The Unspeakable Disease: A Tale of Two Siblings

Interviewees:	Simon Jones,[1-3] Dipak Ram,[4] Ally Shaw[5] 1. St Mary's Hospital, Manchester, UK 2. Honorary Manchester Academic Health Science Centre (MAHSC), UK 3. University of Manchester, UK 4. Royal Manchester Children's Hospital, UK 5. Primary caregiver of patients mentioned

Disclosure:	Jones has declared no payment linked to this article, but has received honoraria/consulting fees from Orchard linked to past activities. Ram has declared no payment linked to this article, but has received honoraria/consulting fees from Orchard linked to past activities. Shaw has declared no payment linked to this article, and has nothing else to declare.
Disclaimer:	The opinions expressed in this article belong solely to the named interviewees.
Support:	The publication of this article was sponsored by Orchard Therapeutics.
Keywords:	*ARSA* gene, gene therapy, lysosomal storage disease, newborn screening.
Citation:	EMJ. 2023;8[3]:30-37. DOI/10.33590/emj/10304055. https://doi.org/10.33590/emj/10304055.

Interview Summary

The deficiency of arylsulfatase A due to the mutations in the *ARSA* gene is the cause of a rare inherited lysosomal storage disease, resulting in the accumulation of sulfatides in the central nervous system (CNS) and peripheral nervous system (PNS). This, in turn, leads to progressive demyelination, neuro-inflammation, and neurodegeneration, and the accumulation in visceral organs.

Affected young children gradually lose the ability to walk, stand, talk, and swallow; they lose their independence and show a steady physical and cognitive regression resulting, ultimately, in their premature death at a younger age. This condition not only devastates young patients, but it also deeply affects their families and carers, both psychologically and economically.

In this interview, Simon Jones, Consultant in Paediatric Inherited Metabolic Disease at St Mary's Hospital, Manchester, Honorary Manchester Academic Health Science Centre (MAHSC), and Professor in Paediatrics and Senior Lecturer at the University of Manchester, UK; Dipak Ram, Royal College of Paediatrics and Child Health (RCPCH) and British Paediatric Neurology Association (BPNA) National Training Advisor for Paediatric Neurology, and Consultant Paediatric Neurologist at the Royal Manchester Children's Hospital, UK; and Ally Shaw, primary caregiver of the patients mentioned in this article, explore how the disease impacts the normal development of predominantly young patients; consider its subtle evolution; and witness the stressful diagnostic odyssey families are experiencing, often leading to the wrong diagnosis, which is compounded by the lack of a national newborn screening.

Jones and Ram speak directly about the diagnosis and management of these patients. This article also includes the experience of a mother of two affected children, one of whom was diagnosed thanks to their affected older sister, who gave the younger child the chance of receiving a timely treatment. In this disease, time is of the essence; often, patients are sadly diagnosed too late, and are destined to palliative care and premature death. It is hoped that this interview and testimony will help raise awareness on this disease, and give a chance to future patients and their families.

With a prevalence rate estimated to be around 1 in 40,000–160,000 worldwide, there is only a small chance that a physician will come across a patient with this devastating lysosomal storage disease during their career.[1] This may lead some healthcare professionals to assume the condition is too rare to invest adequate time to familiarise themselves with its (early) symptoms, prioritising their focus on other diseases with greater incidence.

To complicate the matter, affected young children may not manifest any concerning symptoms until it is too late. For a period, they exhibit apparently healthy growth, meeting the developmental milestones of their non-affected peers. However, this subtle illness is gradually and inexorably causing permanent and cumulative damage in multiple organs, eventually resulting in progressive motor and cognitive deterioration, with loss of motor and neurocognitive functions and, ultimately, death.

