Newborn Screening for SMA - Results After Two Years of a Large Pilot Project

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Research

Abstract

Background: Spinal muscular atrophy (SMA) is the most common neurodegenerative disease in childhood. Since motor neuron injury is mostly not reversible, early diagnosis and treatment are essential to prevent major disability. The aim of this study was to assess the impact of newborn screening (NBS) for SMA on clinical outcome.

Methods: The pilot project started in January 2018 in Germany and is still ongoing. Genetic screening via PCR of the SMN1 gene from dried blood spots was implemented in the routine NBS structure. Follow-up included neurophysiological examinations, CHOP INTEND and HINE-2.

Results: Among 297,163 screened children, 43 cases of SMA were identified, resulting in an incidence of 1:6910. In 21 patients with ≤3 *SMN2* copies, treatment with nusinersen according to the FDA/EMA guidelines was started age 14-39 days. Median follow-up period, regarding motor milestones was 12.3 months (range 1.5-26 months). All pre-symptomatically treated patients remained asymptomatic as far as age at last examination already allows this statement. 41% of patients with 2 *SMN2* copies had already early, mostly subtle signs of disease. These patients reached motor milestones, however with a certain delay. None developed respiratory symptoms. Two untreated patients with 2 *SMN2* copies died. Four untreated patients with 3 *SMN2* copies, one of whom was initially diagnosed with 4 *SMN2* copies by a different method, developed proximal weakness at ages 6-11 months. Two siblings of babies with 4 *SMN2* copies were identified with a missed diagnosis of SMA 3.

Conclusion: Identification of newborns with infantile SMA improves neurodevelopmental outcome enormously. It should be introduced in all countries where therapy is available. Detection of SMA via NBS did not increase the incidence compared to the known incidence rate. Early treatment of patients with 4 *SMN2* copies should be considered.

Introduction

Spinal muscular atrophy (SMA) is the most common neurodegenerative disease in childhood. The estimated incidence in newborns is 1:6,000 to 1:11,000 [1]. A recent study in Germany combining data from neuromuscular centers, genetic institutes and patient registries [2] revealed an incidence of 1:7352 in 2014. The classification of SMA originated from the time before pharmacological treatment was available and is based on the natural history of the disease. Untreated SMA 1 children are never able to sit and most often die from respiratory failure in the first two years of life. Untreated SMA 2 patients show first symptoms between 6 and 18 months and achieve sitting but not walking. SMA 3 manifests after ambulation has been - often only transitorily - acquired. SMA 0 with severe weakness and respiratory insufficiency at birth and SMA 4 with onset late in adulthood account for less than 1% of cases. Before pharmacological treatment became available, SMA was the most frequent monogenic cause of death in infancy [3].

A homozygous deletion in the *SMN1* gene, encoding the SMN (survival motor neuron)-protein, is responsible for the autosomal recessive disorder in more than 95% of cases [4].

Reduced levels of SMN protein result in motor neuron death in the spinal cord. Expression of SMN protein in spinal cord samples is highest during early stages of development [5]. In humans there is a paralogous gene termed *SMN2* that differs from *SMN1* by only a few nucleotides. A critical c.840 C > T transition results in aberrant splicing, excluding Exon 7. Only 5–10% of functional protein result from transcription of *SMN2*. Thus, the severity of symptoms in SMA largely depends on the *SMN2* copy number, however there are other genetic modifiers [6].

In recent years, pharmacological treatment for SMA has been developed. *SMN2* splicing modifiers and gene replacement therapy have shown to alter the course of SMA in humans [7][8][9]. Nusinersen, an antisense oligonucleotide, (Spinraza®) was approved by the FDA in 2016 and by the EMA in 2017 for all subtypes of 5q-SMA. The adeno-associated virus vector-based gene therapy Onasemnogene Abeparvovec (Zolgensma®) was approved by the FDA in July 2019 for SMA 1 in children < 2 years. Trials using orally available splicing modifiers and SMN-independent therapies are currently underway [6].

