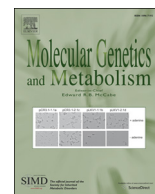




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Commentary

Issues of COVID-19-related distance learning for children with neuronopathic mucopolysaccharidoses

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ABSTRACT

The COVID-19 pandemic has impacted the education of children around the world, forcing a large proportion of teaching to be carried out remotely. The implications of this disruption have yet to be fully elucidated, but initial assessments suggest that COVID-19-related school closures and reliance on virtual learning may have a long-term negative impact on educational attainment and future earnings as well as life expectancy of children in the United States. Among children with neurodegenerative disorders, such as neuronopathic mucopolysaccharidoses (MPS disorders), the effects of the pandemic are likely to be even greater. We aim to shine a spotlight on the impact of COVID-19 on the education, treatment and general wellbeing of children and families affected by MPS disorders by highlighting the important role that educators and therapists play in supporting the neurocognitive function and quality of life of children with neuronopathic MPS disorders. This article will serve as a resource that caregivers, educators, clinicians and therapists can use when considering how best to advocate for children with neuronopathic MPS disorders in circumstances where in-school teaching or in-clinic treatment is compromised or not possible. Given that the current pandemic is likely to have a prolonged course and impact and that similar epidemics and pandemics are a near certainty in the future, it is essential that steps are taken to support the learning and care of children with neuronopathic MPS disorders. We must prioritize strategies to safely resume this fragile community's access to in-person education and supportive care, and to address gaps that have emerged during prolonged pauses in access, whenever possible.

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1. Introduction

The COVID-19 pandemic has impacted the education of children around the world, forcing a large proportion of teaching to be carried out remotely via virtual lessons, with the parent, family member or other adult fulfilling dual roles as a caregiver and teacher for their child at home. The implications of this disruption have yet to be fully elucidated, but initial assessments suggest that COVID-19-related school closures and reliance on virtual learning may have a long-term negative impact on educational attainment and future earnings as well as life expectancy of children in the United States [1,2].

However, these estimates encompass the typically developing population and are not directly applicable to rare disease. Among children with neurodegenerative disorders, such as neuronopathic mucopolysaccharidoses (MPS disorders), the implications of the pandemic are likely to be even greater. Given the degenerative nature of the conditions, these individuals need consistent and, ideally, intensive instruction and treatment to maintain their fragile skills, which if lost, may never be regained, even with compensatory (“make-up”) services. We are a group composed of basic and clinical scientists, rare disease advocates and parents aiming to shine a spotlight on the impact of COVID-19 on the education, treatment and general wellbeing of children and families affected by MPS disorders. We highlight the important role that educators and therapists play in supporting the neurocognitive function and quality of life of children with neuronopathic MPS disorders. We aim to provide a resource that caregivers, educators, clinicians and therapists can use when considering how best to advocate for

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children with neuronopathic MPS disorders in circumstances where in-school teaching or in-clinic treatment is compromised or not possible. This applies both in the short term when many schools are closed, but also during the period when schools begin to reopen, as there are likely to be further interruptions and delays before full school services can resume [3]. The same applies to rehabilitation clinics, which have also had to undergo conversion of in-person to virtual appointments, and varying levels of re-opening to partial capacity [4,5]. In addition to MPS disorders, we hope that several points discussed here will be informative for other rare disease communities.

2. Complexities of neuronopathic change in mucopolysaccharidoses

The MPS disorders are inborn errors of metabolism characterized by the progressive accumulation of glycosaminoglycans in tissues throughout the body, leading to multi-organ dysfunction [6]. There are seven different types of MPS diseases [7]. Some, including MPS I, II, III and VII, have ‘neuronopathic’ phenotypes that are associated with developmental and degenerative functional changes to the central nervous system. The signs and symptoms seen in the neuronopathic MPS disorders encompass global developmental delay and/or progressive impairment of neurocognitive/intellectual and language ability (i.e. regression), behavioral challenges, sleep problems and/or seizures [6,8–15].

The precise neurodevelopmental and neurodegenerative course observed in the neuronopathic MPS disorders varies by phenotype, but a typical pattern includes a period of developmental gains, a plateau phase that may be long or short, followed by the progressive loss of skills [10,16–22]. The age of plateau and decline varies by MPS type and given phenotype [23], and different skill sets may develop and decline at differing times, such as losing the ability to speak words (expressive language) earlier than losing the ability to understand what is said (receptive language) [24]. In MPS II and MPS III, behavioral challenges arise in a similar pattern, and typically diminish after the age of 8–9 years in line with progressive neurocognitive and motor decline [25–27]. Physical manifestations, such as hearing loss and pain due to musculoskeletal or gastrointestinal problems, can further exacerbate the neurocognitive and behavioral challenges experienced by children with these conditions [28]. Examples of typical development trajectories for the neuronopathic phenotypes of MPS I, MPS II and MPS III are shown in Fig. 1. Unfortunately, developmental data for another neuronopathic MPS type (MPS VII) are scarce due to the ultra-rare nature of this form of MPS, so are not included here.

In neuronopathic MPS disorders, school-aged children can experience developmental stagnation or losses in neurocognition, speech and language, and motor skills at different times, in the phases after early developmental gains. The degenerative changes may be subtle and not obvious from day to day, or in some cases from month-to-month observation. School- or therapy-based standardized tools to quantify function often lack the sensitivity to pick up subtle gains and losses, especially when children have severe developmental impairments [29–34]. To illustrate this point, a deterioration in ability to use a pencil may at first appear as needing hand-over-hand (i.e. manually guided) assistance half the time, and eventually appear as needing hand-over-hand assistance most of the time; however this type of loss, which is probably an important sign of a larger neurodegenerative change, cannot be reflected numerically on a standardized school assessment. Instead, this becomes a qualitative description of functional change, which is harder to track and thus assess. Further complicating the challenges to quantifying decline, changes may seem transient for some skills; rather than disappearing completely, a skill may be displayed less frequently or less reliably, until it ceases to be expressed.

Given the complexity of the neurocognitive, motor and behavioral manifestations experienced by children with neuronopathic MPS disorders, these children all require varying permutations of special education programming as well as rehabilitative/supportive interventions, such as speech-language therapy, occupational therapy and/or physical

therapy. The rarity of MPS disorders, which involve a devastating and highly unusual combined developmental and degenerative process, means that it can be difficult for those working with and planning for the affected child to adapt to the challenges presented by these unfamiliar diseases. Therefore, it is critical that educators and therapists have the necessary information and training to understand the disease, and that they collaborate with the families and MPS specialists to understand what approaches are appropriate to develop, maintain and measure skills in neurocognitively fragile children. It is important that children are evaluated regularly by practitioners familiar with both the individual patient and neurodegenerative diseases in general, so that changes can be recognized, and that both clinical and educational interventions can be adapted accordingly. Without careful and consistent monitoring of these outcomes by appropriately trained individuals, it is impossible to determine which interventions are benefiting a child and whether alternative approaches need to be adopted.