This unspeakable condition is a rare inherited lysosomal storage disease caused by deficiency of arylsulfatase A (ARSA), due to mutations in the *ARSA* gene. The reduced ARSA activity results in the accumulation of sulfatides in the CNS and PNS, leading to progressive demyelination, neuro-inflammation, and neurodegeneration, in addition to the accumulation in visceral organs, such as the gallbladder and kidneys.[2]

"The disease progression in the most severe form of the disease follows a typical pattern," said Jones. "Affected young children gradually lose the ability to walk, stand, talk, [and] swallow; they lose their independence and show a steady physical and cognitive regression. Their ability to communicate, express themselves is progressively heavily compromised. They become detached from the world around them, unable to share their feelings, slowly becoming a shadow of their former selves, bedridden until their premature death at a younger age. As this horrible condition devastates these children, it also deeply affects their families, and carers both psychologically and economically, a heartbreaking convergence of negative factors causing an incredible amount of stress for those looking after their sick child."

A caregivers-reported impact on quality of life and disease burden in diagnosed patients provides a grim depiction of what these families experience. Some 94% of carers said that the illness has led to considerable change in their lifestyle, and 50% had seen their emotional relationship with their spouse/partner deteriorate to an extreme degree. In addition, 76% of carers had suffered a loss of income due to the cessation of their professional full- or part-time activity, due to the 15 hours a day spent on average caring for their child.[3]

"Unfortunately, the subtleness of this condition frequently results in a diagnostic odyssey; young patients are often referred to several specialists in an attempt to manage the symptoms appearing at different stages of disease progression, the result of a gradual accumulation of sulfatides in the tissues and organs," explained Ram. "In the late infantile and most severe subtype, for example, the hypotonia, muscle weakness, gait disturbances, abnormal movement patterns, and frequent falls are often the first symptoms that parents or carers notice first, which worry them. They consult their general practitioner, who may or may not refer the young patient to a paediatrician or paediatric neurologist for further investigations. This takes time, and time for these patients is extremely precious. In addition, clinicians may adopt a watch-and-wait approach, hoping that some of these atypical symptoms self-resolve, or provide additional clues on what to do next. Unfortunately, even if this may be the right

rationale for other conditions, a late diagnosis in this scenario leads to fatal consequences."

A study of caregivers in the USA who were caring for, or had cared for, a living or deceased patient classified as having late infantile or juvenile subtypes of the disease, confirmed this assessment.[4] The most common initial symptoms reported in late infantile patients related to problems with gross motor function. Often, this was observed as a delay in developmental progression, particularly in walking, and nearly 70% of late infantile patients never learned to walk independently. In addition to motor function-related observations, such as losing balance, falling over, and relying on holding hands to be able to walk, fine motor or related symptoms were also commonly reported as pre-diagnosis symptoms in late infantile patients. This included problems with eye movement, eating, or swallowing, and hand tremors. In addition, nearly 44% of late infantile patients experienced pre-diagnosis speech problems. In comparison, patients with the juvenile subtype, as expected, exhibited initial symptoms later, and the first symptoms often related to changes in cognitive function (56.3%) or social/behavioural function (43.8%). The initial symptoms were usually noticed at school, following a decline in academic performance, difficulty focusing, or disruptive behaviour.

"The collective incidence of inherited disorders affecting the lysosomes is roughly 1 in 2,300–7,000 live births," explained Jones, "and among the different lysosomal disorders, the general prevalence of this autosomal recessive condition varies within diverse populations, especially when looking at the different degrees of consanguinity."[5]

This disease is a pan-ethnic lysosomal storage disease, with affected patients found in several populations, such as European, Iranian, Indian, Japanese, Jewish, Habbanite Jewish, Lebanese, Muslim Arab, South African, Polynesian, Algerian, Navajo Indian, Alaskan Eskimo, and Christian Arab, with phenotypes ranging from the mild to the severe.[6]

