NOVEL DISEASE MODIFYING TREATMENTS AND ELECTROSTIMULATION IN NEUROMUSCULAR DISORDERS

Medical and social part on EAMDA
46th annual general assembly

Zagreb, October 14th, 2017
Hotel Holiday Zagreb

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This scientific publication accompanies the **EAMDA 46th annual general assembly** held on 14th October 2017 in Zagreb, Croatia.

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Introduction to EAMDA's scientific publication

(46th Annual general assembly, Zagreb, 2017)

After the most significant years in the development of treatment for muscular dystrophy and other neuromuscular disorders, Croatian muscular dystrophy association (SDDH) has the honor to organize EAMDA 46th Annual general assembly (AGA). Among administrative part of the conference, we were happy to introduce with extensive medical and social program for people with different neuromuscular disorders. The main thematic orientation related to the medical part of the program has been devoted to three severe neuromuscular disorders – spinal muscular atrophy (SMA), Duchenne muscular dystrophy (DMD) and amyotrophic lateral sclerosis (ALS).

In the preamble of this edition, the second one of this kind, I use the opportunity to thank the president of EAMDA, Mr. Boris Šuštaršič, on the efforts that information about new medicines are immediately available to all EAMDA member associations, and for his engagements on building the platform for information exchange between EAMDA member organizations.

Long-term work in the movement of people with disabilities and personal experience of living with muscular dystrophy puts Mr. Boris Šuštaršič among the leaders who moves the boundaries. Therefore, the occasion of the greeting speech was an opportunity to express gratitude to Mr. Boris Šuštaršič for all his efforts, and of course, for ones in the future.

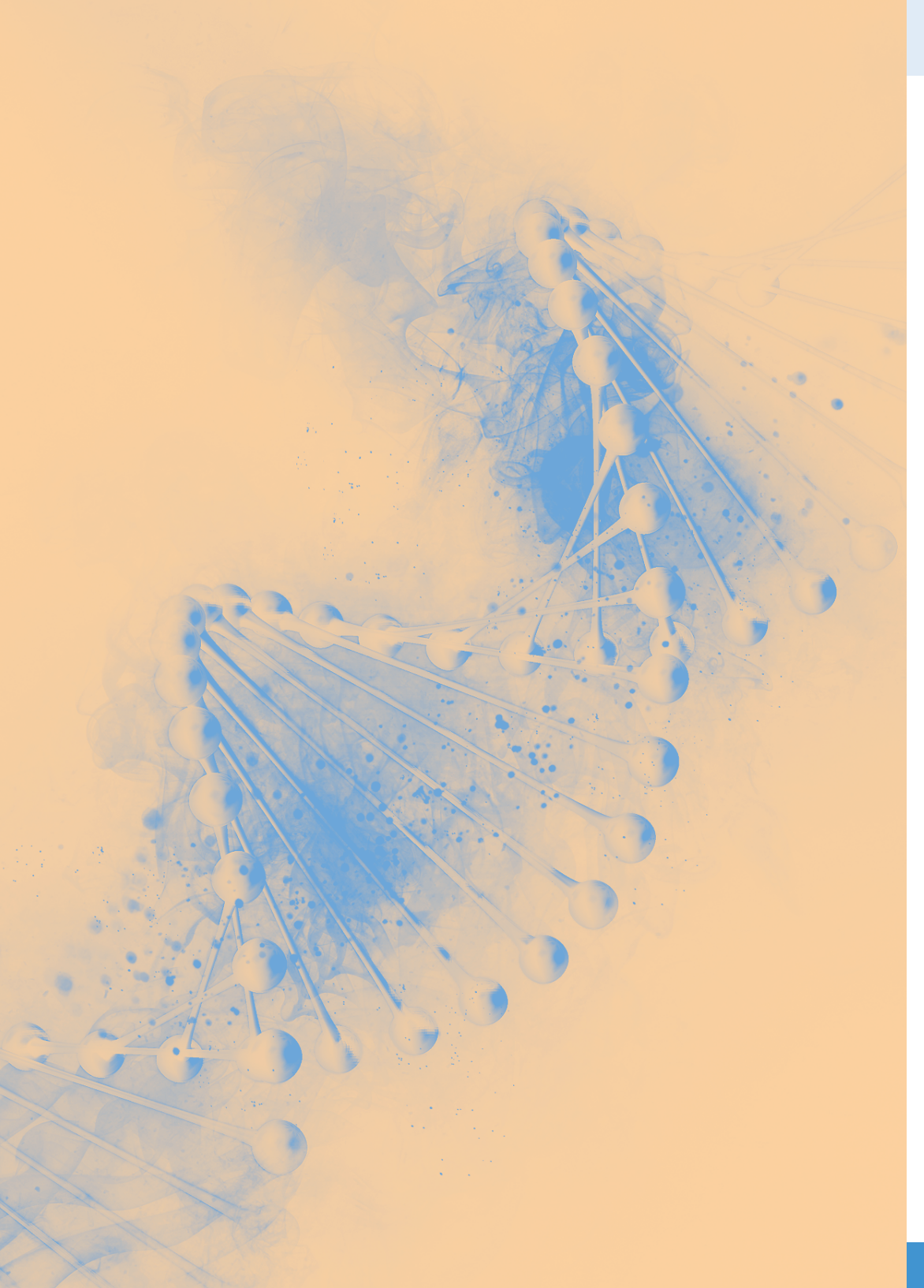
This conference in Zagreb was a chance to get together pharmaceutical industry, medical specialists, and people suffering from muscular dystrophy and other neuromuscular disorders, as well as their parents. This is mainly a holistic approach that gives the opportunity to share experiences amongst all stakeholders and to develop new, better perspectives. A special contribution is made by EAMDA, as availability of information related to executive committee meetings has been improved. The results of mutual projects are also presented in current scientific publication where all presentations have been collected for a permanent record. The crucial part of the publication is an experience with new medical and pharmacological approaches for people with neuromuscular disorders approved by the European Medicine Agency. Enormous efforts are made by parental associations and organizations of persons with muscular dystrophy with a main goal: the new treatments to be included into national health systems of each country. Along with SMA, the topics in this publication are

related to new perspectives for DMD and various healthcare approaches to ALS. New techniques of diagnostics and rehabilitation of people with neuromuscular disorders are also presented.