2.1. Special education, procedural safeguards and advocacy

Individuals with neuronopathic MPS disorders have unique needs and trajectories requiring careful and informed consideration throughout the special education process. For example, for children with MPS II or MPS III who may be non-verbal or hard of hearing and use sign language to communicate [25], speech/language pathologists trained in using alternative forms of communication (e.g. PECS [picture exchange communication system] boards, sign language, augmentative communication technologies such as communication apps and eye gaze systems) may be required. Similarly, strategies must be put in place to manage the behavioral changes associated with MPS disorders, particularly MPS II and MPS III [35].

In the United States, the Individuals with Disabilities Education Act (IDEA) provides access to a free and appropriate public education (FAPE)¹ for eligible children with disabling conditions, and ensures special education and related services based on an individual child's needs [36]. Successful adherence to IDEA requires a team approach, caregiver participation and caregiver consent in the development of an Individualized Education Program (IEP) to provide a basis upon which the specific needs of each child can be addressed, served, and accommodated in the educational setting. By law, every child's IEP must include measurable goals that may reasonably be achieved in 1 year and a description of how progress toward these goals will be measured [36]. Goals are to be based on the student's present level of academic and/or functional skills.

Whereas for many children, IEP goals center around the acquisition or strengthening of new skills, for individuals with neuronopathic MPS disorders, the natural course of the disease can cause children either to lose or never to acquire the types of skills commonly addressed in IEPs. Additionally, the strengths and needs of MPS-affected children may be substantially different from those of children with other conditions: a situation that risks overlooking or omitting opportunities to address the areas within which a child with MPS may either grow or maintain a skill. Therefore, the IEP should be designed with these highly specialized needs in mind so that educational interventions remain appropriate for their rare conditions, and they are not excluded by nature of their very low or worsening functioning. Importance should also be placed on the families' goals for their child and measures that are meaningful to the child and their caregivers.

Many children with neuronopathic MPS disorders have significantly shortened lifespans and will likely not achieve functional independence

¹ FAPE is met when: (a) services are provided free of cost to families; (b) services are provided in the least restrictive environment; (c) students' goals are sufficiently ambitious and challenging; (d) goals take the child's potential (i.e. existing skills and previous trajectories) into account; (e) goals, services, and supports are individualized to the child's needs and from which the child receives benefit; and (f) the educational program prepares them for further education, employment and independent living.

as adults. Thus, it is critical to balance the goal of learning academics with the children's stimulation, happiness and quality of life. Therefore, it may be appropriate for the IEPs for students with neuronopathic MPS disorders to focus on maintaining skills for, and ensuring access to, pleasurable and engaging activities. Consideration should be given to the physical manifestations of the disease (restricted range of motion, chronic pain, and mobility, visual and hearing impairments) and how these manifestations may be accommodated to enable a fuller participation in class activities.

Along these lines, the provision of an appropriate learning environment, along with routine and structured schedules, can have a positive influence on behavior and quality of life in children with neuronopathic MPS disorders [28,37,38]. As far as possible, these children deserve stimulation and inclusion, even when processes of deterioration have begun. By providing a safe place to try new experiences and engage with their peers, the school environment often provides children with hope, modeling, social opportunities, and stimulation that are not available outside of the school setting. Above all, the unique mix of a purpose-built learning environment, instruction from well-trained teachers and therapists, socialization, structure and consistency gives

young people with neuronopathic MPS disorders a fighting chance of experiencing some of the aspects of childhood that all children deserve.

Caregivers of children with MPS disorders report often having to navigate independently the complexities of special education, while simultaneously not knowing how best to advocate for their child's needs, a situation which may place the educators on the IEP team in the primary role of determining the goals and services for a child with a rare disorder. In such circumstances, it is important that caregivers know that they have access to several procedural safeguards and due process rights guaranteed by IDEA as well as by their state's departments of education (Fig. 2).

2.2. Rehabilitative interventions and supportive therapies

Noted above, children with MPS require not only the expertise and support of multiple domains of special education, but also rehabilitative intervention and/or supportive therapies at a high level of service intensity (i.e. full-time or maximal frequency feasible for the family). In-person speech-language, occupational and physical therapy can help alleviate the physical impact of the disease on learning and daily

