5th edition

REPORT

New SMA landscape

LIS-N & LER-N

Educational meeting in SMA

7th & 8th of December, 2021

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About spinal muscular atrophy

Spinal muscular atrophy (SMA) is characterised by degeneration and loss of motor neurons in the brain and spinal cord. The loss of functioning motor neurons leads to progressive muscle weakness and atrophy as muscles stop receiving signals from the central nervous system. SMA is caused by a mutation or deletion in the survival motor neuron 1 *(SMN1)* gene which encodes the survival motor neuron (SMN) protein. A second SMN gene *(SMN2)* produces a shortened and less functional SMN protein. SMA develops when the mutation or deletion is present on both copies of the *SMN1* gene, in which case there will be insufficient SMN protein levels for the motor neurons to survive.[1-3]

SMA with autosomal-recessive inheritance is classified into different subtypes according to age of onset and severity, with the most common subtypes being:[4-7]

- **SMA type 1**, the classic form of SMA also known as infantile-onset SMA or Werdnig-Hoffmann disease, typically manifests itself before the age of 6 months. SMA type 1 is the most severe form of SMA; if untreated, children with SMA type 1 will never be able to sit and their life expectancy is less than two years.
- **SMA type 2** typically appears between 6 and 18 months of age and is a less severe form of SMA. Children with SMA type 2 are able to sit independently but not walk; 70% of the patients are still alive at the age of 25.
- **SMA type 3**, or Kugelberg-Welander disease, develops in children older than 18 months. Children with SMA type 3 are typically able to walk independently and have a normal life expectancy. However, although SMA type 3 is a milder form of SMA, patients with SMA type 3 may progressively deteriorate as they grow older.

A typical presentation of SMA type 1 is muscle weakness and hypotonia, known as the “floppy baby syndrome.” SMA is diagnosed based on the medical history and clinical presentation together with neurophysiological testing and DNA sequencing to confirm the *SMN1* gene mutation or deletion.[4,8]

Patients with SMA are treated with supportive interventions that focus on the quality of life, including physiotherapy, mobility assistance, and respiratory and nutritional support.[4,9-12] Until recently there was no effective drug treatment for SMA and the main focus was then on palliative interventions.

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Introduction

We are proud to share the 2021 LIS-N & LER-N report with you. This was the fifth LIS-N & LER-N meeting since the start, and this year's theme was "New SMA Landscape". The aim of the LIS-N & LER-N meeting is to provide a platform for healthcare professionals caring for patients with SMA in the Nordic countries to meet and interact across national borders, to share and promote knowledge and best practice with the ambition to improve competence in the management of SMA. The 2021 LIS-N & LER-N meeting offered a comprehensive programme of presentations and discussions by eminent specialists in the field of SMA on a variety of topics, chaired and moderated by Professor Thomas Sejersen. Day 1 opened with a presentation by Vanessa Christie-Brown from SMA Europe on the work and upcoming priorities of this umbrella organisation, founded in 2006 to improve the quality of life of people living with SMA, promote timely and sustainable access to effective therapies for patients, and encourage optimal patient care. Next, Dr Elin Hjort from Stockholm hosted a workshop and group discussion focusing on the everyday experiences of living with SMA in a time of change. Day 1 closed with a presentation by Dr Bart Bartels from The Netherlands on the topic "Fatigable or not in SMA" – an aspect of SMA where there is currently no consensus regarding utility and timing in patients living with SMA.

Day 2 began with Professor Mar Tulinius from Gothenburg, who spoke on the topic "SMA through history and future challenges", describing a journey from the early 19th century, via 2010, when palliative care was the only treatment, through to the present day with its range of available treatments and future challenges in the form of, among others, treatment selection, evaluation of response, and new-born screening. Professor Tulinius' talk was followed by a keynote presentation by invited guest speaker Dr Thomas Crawford from Baltimore in the United States, entitled "SMA: An extraordinary, multi-dimensional and very cool story." In his presentation Dr Crawford highlighted a number of issues and challenges in the management of SMA, including categorising the SMA "types", determining the levels of SMN expression, and establishing the natural history of SMA type 2 and 3, respectively. The meeting then concluded with a presentation by Professor Thomas Meyer from Berlin on ways of measuring patients' expectations and perceptions of SMA treatment.

The key take-home message from the 2021 LIS-N & LER- N meeting was that the SMA landscape is a new landscape compared with yesterday; to find their way around it, healthcare professionals will require new treatments, new targets, new scales, a new mindset, and wider professional skills. Biogen will continue to support this process by sharing knowledge and experience around SMA, until all children and adults have access to treatment. A key element in this commitment is the organising and funding of the annual LIS-N & LER-N meeting. We hope you will enjoy reading this report and that it will help you in your daily practice.

Peps Bengtsson, Biogen

Photo: Henrik Rådmark

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VANESSA CHRISTIE-BROWN

Research Programme Manager, SMA Europe

SMA Europe strives to empower people living with SMA and elevate their voice to influence research and healthcare decision-makers, in pursuit of optimal treatment and care. Vanessa Christie-Brown has 11 years of experience in the SMA field, through working for an SMA organisation in the UK and coordinating SMA Europe. Now that the organisation has grown, she is focuses on managing its extensive research programme. She has a background in medical research, in the field of immunology, having worked at The Royal Postgraduate Medical School (Hammersmith Hospital) and Imperial College London in the UK.