Nevertheless, most patients treated after onset of symptoms remain severely disabled. Given the pathophysiology of the disease and data from pre-clinical models demonstrating rapid death of motor neurons [10][11], early intervention is mandatory for a better outcome [12]. Experts agree that newborn screening should be established and first pilot projects for a genetic NBS for SMA are underway [13][14][15][16][17][18].

Methods:

The NBS procedure has been published in a previous manuscript [15]. In short, screening was performed in two federal states of Germany, starting in January 2018. Genetic screening for SMA was offered to all maternity clinics cooperating with the screening laboratory (Labor Becker and colleagues, Munich (initially Labor Becker, Olgemöller) which runs the pilot project. Parents had to give additional informed consent for genetic testing for SMA. The screening laboratory covers about 78% of the newborns in Bavaria (birth numbers about 127.000 per year in 2018) and 37% in North Rhine-Westphalia (birth numbers about 173.000 per year in 2018). In total 312.616 babies/year were tested for SMA in two years. Quantitative PCR was performed from DNA extracted from DBS to screen for a homozygous deletion of exon 7 [19]. Confirmation of the homozygous deletion of exon 7 of the *SMN1* gene and determination of the *SMN2* copy number by MLPA was performed from a new, whole blood sample (Genetikum ®, center for human genetics, Neu-Ulm). Between January 2018 and January 2019, SALSA® MLPA® Probemix P021-A1 SMA was used, and from February 2019 onwards the modified and improved Kit SALSA® MLPA® Probemix P021-B1 SMA was used. Since the reanalysis of a symptomatic child with presumed 4 copies of *SMN2* showed indeed 3 *SMN2* copies [20] despite repeated analysis, all samples were

reexamined with the B1 kit in two different laboratories (Genetikum ®, center for human genetics, Neu-Ulm, and Institute of Human Genetics, RWTH, University of Aachen)

The decision to treat was made according to the recommendations of the "American SMA NBS Multidisciplinary Working Group", published in 2018 [21]: Immediate treatment with Nusinersen was recommended in children with 2 and 3 *SMN2* copies, and a watchful waiting strategy in children with ≥ 4 copies. Patients underwent regular standardized neuropediatric examination, CHOP INTEND and HINE-2 testing, and electrophysiological exams every 2–3 months.

An annual survey, covering all neuropediatric centers in the state of Bavaria, was again performed in January 2020, asking for all new SMA-cases in 2019 for vice-versa incidence calculation and exclusion of SMA cases with false-negative NBS.

Children with normal examination at first visit, no detoriation in the first 4 weeks of life and an ulnar CMAP amplitude > 1 mV were considered asymptomatic.

Data-cut for the inclusion of patients was the 15th of January 2020, exactly 2 years after start of the screening project. In patients 1, 5, 14, 21, 27, 31, 32, 33 and 37, information regarding motor milestones was available after this date and we added this extra information in Fig. 1a and in Fig. 2.

The local ethics committee of the participating universities (project no. 18–269) approved the study. Informed consent was obtained from the participating families, except from those who did not make appointments from the start or did not take up the treatment options.

Results

Participation:

312.616 DBS cards were sent from the participating maternity clinics in Bavaria and North Rhine Westphalia between 15th January 2018 and 15th January 2020. 87% DBS cards (87%) were marked to opt for the SMA screening and were tested. In 13%, parents did not opt for the SMA-NBS. In most of these cases, the obstetricians were not willing to give additional information to the parents concerning the SMA screening due to the additional workload for the extra informed consent. The number of a priori non-participating hospitals declined from six to one during the project. One clinic formally declared willingness to participate, but NBS-cards were uniformly marked as „without SMA", raising doubts if parents were really informed about the pilot project.