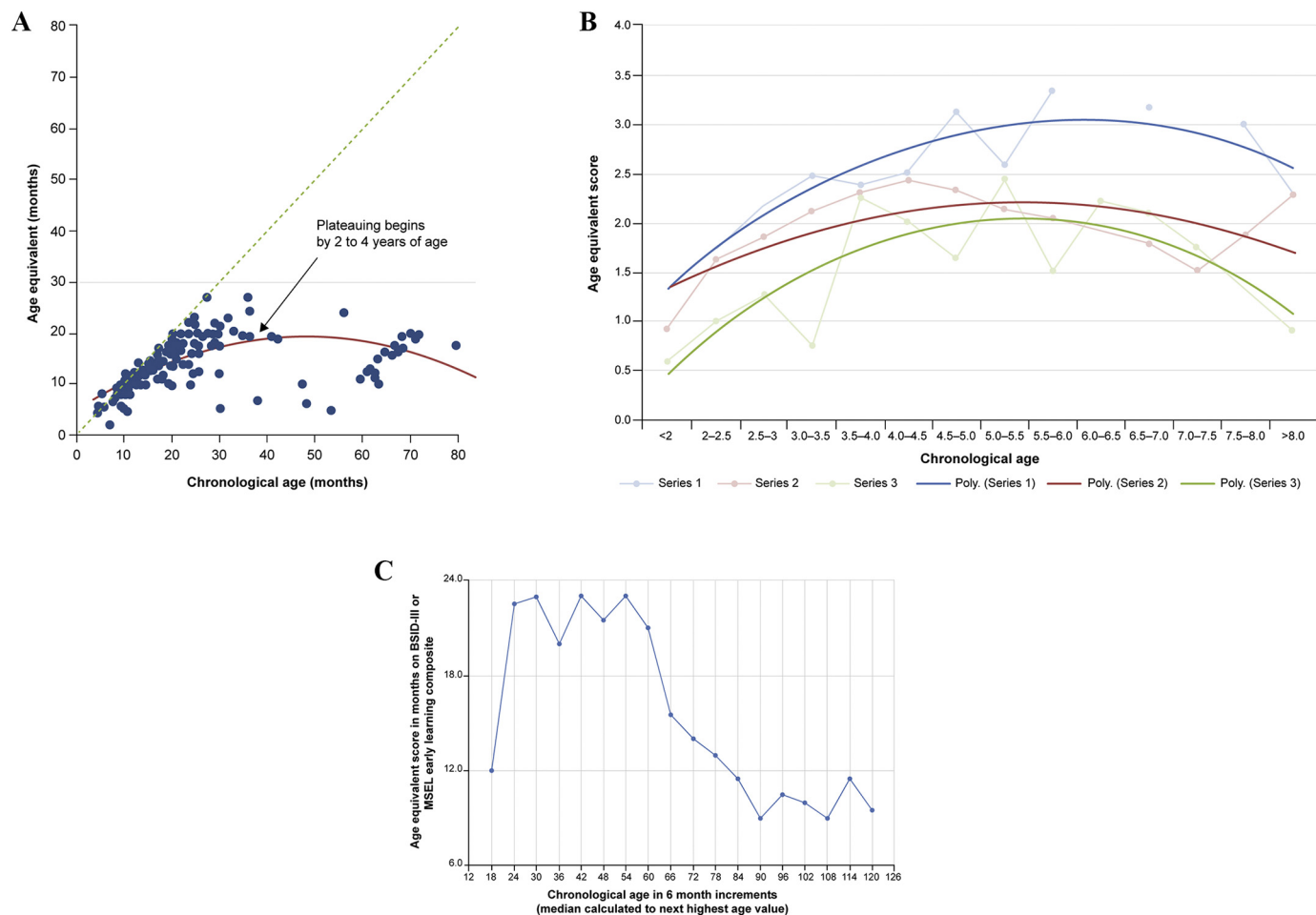


Fig. 1. Neurocognitive development trajectories in patients with (A) mucopolysaccharidoses (MPS) IH (Hurler syndrome), (B) MPS II (Hunter syndrome) and (C) MPS IIIA (Sanfilippo syndrome).

(A) Neurocognitive development in untreated patients with MPS IH. Without treatment, the 30 months age equivalent on the Bayley Scales of Infant Development or the Mullen Scales of Early Learning may be the ceiling in the development of patients with MPS IH. The plateauing line was created by polynomial curve fitting. Reprinted from Shapiro et al [11] with permission from Elsevier.

(B) Neurocognitive development in three studies of patients with neuronopathic MPS II. In series 1, the relatively higher functional level may be due to the multiplicity of tests used in those patients (Griffiths, Merrill Palmer, Terman Merrill, Stanford Binet, and Vineland), many of which are primarily nonverbal. In Series 2 only the Kyoto Scale of Psychological Development (KSPD) was used, including language as well as nonverbal skills. In Series 3, the Mullen Scales of Early Development was used, including language. Scores were medians by age group for each study. Reprinted from Shapiro & Eisengart [23] with permission from Elsevier.

(C) Median age equivalent Scores by 6-month Intervals of chronological age from three studies of MPS IIIA. Each patient was administered either the Bayley Scales of Infant Development-III (Studies 1 and 2) [18,60] or the Mullen Scales of Early Learning (Study 3) [19]. Reprinted from Shapiro & Eisengart [23] with permission from Elsevier.

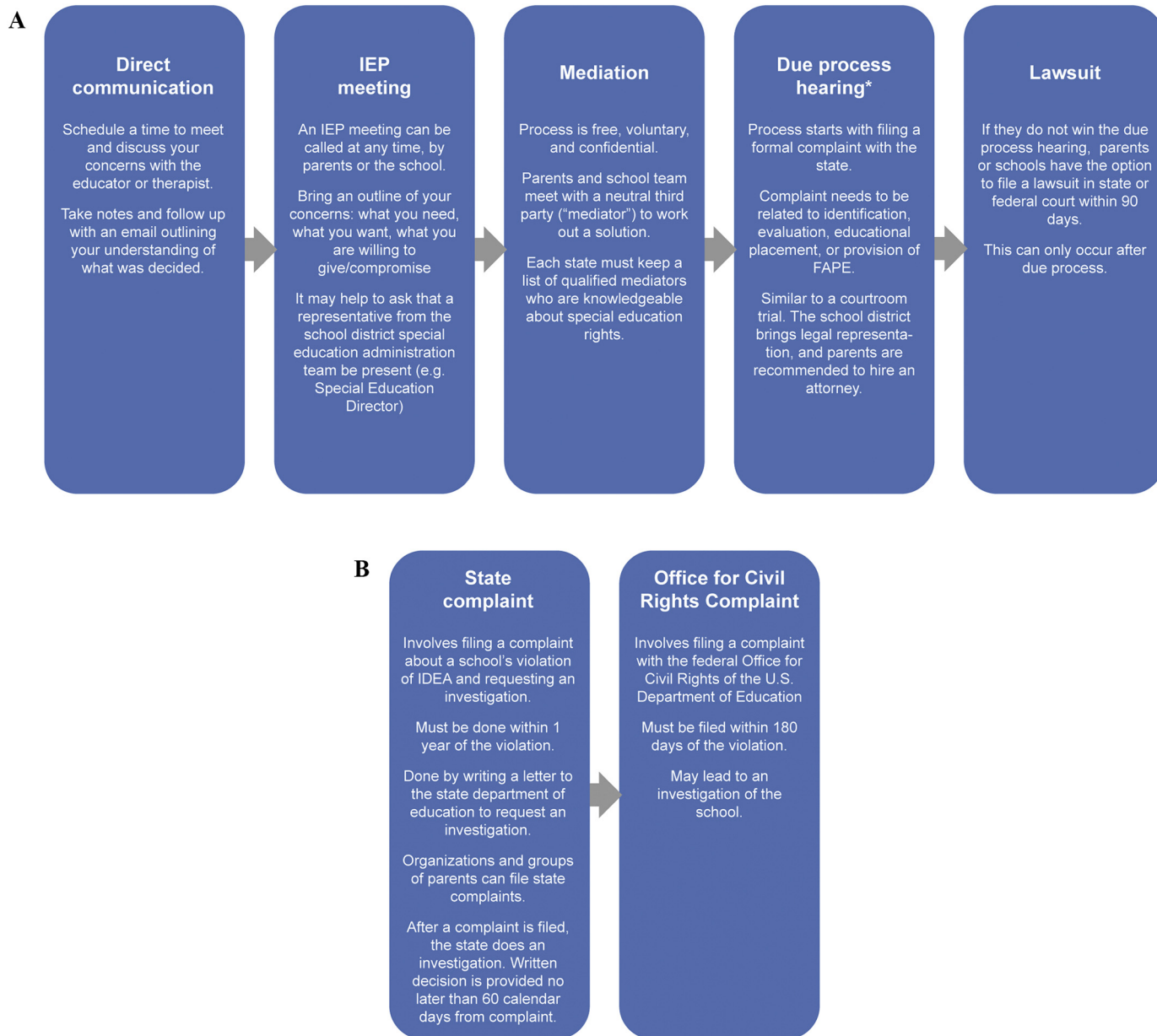


Fig. 2. Processes for resolved individualized education plan (IEP) disputes.

