A Screening Tool to Quickly Identify Movement Disorders in Patients with Inborn Errors of Metabolism

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ABSTRACT: Background: Movement disorders are frequent in patients with inborn errors of metabolism (IEMs) but poorly recognized, particularly by nonmovement disorder specialists. We propose an easy-to-use clinical screening tool to help recognize movement disorders.

Objective: The aim is to develop a user-friendly rapid screening tool for nonmovement disorder specialists to

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detect moderate and severe movement disorders in patients aged ≥4 years with IEMs.

Methods: Videos of 55 patients with different IEMs were scored by experienced movement disorder specialists (n = 12). Inter-rater agreements were determined on the presence and subtype of the movement disorder. Based on ranking and consensus, items were chosen to be incorporated into the screening tool.

Results: A movement disorder was rated as present in 80% of the patients, with a moderate inter-rater agreement (κ = 0.420, P < 0.001) on the presence of a movement disorder. When considering only moderate and severe movement disorders, the inter-rater agreement increased to almost perfect (κ = 0.900, P < 0.001). Dystonia was most frequently scored (27.3%) as the dominant phenotype. Treatment was mainly suggested for patients with moderate or severe movement disorders. Walking, observations of the arms, and drawing a spiral were found to be the most informative tasks and were included in the screening tool.

Conclusions: We designed a screening tool to recognize movement disorders in patients with IEMs. We propose that this screening tool can contribute to select patients who should be referred to a movement disorder specialist for further evaluation and, if necessary, treatment of the movement disorder. © 2023 The Authors. Movement Disorders published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: inborn errors of metabolism; movement disorders; screening tool; diagnosis

Background

Movement disorders are frequently present in patients with inborn errors of metabolism (IEMs). These genetic disorders can lead to disturbances in the physiology and connectivity of brain areas involved in movement in different ways. In particular, the neurons in the basal ganglia are vulnerable to metal deposition, lysosomal storage disorders, and disorders affecting energy metabolism. Also disorders that involve neurotransmitters, such as dopa-responsive dystonia, frequently cause movement disorders.

Recognition of a movement disorder in patients with an IEM is important. In previous studies it has been shown that movement disorder severity correlates with impairment in quality of life, also in patients with multiple other handicaps, and symptomatic treatment of the movement disorder can positively influence quality of life, even when the underlying IEM is not treatable. In addition, recognition of a movement disorder in a patient with other unexplained symptoms may serve as a clue to an underlying IEM and thus prevent diagnostic and treatment delays.

Unfortunately, recognizing and classifying movement disorders can be complex in patients with an IEM. Patients are often treated by many different specialists, who are not always familiar with involuntary movements, and patients may have combined movement disorder phenotypes, making the classification even more difficult. From previous studies we know that movement disorders are under-recognized in patients with an IEM. For example in patients with Niemann–Pick type C, myoclonus is frequently overlooked due to a mixed movement disorder phenotype. In addition, although galactosemia is traditionally not associated with movement disorders, recent observations demonstrate that movement disorders were present in 48.6% of the patients and were quite debilitating in one-third.

Despite this, only 1 patient in this cohort received specific movement disorder treatment.

To assist physicians who work in the field of metabolic disease to recognize movement disorders in patients with an IEM, this paper presents the development of an easy-to-use clinical screening tool that helps identify in particular moderate and severe movement disorders. This screening tool can contribute to enhanced clinical diagnosis of IEMs and to improvement in quality of life through recognition of movement disorders that may benefit from treatment.

In this study, movement disorder experts evaluated videotapes of patients with IEMs for the presence, nature, and severity of movement disorders. They determined which parts of a standardized neurological examination contributed most to the identification of these abnormal movements. Based on these findings, we developed a rapid screening tool to identify moderate and severe movement disorders in patients with an IEM aged ≥4 years.

Patients and Methods

Patients

Patients with an IEM (n = 55) were included, irrespective of the documented presence of a movement disorder. All participants and/or parents provided written informed consent for sharing the videos with other specialists. The study followed the tenets of the Declaration of Helsinki and was approved by the Medical Ethical Committee of the University Medical Center Groningen (METc 2017/574).

Raters

All raters are international movement disorder specialists (n = 12), including three neurologists trained in
pediatric neurology. They were selected based on their known experience in the movement disorder field.

**Videos and Video-Rating**

Videos had been previously obtained in the context of other clinical studies or as part of the clinical routine. The videos contained different parts of a (standardized) neurological examination based on movement disorders rating scales (Scale for the Assessment and Rating of Ataxia (SARA), Burke–Fahn–Marsden Dystonia Rating Scale, Unified Myoclonus Rating Scale (UMRS), and Unified Parkinson’s Disease Rating Scale [UPDRS]). More information on the included video fragments is presented in Table S1. Patients aged below 4 years were excluded because they require a different neurological evaluation.