Timelines:

In Germany DBS cards for NBS are typically collected between the first and the third day of life. Positive results were reported to the neuromuscular center on median day 6 of life (range 3–9 days), a second blood sample was taken on median day 8 (range 6–14 days), confirmation diagnosis and number of *SMN2* copies were available on median day 14 (range 9–23 days).

Incidence, sensitivity and specificity:

Out of the 297,163 newborns screened for SMA between 15-Jan 2018 and 15-Jan 2020, there were 43 cases with a homozygous deletion of exon 7 of the *SMN1* gene, resulting in an incidence of 1:6910. In Bavaria, a survey between pediatric neurologists was done to identify cases who have not been screened for SMA. Taking together data from the NBS and the survey, 29 SMA cases in 255.858 childbirths were found. 24 cases were detected by NBS and 5 additional patients who had not been screened for SMA (4 cases with SMA 1 born in 2019, and one case with SMA 2 born in 2018). Thus, the incidence of new diagnosed pediatric patients was 1:8822.

Molecular genetic findings

All positive tests in the NBS were confirmed by MLPA. Until now, no SMA case overlooked by the NBS has been detected and no false positives have occurred so far. With regard to the *SMN2* copy number, 17 patients had 2, nine patients 3, 15 patients 4 and two patients 5 copies. After the MLPA kit had changed, the copy number of *SMN2* in a child, who developed proximal weakness at eight months (patient 11), had to be corrected from 4 to 3. Thus, the distribution is currently 39.5% with 2 *SMN2* copies, 21% with 3 *SMN2* copies and 39.5% with ≥ 4 *SMN2* copies.

Symptoms and signs at first investigation

Eight patients with 2 *SMN2* copies were not completely asymptomatic on first examination. Ulnar CMAPs were < 1 mV in five children (patients 1, 19, 20, 21 and 31, four of them had additional clinical symptoms: three with a CHOP INTENT Score of ≤ 35 at first examination (Patients 1, 20 and 19, the latter even scored only nine points) and one developed severe muscular weakness of the lower extremities age 2 weeks (Patient 21). One child, without initial electrophysiologic examination, declined severely at the age of 2 weeks (Patient 4).

Two patients showed a decline in muscle strength in the legs during the first weeks of life despite ulnar CMAPs of 1.2 and 1.1 mV, respectively (Patients 32 and 33).

All patients with ≥ 3 copies of *SMN2* were asymptomatic in the first examination and had CMAPs > 1 mV.

No child showed signs of respiratory involvement or bulbar weakness immediately after birth.

Treatment

21 children with ≤ 3 copies of the *SMN2* gene started Nusinersen treatment at a median age of 20 days (range 14–39 days). The median interval between confirmation of the diagnosis and start of treatment was 6.5 days (range 1–16 days). Five patients from four families were not treated: four (including twins) due to refusal by the parents, and one due to lack of reimbursement (a family without permanent German residence or citizenship).

In one child with onset of symptoms at the age of 8 months, treatment was administered when already symptomatic; due to an incorrect initial estimation of the *SMN2* copy number.

In one child with 4 *SMN2* copies, treatment was started at the age of six months. The parents opted for an early start of treatment due to a positive family history.

Electrophysiology

Ulnar CMAP amplitudes of all patient groups are shown in Fig. 1c. Children with a CMAP < 1 mV were considered as symptomatic. After treatment, CMAPs in this group increased, but did not reach the level of the asymptomatic children.

Outcome in treated children with 2 SMN2 copies

Median follow-up period regarding motor milestones (Fig. 2), was 10.5 months for both, symptomatic and presymptomatic patients with 2 *SMN2* copies (average 12.1 in presymptomatic children, range 6–22 months and 13.6 in already symptomatic children, range 9.5–26 months, respectively). All presymptomatically treated children remained symptom-free so far and achieved normal motor milestones. Three of them are already able to walk independently.

