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COMMENTARY

Developmental variability in paediatric *SGCE*-related myoclonus dystonia syndrome

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Myoclonus dystonia syndrome due to a *SGCE* pathogenic variant is a rare condition that typically manifests early in childhood.[1] It is characterized by a motor phenotype combining dystonia and myoclonus of subcortical origin, associated with a high prevalence of psychiatric disorders, particularly anxiety disorders, depression, and obsessive-compulsive disorder.[1] This condition is generally considered minimally progressive in adults,[1] but its natural course in children and adolescents remained largely unknown.

De Francesch et al.[2] offer a longitudinal study over an average follow-up period of 4 years involving 38 patients with myoclonus dystonia from Spanish and Dutch cohorts. The primary finding of this study is the clear progression of motor symptoms over time, affecting both action myoclonus and dystonia.

This study highlights a striking contrast between the progression observed during childhood and adolescence, and the overall stability typically reported in adult patients. It represents an important initial step in characterizing the progressive nature of the disease across the neurodevelopmental trajectory. Notably, the very early onset of motor symptoms (mean age 2–3 years) and their progression, confined to this critical developmental period support the classification of myoclonus dystonia as a neurodevelopmental disorder, although this categorization remains debated. Furthermore, beyond its impact on motor circuit development, the study also suggests dysfunction in the maturation of non-motor circuits. This is supported by a high prevalence of specific learning disorders and the frequent occurrence of psychiatric conditions in young patients — affecting up to 74% of them — including anxiety disorders, obsessive-compulsive disorder, and attention-deficit/hyperactivity disorder.

Longitudinal evaluations of these non-motor symptoms, which has not been thoroughly conducted in this study, would be highly valuable for future research, despite the complexity of execution. Interestingly, this perspective aligns with neuronal-level findings, where several distinctive variations such as larger dendritic spines, more complex morphology, and a higher number of excitatory synapses with greater functional secondary to *SGCE* mutation are shared with other monogenic neurodevelopmental disorders linked to developmental delays or autism spectrum disorders (e.g. *SYNGAP1*, *FMR1*) and schizophrenia (e.g. *SETD1A*), although their significance remains elusive.[3,4] Altogether, we propose that myoclonus dystonia may be considered a neurodevelopmental disorder with mixed neuropsychiatric expression.

The article also raises the point that the neurodevelopmental trajectory of these patients appears heterogeneous. While the general trend points to worsening motor symptoms, it is noteworthy that some young patients experience symptom improvement. These differences in developmental profiles influence therapeutic decisions for each patient, particularly regarding the indication for deep brain stimulation, which remains the most effective treatment for myoclonus dystonia symptoms.[1] The article by De Francesch et al. stresses the importance of identifying biomarkers to predict each patient's developmental trajectory early, paving the way for increasingly personalized medicine. The authors propose that this variability in developmental outcomes may stem from intrinsic factors, such as multiple mutations within *SGCE*, leading to diverse protein dysfunctions, as well as modifiable factors, including epigenetic and environmental influences.

Additionally, compensatory mechanisms that emerge during neurodevelopment (with varying effectiveness across patients) may also contribute to these differences, as suggested by microarchitectural reorganization of the motor cortex and its afferent pathways, which are associated with the severity of motor symptoms.[5] Identifying and addressing modifiable factors, gaining a deeper understanding of the compensatory mechanisms, and developing strategies to enhance them represent significant challenges for the future. Achieving this goal will require multicenter longitudinal studies with larger cohorts and multimodal investigative approaches.

This commentary is on the original article by De Francesch et al. on pages 740–749 of this issue.

DATA AVAILABILITY STATEMENT

No new data were generated or analyzed in support of this research.

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Reverse transcriptase inhibitors in Aicardi-Goutières syndrome: Design and regulatory challenges in clinical trials for rare disease

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Crow et al. report their experience of an open label clinical trial using reverse transcriptase inhibitors in Aicardi-Goutières syndrome (AGS).[1] Despite being a rare disease, there have been significant developments in understanding the biology of AGS.[2] Nine genes have been associated with AGS, that when mutated result in accumulation of DNA or RNA debris and secondary interferon activation. With this molecular understanding, JAK inhibitors, monoclonal interferon antibodies, cGAS inhibitors, and/or reverse transcriptase inhibitors have been proposed to be plausible therapeutic agents.[2] For reverse transcriptase inhibitors, the hypothesis is that inhibition of reverse transcription step in the generation of endogenous retroelements results in less DNA 'debris' and therefore less interferon activation.[1]

The study by Crow et al. was designed to determine safety and biological effects on interferon signalling. Developing therapeutic evidence in rare diseases is challenging and one of the major challenges in this study was compliance. The treatment intervention was short (6 weeks), and a power calculation supported recruitment of 24 patients; yet only 13 patients were recruited, with only four patients completing the full 6-week study protocol. This compliance issue was partly related to the volume of the syrups and the taste.[1] A further challenge was the bureaucratic hurdles that resulted in major delays and contributed to termination of the study with limited conclusions.

The authors described that 'non-clinical factors negatively impacted patient recruitment' and 'structural failings represent a serious impediment to UK paediatric experimental medicine'. Figure 2 in the Crow et al. paper provides a depressing timeline.[1] The study was funded using public funding (Medical Research Council). Medical research ethics committee approval was achieved 9 months after the start of funding and Medicine and Healthcare Regulatory Agency approval was approved 13 months after the start of funding. However, the local research and development approvals for the four different UK sites were not approved until 6 months, 10 months, 18 months, and 20 months after application (Figure 2).[1] The last site only had approval 3 months before the date of last possible patient recruitment.

The COVID-19 pandemic showed what was possible in clinical trials. During a health crisis all ethics and regulatory approvals could be achieved rapidly (sometimes within 24 hours), with agencies quick to provide self-congratulatory commentary.[3] But the heady success of enabling research has now fallen back into bureaucratic, regulatory, and legal delays. This is not exceptional to the UK; in Australia we have countless examples of studies not commencing for 12 to 36 months after funding was awarded, related to regulatory, legal, or multisite transfer agreements. It is 'oft spoken but never written' that slowness in health and university institutional processes can save money (delaying employing

This commentary is on the original article by Crow et al. on pages 750–757 of this issue.