful activity.

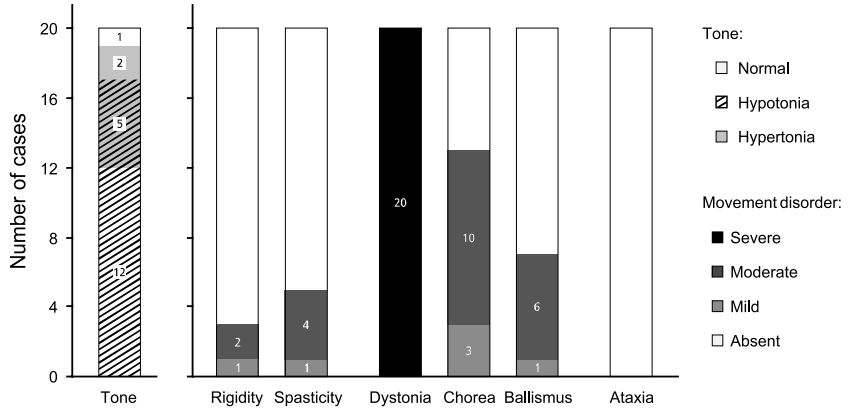

Figure 1. Prevalence and severity of abnormal muscle tone and movements in 20 LND patients.

the legs or one arm was sometimes combined with hypotonia elsewhere. The majority of cases had normal reflexes in arms and legs.

DISCUSSION

The LND patients evaluated in this study demonstrated a characteristic motor syndrome with only minor phenotypic variability. Tone was most frequently decreased, but sometimes coexisted with hypertonia. All patients had a severely disabling dystonia affecting both axial and appendicular muscles. Spasticity was not frequent, and when it occurred, it was usually limited to the legs.

The relatively characteristic motor disorder evident in our prospectively evaluated cases contrasts with the varied descriptions of the motor disorder provided in many prior reports. There are several potential reasons for the discrepancy. First, the majority of cases were described in the non-neurological literature, with very brief or non-critical assessments of the neurological features. Second, movement disorder terminology has been applied using different criteria by different groups for many years, and the majority of cases were described before task forces for nomenclature in movement disorders agreed upon standardized definitions, especially in children. Our assessments were conducted in accordance with the nomenclature described by these task forces. Another potential reason for the varied descriptions of the motor syndrome of LND is its variable expression within patients. It has been our impression that many neurobehavioral signs in patients with LND can be triggered or intensified by anxiety, increasing dystonia, choreoathetosis and tendon reflexes. Anxiety is particularly prominent when the patient encounters a stranger, such as a new caretaker or physician. When anxiety is attenuated, as the patient becomes accustomed to an evaluator, examination features may appear to change during a long visit or over several visits.

In our view, the motor syndrome of LND is best described as dystonia superimposed upon hypotonia. Although other extrapyramidal signs such as chorea

and ballismus may occur, these are less frequent and less severe than dystonia. True spasticity is not common; when it occurs it is often asymmetric or limited to the legs in a pattern suggestive of a cervical or thoracic myelopathy. This interpretation is similar to that provided by other case series where the movement disorder was a prime focus of the study.[3] These findings support the proposal that the majority of motor features of LND might be related to dysfunction of the basal ganglia and related circuitry. Several hypotheses have been presented for a purine-dopamine connection,[2,4] but the exact mechanism by which HPRT deficiency leads to basal ganglia dysfunction remains to be elucidated.

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