ELIN HJORTH

Nurse, Ersta Sköndal Bräcke University College, Stockholm, Sweden

Dr Elin Hjorth is a specialist nurse in paediatric care and has worked in paediatric neurology. In 2020 she defended her PhD thesis, focusing on children with severe SMA and their families: 'Experiences of care and everyday life in a time of change for families in which a child has spinal muscular atrophy.'

BART BARTELS

Physiotherapist, University Medical Center Utrecht, the Netherlands

Dr Bart Bartels is the head of the Child Development and Exercise Center and a post-doctoral researcher at University Medical Center Utrecht in the Netherlands. His research interests include exercise physiology and outcome measures in SMA, in particular studies on fatigability, together with diagnostics and treatment of impaired muscle function in neuromuscular diseases.

THOMAS CRAWFORD

Neurologist, Johns Hopkins Hospital, Baltimore, MD, USA

Dr Tom Crawford is Professor of Neurology at Johns Hopkins University School of Medicine and co-director of the MDA clinic for neuromuscular disorders and neurologist for the Ataxia Telangiectasia Clinical Center at Johns Hopkins Hospital. Dr Crawford's primary research interests involve the basic science and clinical characterisation of SMA and ataxia telangiectasia, including research into the biology of neurofilaments by characterisation of transgenic animal models. Additional specific clinical interests include evaluation and treatment of children with brachial plexus palsies.

MÁR TULINIUS

Neuropaediatrician, Queen Silvia Children's Hospital, Gothenburg, Sweden

Már Tulinius is Professor of Paediatrics at the University of Gothenburg and senior consultant in paediatric neurology at the Queen Silvia Children's Hospital within Sahlgrenska University Hospital. Professor Tulinius has extensive experience in the treatment of neuromuscular disorders in children and adolescents, including acting as a principal investigator on pivotal clinical studies for novel treatments.

THOMAS MEYER

Neurologist and palliative care specialist, Charité – Universitätsmedizin Berlin, Germany

Professor Thomas Meyer is a specialist in neurology with an additional qualification in palliative medicine. He is the founder and head of the ALS outpatient clinic at the Campus Virchow-Klinikum of the Charité University Hospital in Berlin, Germany. Professor Meyer's research interests include optimal provision and use of available treatment options for people with ALS ('managed care'), development and implementation of new healthcare delivery models, and evaluation of new drugs and therapeutic approaches in ALS in clinical studies.

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VANESSA CHRISTIE-BROWN

Research Programme Manager,
SMA Europe, United Kingdom

The work and priorities of SMA Europe

For people living with a debilitating chronic condition such as SMA, patient organisations and advocacy groups provide vital support by representing them and their families. The joining of forces of SMA groups across Europe has resulted in SMA Europe, a powerful stakeholder with a mission to ensure that the voice of people living with SMA is heard when important decisions are made. It also harnesses its extensive network to influence research and access priorities, with a vision of improving the lives of all those affected by SMA. In the opening session of Lis n & Ler n 2021, Vanessa Christie Brown, Research Programme Manager at SMA Europe, presented an overview of the organisation and outlined its work and priorities for the coming years.

SMA Europe is an umbrella organisation for patient and research groups that, as the name infers, works to further the interests of people living with SMA in Europe. As its main vision, SMA Europe strives to promote earlier diagnosis of SMA and improve access to effective treatments and optimal care for people living with SMA, by speaking and networking on behalf of patients and supporting the member groups in their national advocacy and research activities. Founded in 2006 by seven patient and research groups as part of an effort to pool funds for research, SMA Europe has since grown in size and scope; today's organisation comprises 24 member organisations in 23 European countries (Figure 1), with a remit that stretches well beyond that of funding research. In terms of organisation, the main decision-making body of SMA Europe is the General Assembly, which consists of 44 delegates from each member organisation. As the executive body, the General Assembly elects a board of five delegates, which is supported by a permanent staff of five to ensure that day to day activities run smoothly. The key operational units in SMA Europe are the committees, including the scientific advisory board and patient advisory groups as well as the evidence generation committee which is responsible for gathering evidence on the needs of the SMA community, and the newly-formed committee on adult SMA (which also includes non-members of SMA Europe to ensure the widest possible horizon). Another vital role in the SMA Europe structure is played by its partner organisations, which include patient groups such as EURORDIS, Cure SMA and the SMA Foundation; as well as the European

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Medicines Agency (EMA), the ENMC, the EURO-NMD research network, and representatives of the global pharmaceutical industry.

> *"We are now in our 16th year, and we like to believe we have made an impact,"*

Since its start, SMA Europe has worked hard and managed a number of successes in its field. "We are now in our 16th year, and we like to believe we have made an impact," said Vanessa Christie Brown. Among its achievements to date, SMA Europe can chalk up a total of ten rounds of calls for research projects totalling 4.9 million EUR and including studies on broadening the understanding SMA, ensuring patient-centric development of therapies, and improving outcome measures, together with two scientific congresses with more than 600 participants from all stakeholder groups. In addition, the recent launch of the Clinical Trial Readiness Project, a collaboration with an industry consortium in the US, to provide training for clinical centres looking to set up and run clinical studies in SMA, and the New Born Screening Alliance which will ensure that by 2025, new-born screening for SMA is implemented in all member countries. These initiatives have laid the foundations for the organisation's continued strategic work in the next few years. Other achievements include a white paper on new-born screening for SMA.