There are several rules of procedure for resolving disputes between caregivers and schools, such as mediation, due process hearings, and appeals to state or federal court. A standard process is summarized in Panel A, although there are additional options that can occur in parallel or in addition to the primary dispute resolution (Panel B). It is important for caregivers to know how to access advocacy, especially when they disagree with how their child's special education program is designed, implemented and monitored. In many states, caregivers can access special education advocates. The Council of Parent Attorneys and Advocates (COPAA; <https://copaa.org>) is an organization dedicated to the interest of disability advocacy. For caregivers who may lack the financial resources to hire an advocate or an attorney, there are Protection and Advocacy Systems (P&As) to protect individuals with disabilities. There are 57 P&As in the United States and its territories. While they are both state and federally funded, they are independent from the government.

*Note: There is a 2-year statute of limitations on filing a complaint. The violation has to have occurred not more than 2 years before the date the parent or public agency knew or should have known about the action that forms the basis of the complaint [36].

function. For example, Al-Sanna and colleagues found that treatment outcomes were augmented in patients with MPS I who received supportive care, such as hearing aids, speech therapy, physical therapy and psychosocial assistance, alongside enzyme replacement therapy [39]. Regular physical therapy may reduce physical discomfort or support some aspects of mobility [25,40,41], which can have beneficial effects on inattention or other behaviors that may be driven by pain or frustration. Studies in patients with Rett syndrome have also found that improvements in physical fitness may be linked with improvements in functional abilities [42,43]. Alternative therapies such as music therapy, adapted swimming, art and sensory rooms can allow

the child to work on maintaining skills while also enjoying the time spent doing it. More periods of pleasure or calm are deserved experiences for these children, and the relief these supports may offer from the unrelenting stress of disease burden can translate to more days with better function.

3. Impact of COVID-19 on neuronopathic MPS disorders

Within days of the World Health Organization (WHO) declaring a pandemic due to the SARS-CoV-2 virus, physical distancing measures were implemented around the globe, leading to the closure of schools,

clinics and therapeutic centers (e.g. art and music therapy centers), resulting in the transition to online self-, teacher- and/or therapist-led learning. The protection these measures provide to the physical health of young people and their families, and the broader community, is laudable; however, such social-contact-focused disease mitigation measures have inadvertently placed a substantial burden on the wellbeing of families with school-aged children in general and children with neurodevelopmental disorders in particular [4,5,44,45]. This is even more pronounced for families affected by neuronopathic MPS diseases, as it has increased the risk of significant and irreversible deterioration of neurocognitive, communication, and motor skills in children with these conditions, for whom the majority do not yet have treatments to halt neuronopathic declines.

The developmental trajectories for neuronopathic MPS disorders shown in Fig. 1 illustrate a best-case scenario: that is, the measurements were taken when individuals with these conditions had access to in-person special education, socialization and therapeutic services such as speech-language, occupational and physical therapy, all of which serve to delay the loss of neurocognitive, communication and motor skills as long as possible. In the broad population, it is assumed that during the COVID-19 pandemic, neurotypical children will have a shift in their educational trajectories due to reduced access to education that normative trends are built upon [1]; however, despite this shift in trajectory, they can still progress and may, in time, catch up once normal in-school education resumes. By contrast, for children with neuronopathic MPS disorders, it is unlikely that they will catch up and return to their previous skill level and resume their previous trajectory. Instead, their trajectory will likely have permanently changed, even with compensatory services. This is because patients with neuronopathic disease do not fit into the typical model of educational or rehabilitative recovery. The majority of neuronopathic MPS types lack treatments to halt the progressive impact of their disease on brain function; hence, once skills are lost, they generally cannot be recovered to previous levels of attainment [23]. Thus, special educators and therapists have a vital role to play in preserving children's neurocognitive skills by ensuring that the learning environment and teaching and support services offered to patients with neuronopathic MPS disorders remain as close as possible to those provided pre-pandemic.

3.1. Special education

From a practical perspective, there is a lack of clarity for educators on what services and supports can and should be provided during a pandemic to children with severe developmental impairments who may need physical prompts and assistance to perform tasks [46,47]. In some school districts, guidance is available regarding the provision of in-home special education [48,49], whereas in others no such direction is given. Even when guidance is available, it is not mandated; it is up to each school district to determine what to do, which risks inequity and inconsistency, particularly because urban and rural communities have been impacted to different extents by COVID-19 prevalence, mandated safety measures, and varied conceptualizations or anxieties regarding the pandemic. The lack of firm direction also places educators in the unenviable position of balancing how strongly to advocate for the needs of their students whilst navigating frequently changing local policy decisions.

When in-home education by a school district is not possible, there is a need to establish firm guidelines on what is expected from educators working in a virtual format with a student who has a neuronopathic disease. Understandably, many educators may not be specifically trained to deliver their service virtually, so they face the burden of learning as they go. In some instances, educators may be further challenged by a requirement to provide hybrid classes, with some students attending in person and some (often those with special needs) joining virtually.

A key facet of special education is regular progress monitoring to determine if students are on-track to meet their IEP goals. Progress

monitoring occurs at regular intervals during the school year, as indicated on the IEP, and a broader evaluation occurs typically every 3 years to establish ongoing need for services. For patients with neuronopathic MPS disorders, measuring progress may mean measuring the rate of regression in neurocognitive, communication, daily living and motor skills. Even under non-pandemic conditions, the measurement of regression is challenging; it requires consistency in observation (by the same person) and an understanding of the student's baseline level. Neither of these requirements can be easily met when transferring to a virtual educational environment, as the circumstances of assessment will be completely different. Furthermore, some categories of assessment, such as physical demonstrations and responses (e.g. hand-over-hand), cannot be measured remotely, and it is not appropriate for parents to assist with the administration of such assessments. Even when home-based assessment is deemed appropriate, parents may be at a loss regarding what to measure and what goals should be targeted, and they may be uncertain how much they should help with physical measures and neurocognitive assessments. This poses a problem, as without reliable assessment of a student's state of function, there is no basis for IEP teams to make decisions about whether adequate supports are being provided to the child to maintain skills or slow their decline. This has direct implications for these students' right to a free and appropriate public education, which is the cornerstone of IDEA.