Videos were scored blindly and independently. The videos of the 55 patients were rated by each of the three movement disorder specialists, resulting in 165 scores. Prior to the rating, a glossary of terminology used in rating was agreed upon during a meeting (Table S2), and every specialist watched training videos of patients labeled with different types of movement disorders before scoring the study videos. The following items were scored: presence (present or absent) and severity (mild, moderate, and severe) of a movement disorder, dominant movement disorder, other associated movement disorders, five most informative parts of the neurological examination with respect to the presence of a movement disorder (from 1 [most important] to 5), and suggested treatment of the movement disorder. Severity of a movement disorder was based on the impression of the rater. The design of the data collection is shown in Figure S1.

**Development of the Screening Tool**

Properties that were considered to be important for the screening tool were defined. The main aim concerned the ability to detect the presence of a moderate or severe movement disorder. Furthermore, the screening tool should be a short step-by-step tool that is easy to use and to interpret by nonneurologists and should be sensitive to all movement disorder phenotypes. In a second consensus meeting after scoring the videos, the parts of the neurological examination that were considered to be most helpful to detect the presence of a movement disorder were determined by the movement disorder specialists applying the following questions: “Does this examination help detect a movement disorder?” “Can the examination be easily performed and interpreted by nonneurologists?”, and finally “Is the combination of examinations sensitive to all movement disorder phenotypes?” During this meeting, the authors and six of the video raters were present. The other six raters gave their opinion based on the outcome of the meeting. Items were chosen when all participants agreed on the inclusion of that part in the screening tool. In addition, instructions about the performance of the specific tasks and signs of movement disorders that should draw attention were added.11-15

**Statistical Analysis**

Video fragments were ranked based on their contribution to movement disorder identification and pattern recognition as reported by the specialists, irrespective of the movement disorder phenotype.

Consensus about the presence of a movement disorder and the phenotype of the (dominant) movement disorder was defined as an agreement of at least two of three raters. This information was used for further analysis on treatment and severity.

In addition, Fleiss-kappa inter-rater agreement and cluster analyses were performed using SPSS (version 26) to define the inter-rater agreement on the presence of a movement disorder and the specific (dominant) movement disorder phenotype. Kappa ranges from 0 to 0.20 were considered as slight agreement, 0.21 to 0.40 as fair, 0.41 to 0.60 as moderate, 0.61 to 0.80 as substantial, and 0.81 to 1 as almost perfect.16

**Results**

**Patient Characteristics**

Movement disorder specialists scored 55 patients (32 men, mean age: 30.2 years) with 15 different IEMs, comprising 2 children (4–12 years), 16 adolescents (12-18 years), and 37 adults (>18 years). Table S3 presents patient characteristics, and Table S4 provides an overview of the characteristics of the included IEMs.

**Presence of a Movement Disorder and the Movement Disorder Phenotype**

The specialists scored a movement disorder in 130 of the 165 ratings (78.8%), concerning 44 patients (80%) in whom the majority of the specialists concluded that a movement disorder was present and 11 patients (20%) in whom a movement disorder was absent. Severity of the movement disorders varied from mild (57%) to moderate (34.3%) and severe (6.8%). In 5 patients (1.9%), severity was missing.

When considering the consensus of at least two of three raters on the dominant phenotype, dystonia was most frequently scored as the dominant movement disorder (27.3%), followed by ataxia (10.9%), chorea (5.5%), myoclonus (3.6%), parkinsonism (3.6%), and tremor (1.8%). In none of the patients were tics, stereotypies, or other movement disorders, such as spasticity, rated as the dominant phenotype. In 15 patients (27.3%), there was no consensus about the dominant movement disorder phenotype.
Figure 1 presents an overview of the different types of IEMs, the presence of a movement disorder as scored by the majority of the movement disorder specialists, the movement disorder phenotype, and the severity of the movement disorder.

In 92 of the 165 scores (55.8%), more than one movement disorder was rated by the specialists. In 59 (35.8%), there were two movement disorders, in 25 (15.2%) three movement disorders, and in 8 (4.4%) four or more movement disorders. Figure S2 shows the different types of movement disorders for each IEM.

**Inter-Rater Agreement**

A 100% observed agreement (all three raters) between the experts considering the presence of a movement disorder was reached for 39 of the 55 patients (70.9%), of which 35 (63.6%) were considered to have a movement disorder. In 9 patients (16.4%), two raters scored a movement disorder and one did not. The overall inter-rater agreement on the presence of a movement disorder was moderate ($\kappa = 0.420, P < 0.001$). When divided into different age categories, the agreement was moderate for adults ($\kappa = 0.524, P < 0.001$) and children ($\kappa = 0.423, P = 0.101$) and fair for adolescents ($\kappa = 0.205, P = 0.170$).