Eight children with 2 *SMN2* copies already had overt or subtle signs of disease on their first visit at the age of a few days. In all of them, CHOP INTEND and HINE-2 improved under therapy (Fig. 1a). Motor milestones were delayed in comparison to completely asymptomatic children (Fig. 2, supplemental table 1). The eldest (Patient 1) learned to walk independently at the age of 24 months, and shows a tremor. Patient 20, who started with a CHOP INTEND of only 9 points, is able to sit with some help, and to roll over on both sides at the age of 10 months. Patient 21, whose CHOP INTEND declined from 41 to 22 within the first 3 weeks of life, was able to sit unassisted at the age of 10 months. No respiratory involvement has occurred in any early treated patient with 2 *SMN2* copies. So far, no child developed orthopedic complications like scoliosis or contractures, or feeding by gastral tube.

Outcome in untreated patients with 2 SMN2 copies

Two patients with 2 SMN2 copies were not treated. One of them had symptoms already in the first weeks of life, the other remained clinically and electrophysiologically asymptomatic until the age of 3 months, at which time a rapid deterioration started. Both children died at the age of 5.5 months.

Outcome in treated children with 3 SMN2 copies

Median follow-up period regarding motor milestones (Fig. 2), was 13 months (average 13.2 months, range 5–24 months). All presymptomatically treated children with 3 *SMN2* copies remained asymptomatic, as far as the observation period allows to state (since some 3 *SMN2* copy infants do not become symptomatic until 12–15 months of age). All but one (with a minimal delay of milestones in one child with laxity of the joints but without neurophysiological hints of SMA) achieved WHO motor milestones in time. Two patients already have learned to walk independently. No respiratory involvement occurred in any patient with 3 *SMN2* copies, who was treated promptly after birth so far.

Outcome in untreated patients with 3 SMN2 copies

In twins (patients 15 and 16) with 3 *SMN2* copies, parents refused treatment and one family (patient 29) initially refused any medical contact when calling them for positive screening result. A proximal weakness was noticed at the age of 11 months in the twins and at the age of 6 months in patient 29, whose parents did not search medical attention until the age of 11 months. Both families still do not accept pharmacological treatment of the children. After the initial rapid deterioration, the twins had stabilized and showed some minor improvement (HINE-2, Fig. 1b). They had learned independent sitting already before onset of symptoms at age 8 months and did not achieve any further motor milestones. Patient 29 did not learn to roll over at the age of six month and did never achieve unsupported sitting, fulfilling finally the criteria of an SMA type 1.

One child with an initial diagnosis of 4 *SMN2* copies became symptomatic with proximal weakness and neurogenic pattern in the EMG at the age of eight months. Repeat testing of the *SMN2* copy number with an improved kit after several months showed only 3 copies. CMAPs of the ulnar and tibial nerve remained normal. Treatment was started after another five weeks. At that time, the child was unable to bear any weight on the legs. She was making clinical progress under therapy with nusinersen again, and finally achieved the ability to walk independently age 25 month (Fig. 1a, Fig. 2).

Outcome following "strict follow-up" strategy in patients with ≥ 4 SMN2 copies and secondary diagnosis for siblings

Median follow-up period regarding motor milestones (Fig. 2), was 13.2 months (average 13.0 months, range 1.5–26 months). 17 children with ≥ 4 *SMN2* copies remained without symptoms until their last examination.

In two families with newborns with 4 *SMN2* copies the family history was initially reported as unremarkable. During the follow-up, both families reported that the 5-year-old and 6-year old brothers, respectively, had unclear motor developmental symptoms. They had been diagnosed as congenital ataxia and clumsiness, respectively. Symptoms were an unsteady gait and a tremor with onset at the age of 3 years in one and a tendency to tiptoe-walk and muscular fatigue from age 3 years in the other. A homozygous deletion in the *SMN1* gene proved the diagnosis of SMA 3 and treatment was initiated in both. In the two screened index patients, a start of treatment within the first year of life irrespective of the clinical status is being discussed with the parents.