3.2. Rehabilitative intervention and supportive therapy

Outpatient speech-language, occupational and physical therapists face a similar lack of clarity and guidance regarding what level of support they are expected and able to provide. The extent to which they can assess and provide care for their patients is severely limited in a virtual environment, especially when children with neuronopathic MPS often struggle to attend and engage without one-to-one support from an adult next to them. Caregivers who are not specially trained in these disciplines are often challenged to provide their specialized services to their charges, relying only upon the assistance of a virtual consultation with a therapeutic expert. These circumstances create understandable concern that a therapy may be suboptimal, being delivered by a non-expert who cannot recognize if a therapy is going as planned, nor able to adapt a therapy to the child's responses or needs.

3.3. Distance delivery of educational and therapeutic supports

Changes to the learning environment and daily routines, as well as reduced access to special education and rehabilitative/therapeutic services, have had a substantial impact on families living with neurodevelopmental disabilities [50]. Online educational and therapeutic support delivery depends on having: 1) access to the appropriate technology (i.e. high speed, reliable internet access and a computer that appropriately accommodates the child's sensory and motor needs including consideration of screen size), and 2) a caregiver in the home to support the student's focus or simply to keep them safe. For example, with screen-based lessons or tasks, caregivers must ensure that the child does not walk away, turn off the screen, or switch to a preferred video, and children may need someone with them to direct their attention to instruction and limit their options or choices for activities to avoid the child becoming overwhelmed. Furthermore, screen-based education or therapy assumes a certain level of purely verbal comprehension and attention span that many children with MPS may not have. In general, screens are not an appropriate method of instruction for children with severe impairments who require hands-on instruction and support, even if local regulations recommend or stipulate that they be used. In such situations, the child is not immersed in a learning environment, cannot problem-solve technology issues, and may struggle to understand information given the challenges that hearing, vision, and/or neurocognitive impairments cause in respect to comprehending the distinct (and potentially asynchronous) audio and visual inputs from a

Table 1
Advocacy suggestions, consideration and resources for educators and therapists working with patients with neurodegenerative MPS disorders.

Advocacy suggestion	Considerations	Resources	Description
Consult with a specialist clinician with experience of MPS disorders to ensure services are appropriate and beneficial for children during school closures and hybrid learning models; provide more frequent meetings to monitor progress	Schools must ensure that, to the greatest extent possible, each student with a disability can be provided the special education and related services identified in the student's IEP that allows them to access a free appropriate public education. Additional special accommodations may be required for children with neurodegenerative conditions	IDEA and COVID-19: http://sites.ed.gov/idea/topic-areas/#COVID-19 Wrightslaw COVID-19 resources: https://www.wrightslaw.com/info/covid.index.htm PACER CENTER resources: https://www.pacer.org/special/covid-19.asp#:~:text=PACER%20here%20to%20help,%40pacer.org%20for%20assistance.	Federal guidance on COVID-19 and schools Website with extensive resources and training materials on legal and advocacy issues in special education Website that provides educational and advocacy resources for families to support students with disabilities during COVID-19
Collaborate with local school districts to ensure equitable access to school-based services	If schools are providing educational opportunities to general education students, the school must ensure that students with disabilities also have equal access to the same opportunities, including the provision of Free Appropriate Public Education (FAPE) ^a	IDEA and COVID-19: http://sites.ed.gov/idea/topic-areas/#COVID-19 Wrightslaw COVID-19 resources: https://www.wrightslaw.com/info/covid.index.htm	See above
Ensure special education and associated services align to the specific needs and interests of each student	Standard screen-based virtual teaching formats used with neurotypical children may not be suitable for children with neurodegenerative MPS disorders, particularly those with visual or hearing impairment	National Association of School Psychologists: https://www.nasponline.org/resources-and-publications/resources-and-podcasts/covid-19--resource-center/special-education--resources Complex Child: https://complexchild.org/editions/covid-info/	Guidance on COVID-19 special education and service delivery
Considerations for post-COVID return to school for students with disabilities and special healthcare needs	To facilitate adaptation to returning to the school environment, educators should prioritize social-emotional wellbeing over academic goals	American Foundation for the Blind: https://www.afb.org/blog/entry/accessible-education-resources American Speech-Language-Hearing Association: https://www.asha.org/aud/tips-for-helping-students-with-hearing-loss-in-virtual-and-in-person-learning-settings/ National Association of School Nurses: https://schoolnursesnet.nasn.org/covid19ref/school-reopening-closing	COVID-19 resources and information designed for medically complex children and children with disabilities Virtual learning resources for children with visual impairments Virtual learning tips for children who are deaf/Deaf or hard of hearing
Provide families with information and support to help manage the challenges of home-schooling children with neurodegenerative MPS disorders	Caregivers have had to transition rapidly to the role of special needs aide without appropriate training. Practical and psychological support is necessary and invaluable	American Speech-Language-Hearing Association: https://www.asha.org/aud/tips-for-helping-students-with-hearing-loss-in-virtual-and-in-person-learning-settings/ The Arc: https://thearc.org/covid American Academy of Pediatrics Council on Children with Disabilities: https://www.healthychildren.org/English/health-issues/conditions/COVID-19/Pages/COVID-19-Youth-with-Special-Health-Care-Needs.aspx Family Voices: https://familyvoices.org/covid19/	Considerations for post-COVID return to school for students with disabilities and special healthcare needs In-person post-COVID learning tips for children who are deaf/Deaf or hard of hearing COVID-19 resources for people with disabilities, families and service providers COVID-19 information for families of children and youth with special healthcare needs

^a Under IDEA, public schools are required to provide each child with a disability with a free appropriate public education in the least restrictive environment, at no cost to the child's parents. An educational program is "appropriate" when:

- Goals are sufficiently ambitious and challenging
- Goals take the student's "potential" into account
- Individualized to the child's needs and from which the child receives benefit
- Prepares them for further education, employment and independent living.

FAPE standards require adequate foundational (baseline) assessments from which to base goals. IDEA, Individuals with Disabilities Education Act; IEP, individualized education plan; MPS, mucopolysaccharidoses.

screen and computer-based interface. Some students cannot focus on a small screen, such as a tablet, and if they can, they may not know where to focus – at the teacher or the material the teacher is pointing to/interacting with. In instances such as these, caregivers, educators and the IEP team should assess whether the legal definition and requirement for free and appropriate public education is being met. In therapeutic outpatient clinics, feasibility of in-person services should be evaluated in partnership with the family and the managing MPS specialist.