In the past 12 months, SMA Europe has undergone significant changes – the organisation has grown rapidly both in terms of new member groups and scope of interest, which has prompted the board to devise a comprehensive strategy for the coming years to broaden and deepen activities with a clear patient-centric focus. "Our strategy for the coming years really strives to put the patient at the centre of everything we do," explained Vanessa Christie Brown. This strategy consists of three pillars of activity: Research; Therapy & Care; and Healthcare Systems, Policy & Access, respectively, which are underpinned by capacity building and promoted through communications and outreach activities. As Vanessa Christie Brown emphasised: "We want to ensure that all members have the knowledge and the tools to advocate effectively." A number of projects are planned or already in progress within these strategic pillars; under Research, Vanessa Christie Brown highlighted an especially important project for setting research priorities, which has just started and which is being run in collaboration with specialist consultants James Lind Alliance in the UK. This project aims to identify the top ten unanswered questions in SMA research that matter the most to patients, through a process of iterative tailored surveys among key stakeholders including patients, healthcare professionals and researchers, followed by interactive workshops to narrow the range of questions and identify a core set which will then be put to organisations that fund SMA research, including SMA Europe itself. Other key parts of the Research strategic pillar include continued evidence generation in the form of surveys to uncover patient expectations of therapy and identify outcome measures that are meaningful for improving patient's daily lives, and continued hosting of international scientific congresses on SMA. "The international scientific congresses on SMA bring together an international and multidisciplinary group of scientists and healthcare professionals to present and exchange their breakthrough ideas on SMA, cement existing collaborations and stimulate new ones," said Vanessa Christie Brown. Under the heading of Therapy & Care, SMA Europe will continue to work to ensure that the voice of the patient is taken into account in clinical studies in SMA, through patient advisory groups and through continued input into the training curriculum in the flagship Clinical Trial Readiness Project. There will also be continued work on developing standards of care for SMA, with particular focus on physiotherapy and nutrition. Last but not least, the third pillar of Healthcare Systems, Policy & Access comprises projects for mapping access to advanced SMA care and treatments and understanding priorities and barriers, with a view to gaining skills for honing the organisation's advocacy activities in this area. Continued efforts to lobby for implementation of new-born screening for SMA in all member countries play an important role in this work.

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ELIN HJORTH

Nurse, Ersta Sköndal Bräcke
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Everyday experiences of living with SMA in a time of change

Coping with SMA and finding a sustainable way of negotiating everyday challenges can have a profound impact not only on the children themselves but also their families, and healthcare professionals are an important source of support and knowledge at all times. Dr Elin Hjorth from Ersta Sköndal Bräcke University College in Stockholm presented the results of her research on how children living with SMA and their families experience their medical and nurse care and find ways of managing issues and limitations in their daily lives. Dr Hjorth's presentation was followed by group discussions in which Lis-n & Ler-n participants were invited to share their experiences in their respective countries.

Dr Hjorth's research project, which also formed her doctoral dissertation, consisted of two main parts: the first part involved a series of nationwide surveys carried out among families affected by SMA in Sweden and Denmark, in collaboration with researchers at Karolinska University Hospital and the National Rehabilitation Centre for Neuromuscular Diseases in Aarhus.[1–3] Part two was a qualitative ethnographic study in which families of children with SMA were interviewed and observed by study investigators.[4] The surveys, which were distributed in 2013 in Sweden and 2015 in Denmark, included both parents who had lost a child to SMA, and parents who were living with a child with Type 1 or severe Type 2 SMA. The questionnaires were sent to a total of 95 respondents and achieved a response rate of 84%, which is considered high in this type of research. In their responses to the survey questionnaires, parents described the need to develop strategies for resilience in their everyday lives, and underlined the importance of mutual support, trying to live as normally as possible and helping each other to feel confident about the future. Practical matters were also emphasised, such as remembering to rest, asking for help when needed, and not neglecting the needs of healthy siblings. From the perspective of the children with SMA and their healthy siblings, SMA was seen as something quite natural and unproblematic, and even with occasional perks such as not having to queue for events. That said, there was also a sadness among the children about the limitations of life and sense of exclusion imposed by SMA. The survey part of the project also addressed the

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families' experience with healthcare professionals. Some of the key feedback from parents in this part of the research concerned the importance of establishing good relationships with the healthcare professionals caring for the child with SMA; for example, for members of the healthcare team to show that they like the child they are caring for was a small but important thing to parents. Parents also stressed that healthcare professionals should listen to the parents of children with SMA, and be prepared to recognise them as experts on their own individual child – but at the same time, not place too much of the overall responsibility for the care of the child on the parents. Whilst parents were aware that the quality of their child's care was dependent on their proactive involvement, the responsibility should be balanced between professional experts and parents. A major issue for parents was lack of specialist knowledge on SMA outside specialist treatment centres; one suggestion was that the treatment centre could assume a coordinating role and ensure that information is disseminated to local and regional healthcare providers caring for children with SMA. In addition, the parents responding to the survey questionnaire also wanted to remind healthcare professionals of the holistic aspects of SMA care, including the need for respite and rest for the parents, practical support with daily tasks such as cooking, and recognition of the fact that sometimes, playing and socialising may be more important to the child's and family's overall wellbeing than doing exercises.