Adherence to treatment and follow-ups

The overall adherence to the recommended neurological control visits was good. Apart from one family, who even refused confirmation of the diagnosis and two families who decided against therapy, all families with children with ≤ 3 *SMN2* copies complied well with therapy and the recommended follow-up examinations.

Three patients with 4 *SMN2* copies were lost to follow-up at different time points (Fig. 2). Further details and a broad discussion on patient's issues with 4 *SMN2* copies has already been already published [22].

Discussion

We present the outcome of a large cohort of SMA patients detected by a newborn screening project for SMA.

The basic criteria for a newborn screening[23] are given. Sensitivity and specificity are high. Most parents opted for a screening. In a former study it has been shown that there is a wide acceptance of SMA NBS in the British population [24]. Adding a genetic screening to the NBS had no negative effect on the overall acceptance of NBS. A crucial point is to convince the obstetricians that the benefits of the SMA NBS outweigh the additional workload caused by the additional informed consent for a genetic screening.

Our study is the first one to investigate the impact of early diagnosis via genetic NBS for SMA and early treatment on clinical and neurophysiological outcome in a large screening program. In summary, a cohort of 21 children with an expected severe form of SMA was amenable to immediate drug treatment after diagnosis through NBS.

In our group of patients with 2 *SMN2* copies, half of the patients showed subtle albeit significant signs of motor neuron disorder in the first weeks of life. Notably, there were manifestations of reduced muscle strength in the legs or CMAPs < 1 mV (N. ulnaris), which at this time would have been missed on a routine examination. NBS avoided a diagnostic delay which otherwise still is the rule [25, 26]. Since SMN expression is highest prenatally [5], it is reasonable that motor neuron death already occurs to some extent before birth. Our electrophysiological data (Fig. 1c) show that though there is an increase in the CMAPs in all patients, children with preexisting damage of the motor neuron might not achieve normal values.

The group of children with early symptoms developed quite well clinically after prompt diagnosis and treatment. CHOP INTEND and HINE-2 suggest that even in this group a continuous development is possible (Figs. 1 and 2). Our results to date are consistent with the Nurture study, which enrolled 25 patients with SMA shortly after birth, including children with an initially low CHOP INTEND. All participants finally achieved the ability of to sit without support, 92% to walk with assistance, and 88% to walk independently [12], however motor milestones were often delayed in patients with 2 *SMN2* copies.

In the study of Mendell et al [9], two symptomatic children undergoing gene transfer did learn to walk. However due to the limited number of patients and to the short observation period a comparison between different treatment strategies is not possible yet.

Our patients with 2 *SMN2* copies, without any signs prior to initiation of treatment, and all patients with 3 *SMN2* copies developed completely normally so far. This is a clear argument that pre-symptomatic therapy can prevent the death of motor neurons. Even if the long-term outcome is still unclear, preliminary data of the Nurture study show that the effect lasts at least for up to 4 years [12]. No treated child

developed respiratory involvement or died. In contrast, in the Endear study ventilator-free survival was 61% only.

Our two untreated children with 2 *SMN2* copies developed SMA 1 and died at the age of 5.5 months. Three of four untreated patients with 3 *SMN2* copies developed SMA 2 and one patient developed SMA 1. These cases underline the ethical issues, which are linked to newborn screening.