The mutations in the *ARSA* gene in homo- or heterozygosity is the triggering factor, with over 150 mutations (of which more than 70% are missense) reported in these patients.[7] Missense mutations in specific genes encoding for misfolded mutant lysosomal enzymes can cause lysosomal storage disorders. However, most of these misfolded mutant lysosomal enzymes are destroyed, and only a small amount of the mutant enzyme eventually reaches the lysosomal compartment and remains functionally active. This residual enzymatic activity ranges between 0–10% of the normal activity detected from the wild-type *ARSA*.[8] The critical threshold of ARSA enzymatic activity (about 10% of that measured in the wild-type *ARSA*) is considered the minimum, above which the activity is sufficient to prevent the accumulation of sulfatides. In what is known as ARSA pseudo-deficiency, the levels of enzyme activity between 10–15% of wild-type *ARSA* levels result in no sulfatide accumulation, and no disease-related symptoms.

Sulfatides (a type of glycosphingolipid) are the main component of the myelin sheath in both the CNS and PNS. In the CNS, oligodendrocytes situated in the myelin surrounding neural axons are responsible for their synthesis. In the PNS, the neurolemmocytes are the myelin-producing cells.[5] Sulfatides account for 4% of myelin composition, the most abundant sphingolipid. An excessive concentration of sulfatides and deficiency of cerebrosides can lead to an abnormal myelin composition, potentially affecting the development of a stable lipid bilayer.[9] In addition, the sulfatide metabolite galactosylsphingosine can cause cytotoxicity, leading to the death and dysfunction of neuronal cells.[10] The progressive accumulation of sulfatides causes dysfunction of the lysosomal-endosomal system, triggering other secondary pathogenic cascades, which ultimately result in apoptosis.[11] The progressive demyelination in both CNS and PNS correlates with the clinical manifestations of the disease.[12]

Sulfatides can also be found, albeit in low concentrations, in the respiratory tract, gastric mucosa, and uterine endometrium. They accumulate in the epithelium cells of the gallbladder, resulting in sludge, gallstones, haemobilia, cholecystitis, polyposis, papillomatosis, and a small or enlarged gallbladder.[13-20] A retrospective cohort study performed at the Duke University Medical Center, Durham, North Carolina, USA, provided additional evidence on the incidence of gallbladder abnormalities.[21] The small study, which used a prospectively maintained

database, included 87 children who underwent haematopoietic stem cell transplant (HSCT) at the same institution between 1994–2015. Children were stratified into two groups: 58 patients with a diagnosis of adrenoleukodystrophy or Krabbe disease (Cohort 1), and the remaining 29 patients with the lysosomal storage disease subject of this article (Cohort 2). Children in Cohort 2 were more likely to show gallbladder abnormalities on imaging, the most common of which was sludge, compared with children with other lysosomal storage diseases.

"This neurological lysosomal storage disorder displays a broad and heterogeneous clinical spectrum combining age-based progression and a genotype/phenotype continuum. Homozygosity for 0 alleles (0/0) codifying for ARSA enzyme, is reported only in patients characterised as early-onset, whereas phenotypic variability is more evident in the juvenile and adult subtypes," explained Jones. "This means that genotype/phenotype correlation is more evident in those patients presenting with a 0/0 genotype, whereas predicting the phenotype associated with 0/R or R/R profile is much harder and more complex."[6,22]

The three clinical forms are based on the age of symptom onset, the rate of progression of neurological symptoms, and their severity. The late infantile subtype is the most severe form, with the first symptoms developed at just a few months of age up to 30 months. The juvenile clinical form includes patients with symptom onset occurring between 30 months–16 years of age, and lastly patients with the adult clinical form see their symptoms manifest from 17 years onwards. The two late-onset forms, juvenile and adult, at times overlap, and they may present with a more insidious manifestation of a wide range of neurological symptoms, offering more opportunities for therapeutic interventions.