> *"Healthcare professionals should listen to the parents of children with SMA, and be prepared to recognise them as experts on their own individual child."*

In the ethnographic study, the families of two boys with SMA Type 1 and 2, respectively, were interviewed 17 times and observed on six occasions. In the interviews, the families described their strategies for coping with daily life with SMA, and the need to feel hopeful about the future for their children. For both families, advances in care had resulted in stabilisation of the condition, and this in turn allowed the families to feel more confident and safer, both in their present situation and when thinking about the future. Dr Hjorth underlined that the interview responses illustrate how feelings of hope in everyday life – whether the hope is realistic or not – has the potential to influence the experience of living with SMA and plan for the future, for both parents and children.

> *"Feelings of hope in everyday life – whether the hope is realistic or not – has the potential to influence the experience of living with SMA and plan for the future, for both parents and children."*

The group discussions that followed Dr Hjorth's presentation centred largely on the practical difficulties that healthcare professionals face when trying to assess aspects of health-related quality of life in SMA patients and their families. Stabilisation of SMA may improve energy levels and reduce fatigue, which in turn can lead to fewer missed school days for the child, and more time playing and seeing friends. However, these improvements are not captured in the standard muscle function tests used for clinical assessment of SMA, which is a dilemma for healthcare professionals caring for patients with SMA.

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BART BARTELS

Physiotherapist, University Medical Center Utrecht, the Netherlands

Fatigable or not? That is the question in SMA

Measuring fatigability - the inability to sustain repetitive physical activities – could potentially play an important role in the care of SMA patients, as a means of differentiating between patients' perceived fatigue and objective limitations of endurance and performance. Quantifying the level of fatigability and monitor disease progression using markers of endurance could help healthcare professionals target and adapt physical interventions to each patient's individual level of fatigability. In a talk recorded for the Biogen-sponsored 'SMArt talks' webinar series and presented at Lis-n & Ler-n 2021, Dr Bart Bartels from Utrecht in the Netherlands discussed the importance of assessing fatigability in SMA and outlined a test protocol that could be used for this purpose in routine clinical practice.

For most of us, the term 'fatigue' conjures up images of feeling tired after exercise, or after a disturbed night's sleep. However, as Dr Bartels emphasised as he set the scene for presenting his research into fatigue in SMA, fatigue is not merely a subjective sensation of weariness; by using the concept of fatigability to describe a patient's decline in physical performance, the inability to sustain physical activity to be measured and assessed using objective tools.[1] As part of their research, Dr Bartels and his colleagues in Utrecht have assessed the extent to which daily life activities trigger fatigability for patients with SMA.[2] Among children, both gross motor tasks relating to leg function, such as walking, climbing stairs and cycling, and fine motor tasks associated with the function of the hands such as writing, drawing, using scissors and typing on a keyboard were found to induce fatigability. "We noted that fatigability was associated with a wide variety of daily life activities, irrespective of the level of muscle strength needed to perform these tasks," said Dr Bartels. Writing and typing were also highly fatigability-inducing tasks among adults; others included tasks related to the proximal arm functional domain, such as carrying a bag, using cutlery and washing up dishes.[2] A possible pathophysiological cause of fatigability was proposed in 2013 by researchers at the University Medical Center in Utrecht, in a study that found higher rates of neuromuscular junction dysfunction

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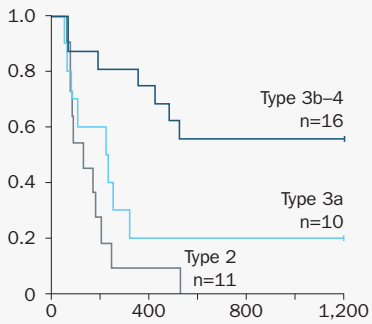
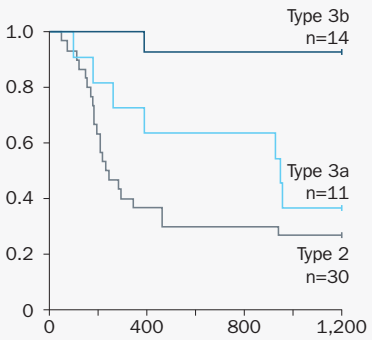
Discriminating between SMA types and sub-types

Plots of probability of not dropping-out vs time to limitation (s)

Endurance Shuttle Walk Test (ESWT)	Endurance Shuttle Box and Block Test (ESBBT)	Endurance Shuttle Nine Hole Peg Test (ESNHPT)
Only for patients who can walk		

Tests were assessed in 61 patients with SMA type 2, 3a, 3b and 4 recruited from the Netherlands national SMA registry and 25 healthy controls aged 8-60 years.
SMA, spinal muscular atrophy.
Adapted from: Bartels B, et al. Orphanet J Rare Dis. 2020:15:75.

among patients with SMA Type 2 and 3 compared with controls.[3] In this study, nearly half of the SMA patients had a pathologic decremental response to repetitive nerve stimulation of 10% or more, which is indicative of neuromuscular junction dysfunction, whereas none of the healthy controls or controls with motor neuron disease showed this response. dysfunction among patients with SMA Type 2 and 3 compared with controls.[3] In this study, nearly half

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of the SMA patients had a pathologic decremental response to repetitive nerve stimulation of 10% or more, which is indicative of neuromuscular junction dysfunction, whereas none of the healthy controls or controls with motor neuron disease showed this response. An important part of Dr Bartel's research was to determine the degree of correlation between fatigability and other predictors of poor physical endurance in SMA; contrary to what might be expected, no correlation was found. In a study of 61 patients with SMA, assessments of perceived fatigue, muscle weakness and impaired motor function using validated tools showed that fatigability affected patients at all levels of these markers.[4] While all patients in the study demonstrated perceived fatigue levels in the normal range, there was no correlation between fatigability and perceived fatigue. Nor could fatigability be predicted from the level of muscle weakness – a hallmark of the SMA disease – or motor function impairment.