The handling of patients with ≥ 4 copies of *SMN2* is still a matter of debate. The burden of therapy and costs must be weighed against benefits in a group of children whose prognosis cannot be accurately predicted, which led to a missing consensus of the SMA NBS Multidisciplinary Working Group in 2018 [21]. In our cohort, three children's close relatives with the same genotype had developed SMA 3 during early childhood. In 2020, the group then modified the recommendations and voted for a treatment of children with 4 and watchful waiting for those with 5 *SMN2* copies [27]. However, the estimation of the *SMN2* copy number poses some methodological problems. In up to 45% of cases, retesting leads to a miscall of the initially determined copy number [20], a problem mainly in patients ≥ 4 copies depending on the quality of the DNA but although relevant in all other patients. In our cohort, one child with 3 *SMN2* copies was initially diagnosed with 4 and became symptomatic. Two children were diagnosed with 4 *SMN2* copies initially and then turned out to have 5. This highlights the necessity of confirming the copy number in a second laboratory, as the treatment algorithm is based on the *SMN2* copy number and newer recommendations include treatment of children with 4 or less *SMN2* copies.

Watchful waiting in patients with 4 *SMN2* copies bears a significant number of additional problems, including increased psychological burden and maladherence. Further aspects have been discussed in detail in a separate paper [22].

Regarding the socio-economic costs of SMA NBS, none of our children incurred additional expenses apart from the medication. Studies on costs of illness per year estimated €70,566 per patient in Germany in 2013 [28]. Very recently, the nusinersen-unrelated total mean healthcare costs in the US were calculated to be $92,618 in the group of nusinersen-treated SMA1 patients [29]. Thus, NBS reduces secondary costs substantially. A better quality of life can be expected as a result of the less severe course of the disease. It was found that symptomatic SMA causes relevant psychosocial issues for both, the patients and the caregivers and that substantial social and economic burden were considerably attributable to the high direct non-healthcare costs [30].

Summary And Conclusion

Genetic NBS for SMA is well accepted. The method is highly sensitive and specific. Prompt treatment significantly improves the outcome in infantile SMA. NBS should be introduced in all countries where therapy is available. Comparison with existing german data confirmed that NBS did not lead to a relevant increase of incidence. Early treatment of patients with 4 *SMN2* copies seems to be prudent to prevent relevant disability.

Abbreviations

SMA (spinal muscular atrophy)

NBS (newborn screening)

DBS (dried blood spots)

CHOP INTEND (The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders)

HINE-2 (Hammersmith Infant Neurological Examination – Section 2)

PCR (polymerase chain reaction)

MLPA (multiplex ligation-dependent probe amplification)

SMN (survival motor neuron)
CMAP (compound muscle action potential)

Declarations

Ethics approval and consent to participate:

The local ethics committee of the participating universities (Ludwig-Maximilians-University of Munich, University of Munster and University of Essen, project no. 18- 269) approved the study.

Consent for Publication:

Informed consent was obtained from the participating families, except from those who did not make appointments from the start or did not take up the treatment options.

Availability of data and materials:

All data from CHOP INTEND, HINE-2 and electrophysiology can be shared and is available at the author's institution in Munich, Dr. v. Haunersches Kinderspital, Lindwurmstr. 4, 80337 München, Germany.

Competing interests:

All authors have indicated they have no potential non-financial conflicts of interest.

Financial Disclosure:

Astrid Blaschek, Bernhard Olgemöller, Erik Harms, Katja Eggermann and Uta Nennstiel have nothing to declare.