Patients with the late infantile form of the disease show delays in psychomotor development, characterised by impairment of speech, and gross and fine motor development. In addition, patients can present with muscular hypotonia, hyporeflexia, spasticity, and hyperreflexia. Other symptoms seen are ataxia, spastic paresis, and optic dystrophy, all of which may be common in other diseases, and lead to difficulties in differential diagnosis. A study including patients from two national cohorts at the University Children's Hospital, Tübingen, Germany, and Amsterdam University Medical Center, the Netherlands, found that paralytic strabismus was an early sign in patients presenting with the late infantile subtype, and hypothesised this could be the result of early cranial nerve involvement.[23]

In the juvenile form, patients develop the same symptoms, but less rapidly. Early juvenile children (symptom onset between 30 months–<7 years of age) typically display poor school performance, some behavioural disturbances, and peripheral neuropathies, which may mimic other conditions (e.g., attention deficit hyperactivity disorder [ADHD]). As the disease progresses, patients become debilitated, losing gait independence and speech. Seizures and recurrent pulmonary infections also occur frequently. Despite the slower pace of regression, once these children lose the ability to walk, the disease progresses at a comparable rate to the late infantile subtype.[24]

Symptoms of the late juvenile subtype become visible between 7–16 years of age, usually associated with behavioural or cognitive issues. Prognosis is variable, with a fast disease progression if motor symptoms are seen at disease onset, while patients with behavioural and cognitive issues at diagnosis tend to have a less severe condition, independently of age at onset.[24] Often the deterioration of school performance, regression of verbal skills, behavioural or emotional disturbances, and fine motor functions damage are the initial symptoms in these patients. Initially, when motor function may still be intact, symptoms may be suggestive of other pathologies, such as schizophrenia, depression, ADHD, and autistic spectrum disturbances. About 61% of patients present only with cognitive symptoms at disease onset, whereas the remaining 39% exhibit only motor symptoms, or a combination of both motor and cognitive symptoms.[24]

Lastly, the hallmark of the adult form is a gradual impairment of intellectual function, emotional instability, behavioural/psychiatric disorders, and epileptic seizures. At a later stage, polyneuropathy occurs, and does not usually present symptoms. This form of the disease shows the first symptoms after puberty (around 16 years of age), but they have been noticed in patients older than 60 years of age. The first symptoms involve poor school or work

performance. Patients may show emotional instability, disorganised thoughts, and sometimes psychiatric symptoms, such as hallucinations or delirium, which may lead to incorrectly diagnosing schizophrenia, psychotic depression, or dementia.

"The difference in the pace of disease progression has implications in how patients are managed," said Ram, and "it is important to diagnose the condition in a timely fashion to be able, where possible, to treat patients or anticipate their needs when they are not treatable, ensuring some optimised care. The sooner these patients are diagnosed, the better it is, and this is particularly important for the most severe subtype."

The accumulation of excess sulfatides resulting from the absence of ARSA enzymatic activity, or a low level of activity, makes them a good starting point to determine the diagnosis.

"The detection of low ARSA levels in the blood, or raised urinary sulfatides, are the main rapid diagnostic tools in our possession," continued Ram. "For the final diagnosis, we rely on additional procedures, which include molecular genetic tests, electrophysiological tests, and brain MRI.[1,25,26] It is important to remember, however, that early-onset patients might have normal or non-characteristic, mildly affected MRIs when they are already symptomatic, which means that this investigative technique should not be used as the main tool to diagnose patient[s], but as a confirmatory one."

Ram's comments were reinforced by the results of a retrospective study in which the authors reviewed the medical records of patients followed at the Amsterdam Leukodystrophy Center, the Netherlands, or Tübingen University Hospital, Germany.[27] They evaluated 104 MRI images, and discovered that nearly a quarter (n=10) of the late infantile patients (n=43) were initially misdiagnosed with chronic inflammatory demyelinating polyneuropathy, unclassified polyneuropathy, Dejerine–Sottas disease, Segawa syndrome, oculomotor apraxia, post-infectious gait ataxia, and spinocerebellar ataxia; and in all these cases, a normal appearing MRI was an important factor for the incorrect diagnosis. The authors stated that CNS symptoms, therefore, may precede MRI abnormalities in these children, and recommended that clinicians pay attention to signs of upper motor neuron involvement, such as scissoring, Babinski signs, elevated muscle tone, and increased tendon reflexes during physical examination, to help avoid misdiagnosis as an isolated peripheral demyelinating polyneuropathy. Misdiagnoses of the juvenile and adult forms are not uncommon, and include ADHD for the former and schizophrenia for the latter.[1,4]