Aware of the need for a set of reliable endurance tests in all functional domains to allow quantification of fatigability in SMA, Dr Bartels and his team designed a test protocol consisting of three validated Endurance Shuttle tests, the Nine Hole Peg Test (ESNHPT), the Box and Block Test (ESBBT) and the Walk Test (ESWT) to serve as outcome measures for fatigability of walking, proximal and

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distal arm function in SMA.[5] In the tests, the study participants were instructed to repeatedly place and return nine pegs in nine holes, move ten blocks over a partition, or walk ten metres at 75% of their previously determined, individualised maximum speed, respectively. Each test ended when the study participant dropped out – that is, was no longer able to keep up the pre-set pace during two consecutive shuttles – or when the maximal duration of 20 minutes was reached. The results indicated that the Endurance Shuttle test protocol compiled by Dr Bartels and his team could discriminate between SMA patients and controls, and also between the different SMA subtypes (Figure 1). On the ESBBT, more than 70% of the SMA patients dropped out of the test, compared with only 5% of the healthy controls; likewise on the ESNHPT, 54.5% of SMA patients dropped out compared with none of the healthy controls ($p<0.001$ on both).[5] Drop-out rates among patients with SMA Type 2 and 3a were 100% and 80%, respectively on the ESBBT and 73% and 64%, respectively, on the ESNHPT, compared with only 44% on the ESBBT and 7% on the ESNHPT among patients with SMA Type 3b. "The Endurance Shuttle tests are reliable and valid for quantifying the fatigability of walking, and proximal and distal arm function in SMA," said Dr Bartels, and concluded by echoing the recommendation in his research, that endurance tests should be included in clinical studies in SMA, as well as added to the standard care protocol as a means of capturing clinically meaningful changes in performance that are not covered by motor function or strength assessments.

> ***"The Endurance Shuttle tests are reliable and valid for quantifying the fatigability of walking, and proximal and distal arm function in SMA."***

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THOMAS CRAWFORD

Neurologist, Johns Hopkins Hospital, Baltimore, MD, USA

SMA: An extraordinary, multi-dimensional, and very cool story

The pathophysiology of SMA continues to challenge scientists and clinicians more than 130 years after the condition was first described in the medical literature. Advances in the care of SMA are making it increasingly important to align our understanding of the pathogenetic mechanisms of SMA with the underlying biology of the disease, rather than merely its clinical features. In a keynote presentation at Lis-n & Ler-n 2021, Professor Thomas Crawford from Johns Hopkins Hospital suggested a new model for describing the pathogenesis of SMA that takes into account state-of-the-art research into the developmental biology of motor neurons.

Professor Crawford began by reminding the audience of two things that are frequently said about SMA, but may not be strictly accurate: firstly, SMA is commonly described as a monogenic disease when it is, in fact, digenic – for SMA to occur requires both absence of a functioning SMN1 gene and presence of a partially-functioning SMN2 gene. Secondly, in Professor Crawford's opinion, SMA should not really be considered just a degenerative disease, but rather as a condition arising from a combination of abnormal development and very slow abnormal decline. While the course of the disease may appear at first glance to involve children affected by SMA losing (or failing to gain) muscle strength, settling on a plateau, and eventually going into a phase of decline, the rate of decline will vary from one individual to the next, and it is not clear whether this phase is still a feature of the primary disease or reflects accumulated complications over time, such as scoliosis, obesity, infections, or pulmonary complications. Professor Crawford pointed out that although the current classification of SMA into Type 1, 2 and 3 is meaningful for healthcare professionals caring for SMA patients in that it reflects the age of onset and clinical presentation in terms of being able to sit, walk etc, the scientific SMA community would probably be better served by a classification system that more closely reflects the biology of SMA as our understanding of the disease continues to grow.

Before delving deeper into the topic of the biology of SMA, Professor Crawford made a brief excursion into the evolution of SMA, describing how the first step occurred around ten million years ago at the time when the Hominini tribe separated from

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the gorillas, when a 500Kb duplication arose in exon 5q13.[1] This was a benign event with no harmful effects. The next key step was a single mutational event that occurred around the time of separation of human and chimpanzee lineages, when a cytosine (C) base at the start of exon 7 was replaced by a thymine (T) base, creating the SMN2 gene. Over the aeons that followed, this duplicated region in exon 5q accumulated countless genetic variations due to cross-over events and other types of rearrangements that are still ongoing to this day – Professor Crawford reminded the audience that in around 0.5% of all SMA cases, the disease arises from a de novo mutation.