3.4. Caregiver and family burden

It is often assumed that families have the skills, resources (financial and otherwise) and time to fill gaps in their child's education and therapy needs when in-school teaching and in-clinic therapy are not available. To care for and teach their child at home full-time, a parent may need either to take time away from work – putting at risk their employment, financial security and access to medical care – or take on the cost of hiring additional help to assist their child with online learning. Even in 'normal' times, ensuring access to what are guaranteed educational opportunities can place families under significant financial stress, with one study estimating that in 2019 alone families affected by rare diseases faced indirect costs of \$10B associated with homeschooling, missing schooling and special education [51]. When required additional help with special education and in-home therapy is not available, it also means that caregivers must be quickly trained as a special needs aide or therapist, following the instructions provided in writing or via video calls with educators and therapists. This adds emotional burden and frustration to both the caregiver and the child as the distinctions between caregiver and teacher or therapist, and home and school or clinic, become blurred. While these stressors have been present for all students and families participating in virtual learning, the realities are even more stark for caregivers of students with neuronopathic MPS disorders, who often need intensive, 24-h supervision and struggle to understand why their lives have suddenly changed. This excessive caregiver burden and social isolation is a longstanding challenge documented in the MPS community pre-pandemic [24,35,38,52], but the abrupt and prolonged absence of typical educational and social supports has placed an exponential level of stress on caregivers and stretched coping abilities to the maximum within families of children with neurodegenerative and neurobehaviorally impairing diseases [53]. Furthermore, the potential to achieve respite through in-person engagement with other parents or to alleviate a child's hyperactivity through physical activity outside is limited during pandemic lockdowns [35].

While the strain on families, educators and therapists is clear, it should be remembered that at the center of the COVID-19-associated disruption are the children, who are missing out on the stimulation and social interaction with teachers, friends and peers that school provides [54]. COVID-19 has negatively impacted the emotional wellbeing of the general population [54–56], with many experiencing feelings of grief for the loss of normal ways of life [57]. This impact is doubtless much worse on students with neuronopathic MPS disorders, who have a reduced understanding of why their worlds have suddenly changed and who have a finite window within which to enjoy their childhoods while their neurocognitive and motor skills still allow. For non-verbal patients who cannot express themselves, the emotional burden, and the ensuing intensity of their likely behavioral responses, will be greater still.

4. Call to action

To prevent further disparities between neurotypical children, neurodiverse children who do not decline, and those with rare and progressive neuronopathic disorders, the special education and supporting care community must advocate for stronger action to ensure that the educational, physical and behavioral needs of these children are addressed and met during both school and clinic closures, as well as during

their reopening. Particularly in cases when the reopening of schools and clinics is incremental and/or staggered, the in-person attendance of children with rare and neuronopathic conditions should be prioritized if these students are otherwise medically cleared to attend. To ensure they continue to access FAPE, children who cannot respond to virtual learning models must be provided with alternatives. A checklist of approaches that educators and therapists may consider when advocating for children with neuronopathic MPS disorders is provided in Table 1, along with links and descriptions of available resources to support these efforts.

It is acknowledged that in the context of an ongoing pandemic, a uniform return to a previous norm of education practices is unrealistic in the short-term, and that incremental changes will be needed to align to specific local policies. The U.S. Centers for Disease Control and Prevention (CDC) recently released guidance for safe in-person instruction that emphasized health equity considerations in opening schools, emphasizing that school reopening plans take into account groups that have been disproportionately affected by COVID-19, including students with disabilities, and that these plans provide "fair access to healthy educational environments" [58]. The unmet educational needs of patients with neuronopathic MPS disorders means that a flexible and pragmatic approach is warranted. For each student, we would encourage educators, clinicians and IEP teams to consider what supports a child needs to access a free and appropriate public education and whether a deviation from these supports due to COVID-19 is both ethical and unavoidable.

5. Conclusion

Given that the current pandemic is likely to have a prolonged course and impact and that similar epidemics and pandemics are a near certainty in the future [59], it is essential that steps are taken to support the learning and care of children with neuronopathic MPS disorders; the failure of which adversely impact these students and their families. We must prioritize strategies to safely resume this fragile community's access to in-person education and supportive care whenever possible. Concurrently, we must also advocate for resources to support appropriate in-home teaching and supportive care when necessary or desired by families to address a child's higher risk for negative outcomes associated with infection during public health emergencies.