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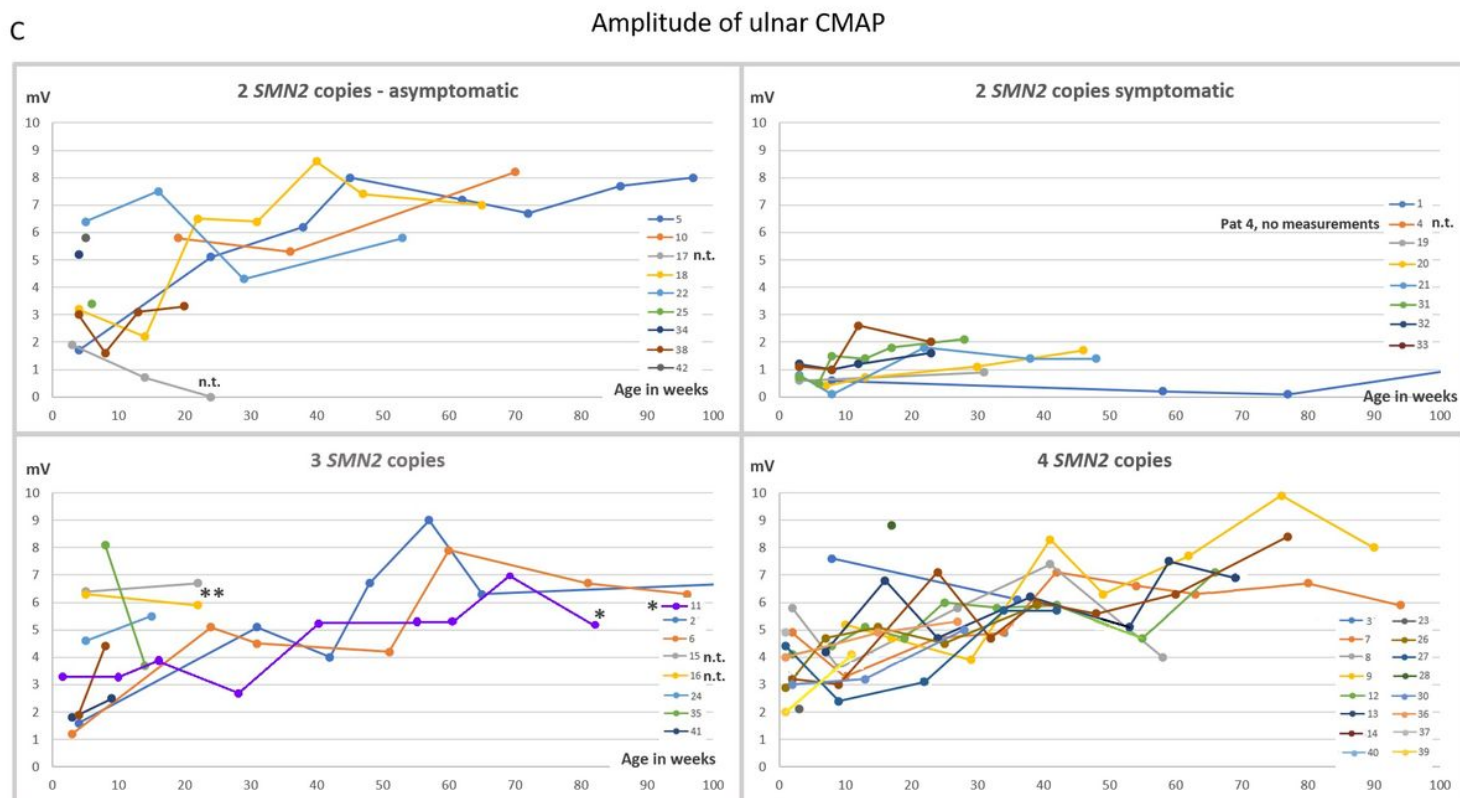
Figures