> *A more modern way of describing of the pathophysiology of SMA is as a condition where the weakness is related to a cell-autonomous disorder, and where the absence of expression of SMN in the motor neuron is responsible for the bulk of the phenotype seen.*

The classic pathophysiology of SMA, as originally described by Werdnig and Hoffmann back in the 1890s, involves denervation atrophy and the presence of fewer – although normally functioning – motor units. A characteristic finding in autopsy studies is that the ventral nerve roots in the spine, which should normally be around two-thirds of the size of the dorsal roots, are atrophied and tiny in size. A more modern way of describing of the pathophysiology of SMA is as a condition where the weakness is related to a cell-autonomous disorder, and where the absence of expression of SMN in the motor neuron is responsible for the bulk of the phenotype seen. However, in Professor Crawford's opinion, this traditional way of approaching the pathogenetic mechanisms of SMA does not fully account for the curious clinical course of SMA, where all patients irrespective of SMA type achieve a plateau of function prior to going into a long, slow decline. Instead, Professor Crawford outlined a new model for understanding the pathogenesis of SMA that is based on the latest research findings both in humans and experimental mouse models. First of all, autopsy studies have shown that SMN expression is very high during the second and third trimester and in the first three months of life (Figure 1);[2] by the time infants affected by SMA begin to decline, SMN expression has already declined to such a low level that it is hard to explain how the two factors could possibly be related. Professor Crawford also highlighted research led by his colleague at Johns Hopkins, Professor Charlotte Sumner, which supports a hypothesis that SMA may occur as a result of constrained developmental maturation of motor neuron axons. Autopsies of infants and children with SMA found large numbers of small, unmyelinated 'abutting' axons which had the appearance of foetal ventral roots.[3] In a mouse model of SMA, motor neurons that did not fully mature during the normal developmental sequence degenerated after birth in a matter of weeks, suggesting that SMA represents a developmental pathology. Together with the finding that in the natural history of SMA Type 2 and 3, muscle strength will peak at around the same age and decline at roughly equal rates for all patients, this strongly supports a model of SMA pathogenesis where normal muscle development in the first years of life will initially mask the degeneration of motor neurons that is occurring as a consequence of impaired prenatal development, and SMA occurs when the balance between development and degeneration tips over towards the latter. Professor Crawford explained that in this model, there is no plateau phase, only a long slow decline. Although this model of SMA pathogenesis has yet to be validated, it represents a hypothesis that fits all the known facts, and provides an explanation for the curious clinical course of SMA.

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SMA through history and future challenges

First described in the late 19th century, SMA is now known to be a leading cause of neuromuscular disease, affecting between 1 in 6,000 and 1 in 10,000 people.[1] Identification of the genetic mechanisms responsible for SMA in the 1990s has led to increased knowledge and improvements in care that continue to benefit patients and families living with SMA across the world. Professor Már Tulinius from Gothenburg in Sweden opened day two of Lis-n & Ler-n 2021 with an historical perspective on SMA and a look ahead to future challenges for specialists caring for SMA patients.

The condition that we today refer to as SMA was first described in 1891 and 1893 (Figure 1), when neurologists Guido Werdnig from Austria and Johann Hoffmann from Germany described a total of nine cases of children who all developed severe muscle weakness during the first year of life, and died before the age of six years with signs of motor neuron degeneration and skeletal muscle atrophy on post mortem examination. The most severe form of SMA, type 1, is also sometimes referred to as Werdnig-Hoffmann disease. In Scandinavia, the condition was first described by a professor in Copenhagen who reported on a total of 112 cases of what was referred to as "progressive infantile muscular atrophy" in 1950.[2] Elsewhere, a milder form of the same condition was described in 1955 by Wolfart in the United States, and in the Nordic region by Swedish neurologists Kugelberg and Welander in 1956, as a syndrome of proximal and symmetric muscle weakness mainly affecting the lower extremities, with onset after the age of two years and a much more favourable prognosis than the infantile form of the disease.[3] The term Kugelberg-Welander disease is occasionally used for the milder form of SMA, type 3. In the decades that followed, from the 1960s through to the 1980s, a large number of cases of SMA were described, sparking a discussion on the aetiology of the disease and possible underlying genetic causes for the different forms.

> ***"During this period, it became clear that SMA was in fact one of the most common neuromuscular diseases."***

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"During this period, it became clear that SMA was in fact one of the most common neuromuscular diseases seen by neurologists," said Professor Tulinius. However, uncovering the genetic aspect of the pathophysiology of SMA did not begin until 1990, when chromosome 5q was identified as the locus of the genetic defect in SMA. Shortly afterwards, in 1992, it became possible to diagnose SMA prenatally, but it was not until 1995 that the survival motor neurone (SMN) gene was first characterised. The so-called SMA area on chromosome 5q contains the SMN1 gene; SMA occurs when defects such as deletions or mutations in this gene are present on both chromosomes. The SMA area on chromosome 5q also contains the SMN2 gene, which is almost identical to the SMN1 gene. While the SMN2 gene produces a truncated, non-functional SMN protein – unlike the SMN1 gene where the resulting SMN protein is full-length and fully functional – in conditions such as SMA where the SMN1 gene is missing or not working, the SMN2 gene can to some extent compensate for the deficiency in protein synthesis.[4]