In 15 patients, at least one of the other raters scored a mild movement disorder, whereas the other raters scored no movement disorder. Of these patients, 7 of 10 patients had galactosemia, 5 of 7 patients had dopa-responsive dystonia (including 3 patients on levodopa [L-dopa] therapy), 1 of 2 patients had propionic academia, 1 of 4 patients had Wilson’s disease, and 1 of 5 patients had glutaric aciduria type 1. In these patients, dystonia was rated most frequently (10 times), followed by myoclonus (5 times) and parkinsonism or chorea (both 3 times). Ataxia, tics, stereotypes, and other disorders affecting movement were all rated once.

When excluding the patients in whom at least one of the raters scored a mild movement disorder, the inter-rater agreement on the remaining 19 patients with moderate or severe movement disorders improved to almost perfect ($\kappa = 0.900, P < 0.001$). In only one patient, two raters found a moderate movement disorder (both parkinsonism), whereas the third rater found no movement disorder. There was no disagreement about the presence of a movement disorder in patients in whom a movement disorder was rated as severe by at least one of the raters.

The inter-rater agreement on the dominant movement disorder phenotype, including the class “no movement disorder,” was fair ($\kappa = 0.241, P < 0.001$). After excluding the distinction between dominant and nondominant movement disorders, there was some improvement in the inter-rater agreement on the different movement disorder phenotypes (Table 1). The best overall inter-rater agreement was reached for ataxia ($\kappa = 0.518, P < 0.001$) and the worst for the rest group “other,” mainly indicating spasticity ($\kappa = 0.185, P = 0.017$).
Indication for Treatment of the Movement Disorder

Figure 2 shows whether the raters considered there was an indication for treatment of the movement disorder for the individual patients, irrespective of the patients’ complaints. In 59 of the 265 scored movement disorders (both dominant and associated phenotypes) (22%), involving 25 patients (45.5%), medical treatment was suggested: dystonia 27 times, myoclonus 11 times, parkinsonism 7 times, tremor 6 times, other (mainly spasticity) 4 times, chorea 3 times, and ataxia and tics once. Furthermore, physical therapy was suggested in 10% of the patients scored with ataxia.

Table 1

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>κ-Value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ataxia</td>
<td>0.518</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chorea</td>
<td>0.423</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>0.325</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dystonia</td>
<td>0.236</td>
<td>0.002</td>
</tr>
<tr>
<td>Tremor</td>
<td>0.279</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>0.248</td>
<td>0.001</td>
</tr>
<tr>
<td>Other</td>
<td>0.185</td>
<td>0.017</td>
</tr>
</tbody>
</table>

Treatment was suggested by the raters in 83.3% of the severe movement disorders, whereas this was the case in only 17.6% of the moderate and 11.3% of the mild movement disorders.

Design of the Screening Tool

Figure 3 presents an overview of the parts of the neurological examination that were found to be most contributive to the decision on whether there was a movement disorder. Observation of the arms (e.g., including arms in rest, arms stretched forward in several positions, and finger-to-nose test); walking, writing, and drawing a spiral; examination of eye movements; and tapping were considered as most important. In Figure S3, the most informative parts of the neurological examination are split out for the patients with and without a movement disorder.

In a subsequent consensus meeting after scoring of the videos, the tasks of walking, observations of the arms, and drawing a spiral were selected for incorporation in the screening tool. The screening tool is shown in Figure 4, including the most important aspects to be considered during the execution of the tasks. The assessment of each clinical feature leads to two possible judgments: “yes” or “no.” To validate the screening tool in a future study, the most lenient ≥1 item cutoff score will be used, indicating the presence of a movement disorder.

FIG. 2. Suggested medical treatment for the different types of movement disorders divided by severity. This flow diagram shows on the left the different types of movement disorders, both dominant and associated phenotypes, that were scored. The color of the line represents the type of movement disorder throughout the figure, and the dimension is proportional to the number of scores (total n = 165). In the center, the scored severity of the movement disorder is shown, and on the right this is further divided into whether the movement disorder specialist thought there was an indication for treatment, and if there was, what kind of treatment they suggested. [Color figure can be viewed at wileyonlinelibrary.com]
Discussion

We developed a screening tool to facilitate the identification of movement disorders in patients with an IEM. This tool contains observation of walking, different positions of the arms, and drawing a spiral. We hypothesize that this tool will help decide which patients need to be referred to a multidisciplinary team, involving at least a movement disorder specialist and a metabolic internist or a pediatrician, for phenotypic refinement and movement disorder management. The tool needs further validation, but as far as we know, this is the first attempt to develop a screening instrument for non-neurologists that can be used in patients with an IEM.