Figure 1

(A) HINE-2, (B) CHOP INTEND and (C) Ulnar CMAPs of different patient groups. *In Pat 11, symptomatic age 8 months, treated from age 10 months. In the course, the SMN2 copy number was corrected to 3 SMN2 copies. **Pat 15 and 16, not treated: Further measurements were refused by the parents. n.t.=not treated
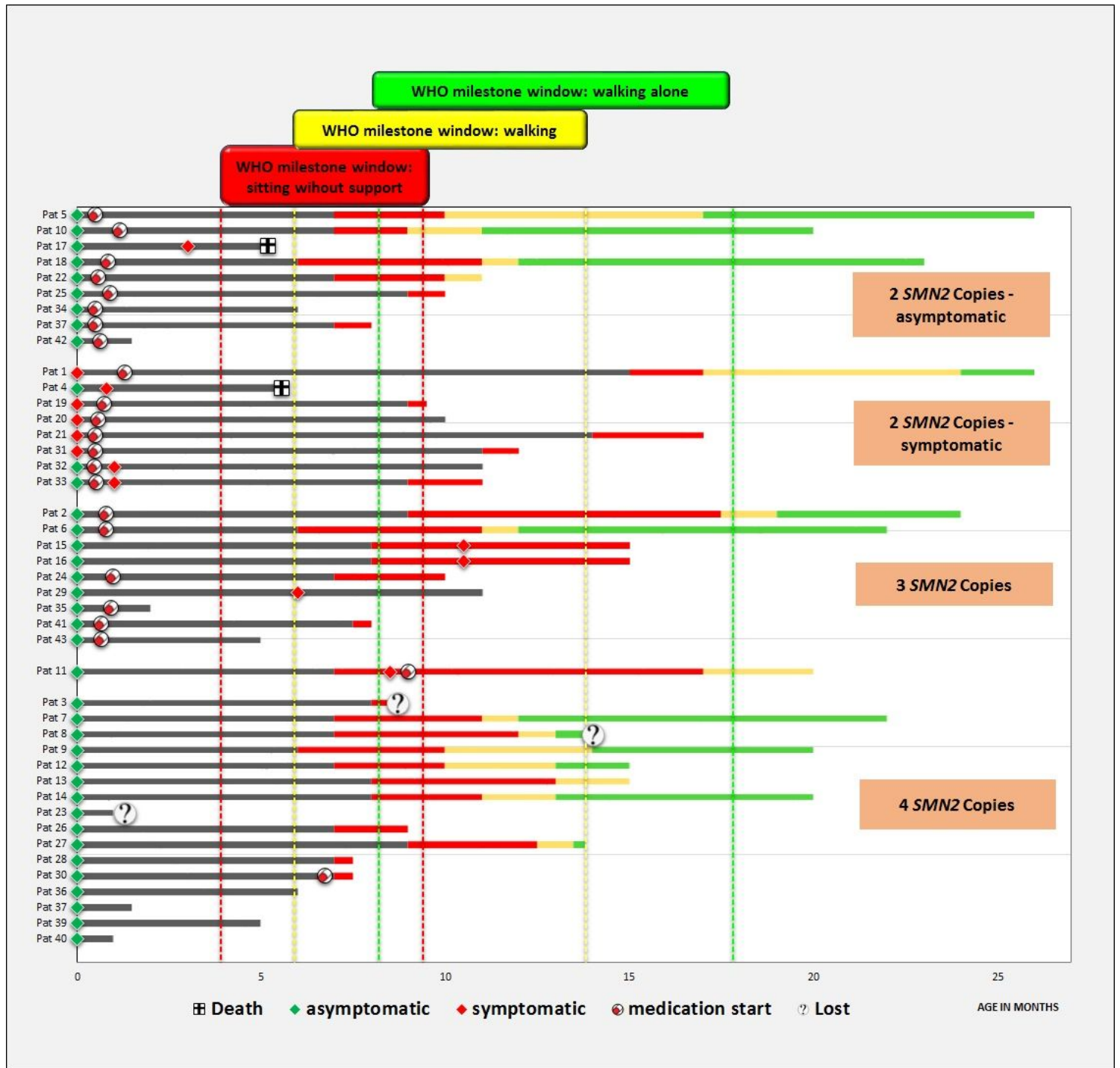

Figure 2

Achievement of WHO motor milestones of different patient groups. Bar colors: red=age when sitting independently, yellow=age when walking with assistance, green=walking independently. The bars on top indicate the respective WHO time window for normal development. *Pat 11 was initially diagnosed with 4

SMN2 copies, became symptomatic age 8 months and was treated from age 10 months. The SMN2 copy number was corrected to 3 SMN2 copies.

Supplementary Files

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- SupplementalTableextended.docx