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References

- [1] A.D. Benner, R.S. Mistry, Child development during the COVID-19 pandemic through a life course theory lens, *Child Dev. Perspect.* 14 (2020) 236–243.
- [2] D.A. Christakis, W. Van Cleve, F.J. Zimmerman, Estimation of US children's educational attainment and years of life lost associated with primary school closures during the coronavirus disease 2019 pandemic, *JAMA Netw. Open* 3 (2020), e2028786.
- [3] C. Binkley, Survey: Even as schools reopen, many students learn remotely, *AP News* (2021) <https://apnews.com/article/survey-schools-reopen-many-students-still-learn-remotely-e4d47c469e5bbd96868766771064f620>.
- [4] R. Baweja, S.L. Brown, E.M. Edwards, M.J. Murray, COVID-19 pandemic and impact on patients with autism spectrum disorder, *J. Autism Dev. Disord.* (2021) <https://doi.org/10.1007/s10803-10021-04950-10809>.
- [5] A.A. Eshraghi, C. Li, M. Alessandri, D.S. Messinger, R.S. Eshraghi, R. Mittal, et al., COVID-19: overcoming the challenges faced by individuals with autism and their families, *Lancet Psychiatry* 7 (2020) 481–483.
- [6] E.F. Neufeld, J. Muenzer, The mucopolysaccharidoses, in: C.R. Scriver, A.L. Beaudet, W.S. Sly, D. Valle (Eds.), *The Metabolic and Molecular Bases of Inherited Disease*, McGraw-Hill, New York, NY, USA 2001, pp. 3421–3452.
- [7] B. Celik, S.C. Tomatsu, S. Tomatsu, S.A. Khan, Epidemiology of Mucopolysaccharidoses Update, *Diagnostics* (Basel) 11, 2021.
- [8] M.C. Bax, G.A. Colville, Behaviour in mucopolysaccharide disorders, *Arch. Dis. Child.* 73 (1995) 77–81.
- [9] J.A. Gilkes, C.D. Heldermon, Mucopolysaccharidosis III (Sanfilippo syndrome) – disease presentation and experimental therapies, *Pediatr. Endocrinol. Rev.* 12 (Suppl. 1) (2014) 133–140.
- [10] J.B. Holt, M.D. Poe, M.L. Escolar, Natural progression of neurological disease in mucopolysaccharidosis type II, *Pediatrics* 127 (2011) e1258–e1265.
- [11] E.G. Shapiro, S.A. Jones, M.L. Escolar, Developmental and behavioral aspects of mucopolysaccharidoses with brain manifestations – neurological signs and symptoms, *Mol. Genet. Metab.* 122S (2017) 1–7.
- [12] E.G. Shapiro, L.A. Lockman, M. Balthazor, W. Krivit, Neuropsychological outcomes of several storage diseases with and without bone marrow transplantation, *J. Inher. Metab. Dis.* 18 (1995) 413–429.
- [13] E.G. Shapiro, I. Nestrail, K. Rudser, K. Delaney, V. Kovac, A. Ahmed, et al., Neurocognition across the spectrum of mucopolysaccharidosis type I: age, severity, and treatment, *Mol. Genet. Metab.* 116 (2015) 61–68.
- [14] S.P. Wallace, C.A. Prutting, S.E. Gerber, Degeneration of speech, language, and hearing in a patient with mucopolysaccharidosis VII, *Int. J. Pediatr. Otorhinolaryngol.* 19 (1990) 97–107.
- [15] G. Wegrzyn, J. Jakobkiewicz-Banecka, M. Narajczyk, A. Wisniewski, E. Piotrowska, M. Gabig-Ciminska, et al., Why are behaviors of children suffering from various neuronopathic types of mucopolysaccharidoses different? *Med. Hypotheses* 75 (2010) 605–609.
- [16] D. Buhman, K. Thakkar, M. Poe, M.L. Escolar, Natural history of Sanfilippo syndrome type A, *J. Inher. Metab. Dis.* 37 (2014) 431–437.
- [17] J.H. Seo, T. Okuyama, E. Shapiro, Y. Fukuhara, M. Kosuga, Natural history of cognitive development in neuronopathic mucopolysaccharidosis type II (Hunter syndrome): contribution of genotype to cognitive developmental course, *Mol. Genet. Metab. Rep.* 24 (2020) 100630.
- [18] E.G. Shapiro, I. Nestrail, K.A. Delaney, K. Rudser, V. Kovac, N. Nair, et al., A prospective natural history study of mucopolysaccharidosis type IIIA, *J. Pediatr.* 170 (278–287) (2016) e271–e274.
- [19] K.V. Truxal, H. Fu, D.M. McCarty, K.A. McNally, K.L. Kunkler, N.A. Zumbege, et al., A prospective one-year natural history study of mucopolysaccharidosis types IIIA and IIIB: implications for clinical trial design, *Mol. Genet. Metab.* 119 (2016) 239–248.
- [20] C.B. Whitley, M. Cleary, K. Eugen Mengel, P. Harmatz, E. Shapiro, I. Nestrail, et al., Observational prospective natural history of patients with Sanfilippo syndrome type B, *J. Pediatr.* 197 (2018) 198–206 (e192).
- [21] J.E. Wraith, M. Scarpa, M. Beck, O.A. Bodamer, L. De Meirleir, N. Guffon, et al., Mucopolysaccharidosis type II (Hunter syndrome): a clinical review and recommendations for treatment in the era of enzyme replacement therapy, *Eur. J. Pediatr.* 167 (2008) 267–277.
- [22] I.D. Young, P.S. Harper, The natural history of the severe form of Hunter's syndrome: a study based on 52 cases, *Dev. Med. Child Neurol.* 25 (1983) 481–489.
- [23] E.G. Shapiro, J.B. Eisengart, The natural history of neurocognition in MPS disorders: a review, *Mol. Genet. Metab.* (2021) <https://doi.org/10.1016/j.ymgme.2021.1003.1002>.
- [24] J.B. Eisengart, K.E. King, E.G. Shapiro, C.B. Whitley, J. Muenzer, The nature and impact of neurobehavioral symptoms in neuronopathic Hunter syndrome, *Mol. Genet. Metab. Rep.* 22 (2020) 100549.
- [25] J. Muenzer, M. Beck, C.M. Eng, M.L. Escolar, R. Giugliani, N.H. Guffon, et al., Multidisciplinary management of Hunter syndrome, *Pediatrics* 124 (2009) e1228–e1239.
- [26] M.J. Valstar, S. Neijs, H.T. Bruggenwirth, R. Olmer, G.J. Ruijter, R.A. Wevers, et al., Mucopolysaccharidosis type IIIA: clinical spectrum and genotype-phenotype correlations, *Ann. Neurol.* 68 (2010) 876–887.
- [27] I.D. Young, P.S. Harper, Psychosocial problems in Hunter's syndrome, *Child Care Health Dev.* 7 (1981) 201–209.
- [28] M.L. Escolar, S.A. Jones, E.G. Shapiro, D.D.G. Horovitz, C. Lampe, H. Amartino, Practical management of behavioral problems in mucopolysaccharidoses disorders, *Mol. Genet. Metab.* 122S (2017) 35–40.
- [29] K.A. Delaney, K.R. Rudser, B.D. Yund, C.B. Whitley, P.A. Haslett, E.G. Shapiro, Methods of neurodevelopmental assessment in children with neurodegenerative disease: Sanfilippo syndrome, *JIMD Rep* 13 (2014) 129–137.
- [30] E.G. Shapiro, C.B. Whitley, J.B. Eisengart, Beneath the floor: re-analysis of neurodevelopmental outcomes in untreated Hurler syndrome, *Orphanet J. Rare Dis.* 13 (2018) 76.
- [31] J.H. van der Lee, J. Morton, H.R. Adams, L. Clarke, B.J. Ebbink, M.L. Escolar, et al., Cognitive endpoints for therapy development for neuronopathic mucopolysaccharidoses: results of a consensus procedure, *Mol. Genet. Metab.* 121 (2017) 70–79.
- [32] J.H. van der Lee, J. Morton, H.R. Adams, L. Clarke, J.B. Eisengart, M.L. Escolar, et al., Therapy development for the mucopolysaccharidoses: updated consensus recommendations for neuropsychological endpoints, *Mol. Genet. Metab.* 131 (2020) 181–196.
- [33] H.R. Martin, M.D. Poe, D. Reinharstsen, R.E. Pretzel, J. Roush, A. Rosenberg, et al., Methods for assessing neurodevelopment in lysosomal storage diseases and related disorders: a multidisciplinary perspective, *Acta Paediatr.* 97 (2008) 69–75.
- [34] M.J. Valstar, J.P. Marchal, M. Grootenhuis, V. Colland, F.A. Wijburg, Cognitive development in patients with mucopolysaccharidosis type III (Sanfilippo syndrome), *Orphanet J. Rare Dis.* 6 (2011) 43.
- [35] F. Hoffmann, S. Hoffmann, K. Kunzmann, M. Ries, Challenging behavior in mucopolysaccharidoses types I-III and day-to-day coping strategies: a cross sectional explorative study, *Orphanet J. Rare Dis.* 15 (2020) 275.
- [36] IDEA: Individuals with Disabilities Education Act, US Department of Education, 2004 <https://sites.ed.gov/idea/>.
- [37] M.A. Cleary, J.E. Wraith, Management of mucopolysaccharidosis type III, *Arch. Dis. Child.* 69 (1993) 403–406.
- [38] J. Roberts, C. Stewart, S. Kearney, Management of the behavioural manifestations of Hunter syndrome, *Br. J. Nurs.* 25 (2016) 26–30 22, 24.
- [39] N.A. Al-Sanna, L. Bay, D.S. Barbooth, Y. Benhayoun, C. Goizet, N. Guelbert, et al., Early treatment with laronidase improves clinical outcomes in patients with attenuated MPS I: a retrospective case series analysis of nine sibships, *Orphanet J. Rare Dis.* 10 (2015) 131.
- [40] A. Tytki-Szymanska, J. Marucha, A. Jurecka, M. Syczewska, B. Czartoryska, Efficacy of recombinant human alpha-L-iduronidase (laronidase) on restricted range of motion of upper extremities in mucopolysaccharidosis type I patients, *J. Inher. Metab. Dis.* 33 (2010) 151–157.
- [41] V. Valayannopoulos, F.A. Wijburg, Therapy for the mucopolysaccharidoses, *Rheumatology* (Oxford) 50 (Suppl. 5) (2011) v49–v59.
- [42] M. Lotan, E. Isakov, J. Merrick, Improving functional skills and physical fitness in children with Rett syndrome, *J. Intellect. Disabil. Res.* 48 (2004) 730–735.
- [43] J. Gleason, W. Ross, A. Fossi, H. Blonsky, J. Tobias, M. Stephens, The devastating impact of Covid-19 on individuals with intellectual disabilities in the United States, *NEJM Catal. Innov. Care Deliv.* (2021) <https://doi.org/10.1056/CAT.1021.0051>.
- [44] E. Di Giorgio, R. Polli, M. Lunghi, A. Murgia, Impact of the COVID-19 Italian lockdown on the physiological and psychological well-being of children with Fragile X syndrome and their families, *Int. J. Environ. Res. Public Health* 18 (2021) 5752.
- [45] S. Shorey, L.S.T. Lau, J.X. Tan, E.D. Ng, A. Ramkumar, Families with children with neurodevelopmental disorders during COVID-19: a scoping review, *J. Pediatr. Psychol.* (2021) 514–525.