"The challenge we currently have is to find patients before it is too late", said Jones. "Our team at the Royal Manchester Children's Hospital has recently published the results of a 12-month study on the number of patients referred to us for treatment.[28] The findings are chilling, with only four out of 17 UK patients asymptomatic at [the] time of diagnosis and therefore eligible for gene therapy, which is available in the UK after European Medicines Agency (EMA) approval in 2020. The rest could only receive supportive care. It is a particularly difficult situation; the window for treatment is extremely narrow, especially for early-onset children. For them to have a chance, they should be minimally or asymptomatic at diagnosis, but without a national newborn screening [programme], finding them early is a nearly impossible task. Unfortunately, the patients we were able to treat were identified thanks to an older affected sibling whose disease was too advanced to be eligible for treatment. In essence, the older sibling saved the younger one, a heartbreaking scenario for families to process and accept; it really becomes a story of two siblings."

Until the EMA's approval of a gene therapy, there was no sufficiently effective therapy for some patients. Symptoms can be treated pharmacologically, for instance, using anti-epileptic drugs for seizures or myorelaxants for muscular spasms. Gastro-oesophageal reflux and constipation can be managed with targeted treatments. Pharmacological support may also be necessary to treat pain. Swallowing difficulties can be attenuated using supplements, modifying the consistency or volume of meals, and by placing a feeding tube to alleviate discomfort and help prevent aspiration pneumonia.

The gradual physical decline of patients will require the adoption of a wheelchairs, walkers, and electronic communication devices to optimise quality of life. Psychological support is often

necessary for both the patient and their family. This supportive care may extend the lifespan of a patient by dealing with growing complications, such as nutritional challenges and pulmonary infections, but overall, quality of life remains poor and, despite the alleviation of symptoms, the rate of disease progression is not reduced.[1]

"In the past two decades, [allogeneic] allo-HSCT has been the only available treatment for the juvenile form of the disease," said Jones. "The rationale of this approach is that monocytes derived from donor cells can cross the blood–brain barrier, becoming a local source of missing enzyme for the neighbouring cells in the CNS, preventing the process of demyelination and neurodegeneration."

The results seen in late infantile and early juvenile subtypes have been limited in demonstrating a significant impact on motor and cognitive decline, possibly due to the inability of donor-derived cells to produce supraphysiological levels of ARSA enzyme. Some patients have shown rapid disease progression following allo-HSCT compared with non-transplanted patients, which may suggest the negative impact of this procedure as a trigger to accelerate disease progression. In addition, the benefits on late infantile patients appear to be extremely limited, even when patients are in the pre-symptomatic phase of the disease.

"It is likely that in these children, the adequate enzymatic levels needed are reached too late, and in the meantime the disease has already entered the rapidly progressive phase," said Jones. "In most of these patients, motor and cognitive decline, including the ability to communicate verbally, was observed even after allo-HSCT, leading to the conclusion that this option is not particularly useful in symptomatic patients, or in those with the most severe disease subtype. In addition, engrafted donor-derived microglial cells are only able to produce a physiological level of the ARSA enzyme, which [is] insufficient to cross-correct the patient's defective neuronal cells."

When considering the effects of allo-HSCT on neuropathic pain, the results have been disappointing, showing a slow worsening in the years following the transplant.[29,30] The safety implications of allo-HSCT also need to be considered, as the procedure is associated with a risk of severe complications, transplant rejection, graft-versus-host disease, and mortality risks due to the intense conditioning regimen used. Additional limitations include the availability of a compatible donor, which may delay treatment and compromise its efficacy. In current clinical practice, allo-HSCT is restricted to pre- or pauci-symptomatic patients showing a late disease onset and slow progression.