This screening tool is designed to screen for the presence of a movement disorder in general but not for specific movement disorders subtypes. To create the tool, movement disorder specialists scored the presence and the phenotype of movement disorders in patients with an IEM on video. In a consensus meeting, tasks were selected for incorporation in the screening tool, considering that the tool should be sensitive to all movement disorder phenotypes and must be easy to use and to interpret for non-neurologists. Based on these criteria, a step-by-step screening tool consisting of four tasks was created, taking approximately 2 minutes in total. As the main purpose of the screening tool is the identification of moderate and severe movement disorders, these four tasks were considered to be sufficient to fulfill this goal.

A movement disorder was identified in 80% of the patients, and the inter-rater agreement on the presence of a moderate or severe movement disorder was very good. The distinction between no movement disorder and a mild movement disorder seemed to be more difficult. Interestingly, a low consensus about the presence of a mild movement disorder was in particular present in patients with dopa-responsive dystonia and galactosemia. Three of these patients with dopa-responsive dystonia were treated with l-dopa. This may underscore that levodopa treatment effects were very successful in these patients, resulting in mild phenotypes that were hardly discernible for the presence of dystonia by the experts. Analogous to literature, movement disorders in patients with galactosemia can be subtle and may be therefore overlooked even by experts.

Another factor that may have contributed to the relatively low inter-rater agreement in patients with a mild movement disorder was the fact that the experts rated videos instead of evaluating the patient in person and that they did not have any information on the patients’ complaints, limitations in daily life, medical history, diurnal fluctuations, additional investigations, or diagnosis. A study of Van der Salm et al, in which experts had to rate videos of patients with (functional) jerks, showed that the inter-rater agreement increased markedly when more information was available.

The inter-rater agreement on the specific phenotype varied from moderate (ataxia and chorea) to slight (“other”), with a fair agreement for myoclonus, dystonia, tremor, and parkinsonism. The variety can be partially explained by the fact that patients with an IEM often present with complex movement disorder phenotypes. This was also the case in the majority of our participants. Although not focused on movement disorders in IEMs, a study on inter-rater agreement on
mixed movement disorder phenotypes showed an inter-rater agreement for the presence of dystonia, chorea, and stereotypies of, respectively, $\kappa = 0.39$, $\kappa = 0.39$, and $\kappa = 0.22$ in patients with an NMDAR (N-methyl-D-aspartate) antibody-encephalitis. This is consistent with our findings.

In addition, the raters were asked whether they would treat the movement disorder of the individual patients, and in 25 patients (45.5%) treatment was suggested, mainly in patients with a moderate or severe movement disorder. This was irrespective of the patients’ complaints, as no information on this was
provided, meaning that this percentage is not a reflection of real-life practice. However, from earlier studies we know that in patients with an IEM, impaired quality of life is mainly caused by difficulties with physical functioning.⁷ As movement disorders contribute to this, it shows again the importance of adequate recognition and phenotyping of involuntary movements.

This study has some limitations, including the lack of gold standard for the diagnosis of movement disorders. Although electrophysiological testing may help confirm tremor and myoclonus, this was not available for the majority of the included patients. The use of videos instead of examining the patients in real life may also have influenced the outcome, as some symptoms, such as rigidity or spasticity, are not visible on video. Furthermore, the videos were not completely standardized, and therefore, examination segments were variable. Expert agreement would probably further improve when given the opportunity to directly examine the patients live. To end, children were underrepresented in this cohort. However, because input of child neurologists was used in the development of the screening tool, we think that movement disorders in children can be detected using our screening tool as well. In the validation stage, we need to include a larger group of children to confirm this.

In this study, we show that movement disorder specialists highly agree on the presence of moderate and severe movement disorders in patients with IEMs. The recognition of moderate and severe movement disorders is particularly important because treatment was also mainly suggested for these groups. Based on the results, we designed a screening tool to assist nonmovement disorders specialists to recognize involuntary movements in patients aged ≥ 4 years with an IEM. In the near future, we will validate and further design the screening tool to see whether it can be used to select patients who need to be referred to a multidisciplinary team for further evaluation and, if necessary, treatment of the movement disorder.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References


Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site.
Author Roles

L.H.K. and M.R.K.: design, execution, analysis, writing
D.A.S., T.J.K., and M.A.J.T.: design, execution, editing of final version of the manuscript

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