- [46] P. Tremmel, R. Myers, D.A. Brunow, B.L. Holt, Educating students with disabilities during the COVID-19 pandemic: lessons learned from commerce independent school district, *Rural Spec. Educ. Q.* 39 (2020) 201–210.
- [47] J.K. Frederick, G.R. Raabe, V.R. Rogers, J. Pizzica, Advocacy, collaboration, and intervention: a model of distance special education support services amid COVID-19, *Behav. Anal. Pract.* 13 (2020) 1–9.
- [48] L. Leanmanczyk, KARE 11 Investigates: MN allows in-home help for special education students, KARE 11, 2020 <https://www.kare11.com/article/news/investigations/kare-11-investigates-mn-allows-in-home-help-for-special-education-students/89-cf0d4fd8-7ec4-4481-b2fa-4f6b8f31adba>.
- [49] A.M.I. Lee, Special Education and the Coronavirus: Legal FAQs about IEPs, <https://www.understood.org/en/school-learning/special-education-coronavirus-faqs> 2020.
- [50] A. Masi, A. Mendoza Diaz, L. Tully, S.I. Azim, S. Woolfenden, D. Efron, et al., Impact of the COVID-19 pandemic on the well-being of children with neurodevelopmental disabilities and their parents, *J. Paediatr. Child Health* (2021) <https://doi.org/10.1111/jpc.15285>.
- [51] The National Economic Burden of Rare Disease Study, EveryLife Foundation For Rare Diseases, https://everylifefoundation.org/wp-content/uploads/2021/02/The_National_Economic_Burden_of_Rare_Disease_Study_Summary_Report_February_2021.pdf 2021.
- [52] E. Shapiro, C.M. Lourenco, N.O. Mungan, N. Muschol, C. O'Neill, S. Vijayaraghavan, Analysis of the caregiver burden associated with Sanfilippo syndrome type B: panel recommendations based on qualitative and quantitative data, *Orphanet J. Rare Dis.* 14 (2019) 168.
- [53] M. Kowanda, L. Cartner, C. Kentros, A.R. Geltzeiler, K.E. Singer, W.C. Weaver, et al., Availability of services and caregiver burden: supporting individuals with neurogenetic conditions during the COVID-19 pandemic, *J. Child Neurol.* (2021) <https://doi.org/10.1177/08830738211001209> PMID: 33829918 PMCID: PMC8033176.
- [54] M.C. Cardenas, S.S. Bustos, R. Chakraborty, A 'parallel pandemic': the psychosocial burden of COVID-19 in children and adolescents, *Acta Paediatr.* 109 (2020) 2187–2188.
- [55] A. Ammar, P. Mueller, K. Trabelsi, H. Chtourou, O. Boukhris, L. Masmoudi, et al., Psychological consequences of COVID-19 home confinement: the ECLB-COVID19 multicenter study, *PLoS One* 15 (2020), e0240204.
- [56] M.W. Gallagher, M.J. Zvolensky, L.J. Long, A.H. Rogers, L. Garey, The impact of Covid-19 experiences and associated stress on anxiety, depression, and functional impairment in American adults, *Cognit. Ther. Res.* (2020) 1–9.
- [57] Y. Zhai, X. Du, Loss and grief amidst COVID-19: a path to adaptation and resilience, *Brain Behav. Immun.* 87 (2020) 80–81.
- [58] D.o.V.D. National Center for Immunization and Respiratory Diseases (NCIRD) (Ed.), Operational Strategy for K-12 Schools Through Phased Prevention, Centers for Disease Control and Prevention, 2021 <https://www.cdc.gov/coronavirus/2019-ncov/community/schools-childcare/operation-strategy.html>, [accessed 7 April 2021].
- [59] S.M. Kissler, C. Tedijanto, E. Goldstein, Y.H. Grad, M. Lipsitch, Projecting the transmission dynamics of SARS-CoV-2 through the postpandemic period, *Science* 368 (2020) 860–868.
- [60] F. Wijburg, S. Parker, P. Drevot, A. Le Meur, A. Chakrapani, V. Coutinho, et al., Design, baseline characteristics, and 18–24 months follow-up from the MPS IIIA natural history study, *Mol. Genet. Metab.* 126 (2019) S153.