"Nala was just an absolute character, very theatrical, always singing, always dancing, had everyone laughing," recounted Ally Shaw, the mother of two young girls. "When she was about 6 month[s] old, I started noticing something unusual; she would not put her feet flat, and as a first-time mother I thought that was not normal.

"I, therefore, consulted the doctors, and they would reassure me that nothing was out of the ordinary; after all, she was only 6 month[s] old; [there was] nothing they would do at this stage. They suggested to wait until she was walking, and then they could reassess. When she did start walking, I continued to have concerns, but I still wasn't being taken very seriously by the specialists.

"Eventually, she was referred to physiotherapists. She went to them every few months to start with, and they just kept saying she would grow out of it. They did not have any worrying concerns, and she got discharged.

"Nala continued to walk a bit strange, and 6 months later I went back to a physiotherapist, but was not taken seriously until she started falling over a lot and develop tremors when she was about 2 and a half. And that is when I started to look online, and really think there was something more seriously wrong.

"Originally, I thought she had a brain tumour or cerebral palsy, since the symptoms were very similar. Eventually, I managed to get her seen by a paediatrician who ruled out the brain tumour, suspecting a diagnosis of cerebral palsy instead.

"I still had doubts. I did not believe that it was cerebral palsy because of how fast she was changing, [and] I was very much convinced it was a brain tumour. By this point, even with my massive concerns, it seemed like there was no rush to do anything, and she was put on a

waiting list in late February–early March of 2022, and by the April Nala had gotten to the point where she could not walk at all.

"At night-time she was screaming as if she was in great pain, and this went on for a couple of weeks until I phoned an ambulance that took her to the Newcastle Royal Victoria Infirmary [UK], a children's hospital. Upon arrival, they were instantly concerned that something was seriously wrong, and within 2 hours we were seen by a team of neuro-doctors who thought she may have a brain tumour.

"She was rushed for an emergency MRI, and within about 45 minutes the doctor came to tell me and my husband, Jake, that they had found a leukodystrophy.

"I had never heard of metachromatic leukodystrophy (MLD); I do not think anyone's ever heard of MLD unless it horribly gets thrown in your life. I did not have a clue what it was, [or] how bad it was. No idea.

"We were told instantly there was absolutely nothing to do because Nala had completely stopped walking, and no active treatment could be offered. When we were told that Teddi, Nala's younger sister, had the same disease, we were in shock; however, they said that there might have been an available gene therapy treatment for her. As a parent, being told that only one child can be helped is almost crueller than being told that both cannot.

"MLD is probably just one of the most horrible diseases I have ever known. To watch a child be stripped of everything is just horrendous. Since Nala got diagnosed, she lost all her skills very rapidly, and within weeks she had lost the ability to speak, to eat, and to hold her own body up.

"When Teddi had to go into hospital for a long period of time for treatment, I could not expect my employers to keep my job just open, and I gave it up. It has been a massive struggle for me and Jake, and without the community support, I think we would struggle to even pay bills.

"What I am going through is the reason why I have become a great advocate of newborn screening. If MLD was screened at birth, my child would not be dying, and she would have potentially had the treatment that her sister had, changing our lives from watching a child slowly leaving us to a growing one. Knowing that she is going to die is the hardest thing.

"My advice to other parents is that if they strongly suspect something is wrong with their children, they must push and fight and fight, because unfortunately it is about who shouts the loudest."

"MLD is [a] horrific disease," concluded Jones, and "without newborn screening more children and families will suffer. We do have a chance to prevent this suffering if we act quickly, because we do have an approved treatment available. Now is the right time to act."

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UK-NoP-2300012 | DOP: Aug 2023