In the early 2000s, Professor Tulinius and his colleagues at Sahlgrenska University Hospital in Sweden reported on an epidemiological study on childhood neuromuscular disorders in the western part of Sweden, which showed an annual incidence of SMA of 1 in 12,000 children.[5] In the period from 1980 to 2006, a total of 47 children were diagnosed with SMA in western Sweden; 16 of these children had SMA Type 1, all with two copies of the SMN2 gene. Among the children with SMA Type 1, the age of disease onset ranged from 0.1 to 0.3 years, and the age at death ranged from 0.4 to 0.9 years, with the exception of two children who received treatment with continuous positive airway pressure (CPAP) and survived for 1.4 and 4.5 years, respectively.[5] The first standard of care for SMA to be introduced in the Nordic countries was referred to as the Scandinavian reference programme and appeared in 2005; this was soon discontinued in favour of the first published consensus statement for standard of care in SMA, which was published in 2007.[6] These guideline documents covered all the key elements of caring for patients with SMA, from diagnostics and genetic testing to pulmonary and nutritional support, orthopaedic interventions and rehabilitation, medications and immunisations, psychosocial support, and palliative care provision. Updated recommendations were published in 2018, to take into account scientific and clinical advances in these fields.[7,8] From his own experience as one of the originators of the first Scandinavian reference programme for SMA, Professor Tulinius stressed the importance of recognising the complexity of SMA patients and the variability of their needs when devising a care programme. "Multidisciplinary management is the cornerstone of SMA care," he said. The multidisciplinary team, which should comprise not only the neuromuscular disease specialist and paediatric nurse, but also specialists in fields such as physiotherapy, respiratory medicine and orthopaedics, has a key role to play not only at the point of diagnosis, but also to facilitate shared decision-making with patients and their families, and also to guide the transition from paediatric to adult care when the time comes.

> ***"Multidisciplinary management is the cornerstone of SMA care."***

Professor Tulinius's team at Sahlgrenska currently cares for a total of 72 patients with SMA; the centre is part of the EURO-NMD European Reference Network (ERN). Current research projects at the centre include analyses of specific proteins in the cerebrospinal fluid of patients with SMA that could function as biomarkers of neurodegeneration. One such protein is the neurofilament light protein (NFL), which is a well-established biomarker for axonal degeneration across a wide range of neurodegenerative diseases.[9] NFL levels in CSF have been shown to correlate with stabilisation

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of motor function in children with SMA Type 1.[10] Looking ahead, Professor Tulinius is looking forward to the introduction of newborn screening for SMA in Sweden in the near future. “An application to include SMA in the national newborn screening programme in Sweden has been submitted to the National Board of Health and Welfare – I hope we will not have to wait until 2025 for approval,” said Professor Tulinius, referring to the ongoing SMA Europe project that was highlighted in the opening presentation of the meeting.

Other challenges that Professor Tulinius can see ahead for specialists working in the field of SMA include the continued need to promote multidisciplinary management, and improving collaboration between specialist treatment centres and local caregivers to help patients and families cope with SMA nearer their own homes.

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Measuring what matters: adult patients' expectations and perceptions

The patient perspective of adult individuals living with SMA is seldomly reflected in clinical studies in SMA. In the concluding talk at Lis-n & Ler-n 2021, Professor Thomas Meyer from Berlin described the results of a multicentre, observational study in adults with SMA that highlight how established and validated tools can be used to gauge patient priorities and perceptions in terms of their functional deficits and the treatment they receive.

Even within the established SMA categories, there is considerable variation among patients in terms of the milestones reached, the severity of the disease and the expectations of treatment. The study led by Professor Meyer included a total of 151 patients from nine different SMA centres across Germany.[1] The median age at inclusion was 36 years (range 15 to 69 years) and the median age at symptom onset was 5.3 years. The majority of the patients (60%) in the study had SMA Type 3. One of the main instruments used to capture the patients' degree of functional impairment was the extended version of the Amyotrophic Lateral Sclerosis Functional Rating Scale (ALS-FRS-ex). This is an established tool for assessment of motor function of the bulbar region, extremities and trunk, including breathing ability and the need for ventilatory support. ALS-FRS-ex has been validated for use with patients with ALS; the investigators in this study agreed that it also has utility in SMA and it was included as an exploratory endpoint. The ALS-FRS-ex questionnaire consists of a total of 15 items, each rated from 0 to 4 and with a total score ranging from 0 (poor function) to 60 points (full function). The patients included in the German study had an overall median ALS-FRS-ex at baseline of 40 points; patients with SMA Type 3 had the highest median score of 46 points, versus 25 points for SMA Type 1 patients and 33 points for those with SMA Type 2.

> ***"Even within the established SMA categories, there is considerable variation among patients in terms of the milestones reached, the severity of the disease and the expectations of care ."***

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Treatment Satisfaction Questionnaire for Medication (TSQM-9)

Effectiveness	Convenience	Global satisfaction
1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?	**4.** How easy or difficult is it to use the medication in its current form?	**7.** Overall, how confident are you that taking this medication is a good thing for you?
2. How satisfied or dissatisfied are you with the way the medication relieves your symptoms?	**5.** How easy or difficult is it to plan when you will use the medication each time?	**8.** How certain are you that the good things about your medication outweigh the bad things?
3. How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?	**6.** How convenient or inconvenient is it to take the medication as instructed?	**9.** Taking all things into account, how satisfied or dissatisfied are you with this medication?

TSQM, Treatment Satisfaction Questionnaire for Medication.
Meyer T, et al. Eur J Neurol. 2021;10.1111/ene.14902.

Another important tool that was included in the baseline assessments was the Measure Yourself Medical Outcome Profile (MYMOP2), a brief, patient-generated, problem-specific questionnaire in which the respondent is asked to identify the two symptoms or impairments that bother them the most and rate these on a seven-point Likert scale from 0 to 6 where 0 represents 'as good as it could be' and 6 represents 'as bad as it could be' (Figure 1). The mean symptom severity on the MYMOP2 scale at baseline was 3.7. The responses showed that patients ranked their target symptoms differently depending on SMA type: patients with SMA Type 1 and 2 more commonly rated symptoms and functional impairment related to the upper extremities as the most bothersome, whereas patients with Type 3 SMA tended to be more bothered by functional deficits in the legs. Patients with SMA Type 1 and 2 also rated respiratory and bulbar function impairment as bothersome to a greater extent than patients with SMA type 3. The investigators were surprised to find that the patients with SMA type 1 and 2 were disinclined to rate impaired leg function – a prominent feature of the clinical presentation for these patients – as the most bothersome, indicating a possible discrepancy between patients' degree of functional deficit and treatment expectations.

> *"Patients with SMA type 1 and 2 were disinclined to rate impaired leg function as the most bothersome, indicating a possible discrepancy between patients' degree of functional deficit and disease perception."*

Professor Meyer speculated that this discrepancy may reflect either that patients with SMA type 1 and 2 have no real expectations of improvements of these functional deficits, or that they simply give less priority to the subjective burden of this deficit compared with other symptoms – further research will be required to provide an answer to this question.

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Take-home summaries

The work and priorities of SMA Europe
Vanessa Christie-Brown, Research Programme Manager, SMA Europe, United Kingdom

Since its foundation in 2006, SMA Europe has evolved into a powerful international stakeholder, promoting and generating patient-relevant research, ensuring the needs of people across Europe are taken into account throughout the drug development process, generating evidence on access to diagnosis, treatment and care in Europe and empowering member advocacy and research organisations across Europe in their efforts to improve the lives of people and families affected by SMA. Key priorities for SMA Europe in the coming years include identifying research priorities, mapping out access to diagnosis, treatment and care in Europe, hosting international scientific congresses in the field of SMA, and promoting new-born screening for SMA in all member countries.

Everyday experiences of living with SMA in a time of change
Elin Hjorth, Nurse, Ersta Sköndal Bräcke University College, Stockholm, Sweden

A research programme of nationwide surveys and qualitative interviews with families affected by SMA in Sweden and Denmark found that coping with SMA and being forced to develop resilience and confidence in the face of everyday challenges affected both patients and families in a profound way. For parents, having a mutually respectful relationship with the healthcare professionals caring for the child played a vital role. Advances in the care and treatment of SMA have allowed the families to feel more confident about their present situation and for the future.

Fatigable or not? That is the question in SMA
Bart Bartels, Physiotherapist, University Medical Center Utrecht, the Netherlands

Fatigability is a disabling and frequently reported complaint among patients with SMA. By measuring fatigability in relation to SMA disease progression using validated endurance tests, healthcare professionals can capture clinically meaningful changes in physical performance that are not covered by other assessments, with a view to adapt and individualise physical interventions.

SMA: An extraordinary, multi-dimensional, and very cool story
Thomas Crawford, Neurologist, Johns Hopkins Hospital, Baltimore, MD, USA

The current way of describing the pathophysiology of SMA – as a condition of muscle weakness related to a cell-autonomous disorder, caused by the absence of SMN expression in motor neurons – cannot fully account for the curious clinical course of SMA in which all patients, irrespective of SMA type, appear to reach a plateau of function before going into a long, slow decline. Instead, it would be more consistent with the underlying biology of SMA to describe it as a combination of developmental and degenerative forces: a range of developmental pathology that is partly determined by the SMN2 copy number, and which is often masked by normal muscle development in the first period of life, followed by clinical weakness that emerges clinically at a time related to the level of early pathology.

SMA through history and future challenges
Már Tulinius, Neuropaediatrician, Queen Silvia Children's Hospital, Gothenburg, Sweden

The first cases of SMA were reported in the medical literature in the late 19th century, and a century later the genetic mechanism responsible for the condition was identified as defects in the SMN1 gene on chromosome 5q. In Sweden, the annual incidence of SMA is around 1 in 12,000 children. Evidence-based guidelines recommend a multidisciplinary approach to caring for patients with SMA, involving clinicians and nurses as well as specialists in physiotherapy, respiratory medicine and orthopaedics not only for the diagnosis of SMA, but also to facilitate shared decision-making with patients and families, and guide the transition from paediatric to adult care.

Measuring what matters: adult patients' expectations and perceptions
Thomas Meyer, Neurologist and palliative care specialist, Charité – Universitätsmedizin Berlin, Germany

There is considerable variation within each category of SMA patients in terms of the milestones reached, the severity of the disease and the expectations of treatment. Adult SMA patients' responses to validated questionnaires in a multi-centre, observational study indicate that higher levels of functional impairment do not necessarily correlate with a high perceived burden of symptoms and deficits. This lack of correlation may reflect a lack of expectations of improvement, or differences in priority between different symptoms and deficits.

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