No less attention has been given to the second (social) part of the conference, where people with SMA and their parents presented experiences of living with the disease.

Once again, I would like to thank the president of EAMDA, Mr. Boris Šuštaršič, on his dedicated work, and to all the lecturers and other participants of 46th Annual General Assembly in Zagreb.

Marica Mirič,
President of Croatian muscular dystrophy association (SDDH)



Medical, social and administrative part of the conference: Hotel Holiday Zagreb, Croatia

EAMDA 46th Annual General Assembly

Zagreb, October 14th, 2017 (Hotel Holiday Zagreb, Jankomir 27, 10090 Zagreb)

Official opening and speeches (conference hall "HOLIDAY")

07:30 - 08:00	Registration of delegates
08:00 - 08:30	Marica Miric, President of MDA of Croatia; Zorislav Bobus, MD, President of SOIH Boris Sustarsic, President of EAMDA

I) MEDICAL PART (conference hall "HOLIDAY")

Section chairperson: prof. dr. sc. Nina Barisic

08:30 - 08:45	**Proxymal SMA-standards of care in pedatric age group and emerging therapeutic strategies** prof. Nina Barisic, MD, PhD University Clinical Hospital Centre Zagreb, Croatia
08:45 - 09:00	**SMA and SMN-Related SMA variants in Adults** prim. Davorka Vranjes, MD University Clinical Hospital Centre Zagreb, Croatia
09:00 - 09:15	**Biogen update** Caroline Daly, Senior Manager, Public Affairs, Patient Advocacy Biogen International GmbH, Zug, Switzerland
09:15 - 09:30	**Treatment of SMA patients with nusinersen: the Slovenian experience** Damjan Osredkar, MD, PhD Head of the Dpt. of Pediatric Neurology, University Children's Hospital Ljubljana, Slovenia

09:30 - 09:45	**Pompe disease** Danijela Petkovic Ramadza, MD University Clinical Hospital Centre Zagreb, Croatia
09:45 - 10:00	**New perspectives in DMD management** Dr. Sunay Ozdas, Regional Medical Head of CEE & MENA & APAC PTC Therapeutics PTC Therapeutics, Zug, Switzerland
10:00 - 10:30	**Plenary debate**
10:30 - 11:00	**Coffe break**
	Chairperson: prim. Davorka Vranjes, MD
11:00 - 11:15	**Myozyme program & treatment** SANOFI, Croatia
11:15 - 11:30	**Nutrition considerations in NMD** Prim. dr. Gordana Kovacevic MSc, Pediatric neurologist Mother and child health care Institute, Belgrade, Serbia
11:30 - 11:45	**Different healthcare in different countries for patients with ALS/MND** Assist.Prof. Ales Praznikar, MD MSc; neurologist, rehab. med. specialist Head of Department for Neurorehabilitation, UMC Ljubljana, Slovenia
11:45 - 12:00	**Muscle biopsy in the area of exome and transcriptome sequencing** Mija Meznaric Assistant Professor, MD, PhD University of Ljubljana, Medical Faculty Institute of Anatomy, Ljubljana, Slovenia
12:00 - 12:15	**Teenlifting: electrostimulation of muscles** dr. Sanja Malbasa Gosovic TEENLIFTING d.o.o., Zagreb, Croatia
12:15 - 12:30	**Teenlifting: an example of rehabilitation - person with SMA** Tea Černigoj Pušnjak, MSc, Ljubljana, Slovenia
12:30 - 13:00	**Plenary debate**
13:00 - 14:30	**Lunch**

II) SOCIAL PART (conference hall "HOLIDAY")

14:30 - 15:00	**The biggest challenges and obstacles for people with NMD in Bulgaria** Jana Popova, Bulgaria
15:00 - 15:30	**Experience with Spinal Muscular Atrophy type 1** Ana Alapic and Mate Beslic, Croatia
15:30 - 16:00	**Experience with Spinal Muscular Atrophy type 2** Stella Franjic, Croatia
16:00 - 16:30	**Experience with Duchenne Muscular Dystrophy** (Nonsense mutation) Andrea Ruzic and Pavao Ruzic, Croatia
16:30 17:00	**Plenary debate**

III) ADMINISTRATIVE PART (conference hall "ZAGREB"):

17:00 - 19:00	**46th Annual General Assembly (representatives of member associations only)**
19:00 -	**Dinner**

FRIENDS OF THE CONFERENCE

Nina Barisic

Professor, MD, PhD, specialist in pediatrics, neuropediatrician

Professor of Paediatrics, University of Zagreb Medical School, Head of Division for Child Neurology, Clinical Medical Centre Zagreb, Croatia

Leader of Referral Centre for paediatric neuromuscular disorders Ministery of health, Republic of Croatia

President of Croatian Child Neurology Society

Proxymal spinal muscular atrophy (SMA)-standards of care in pediatric age groups and emerging therapeutic strategies

Nina Barišić[1] and Anita Ursić[2]

[1] Department of Pediatrics, Zagreb Medical School, University Hospital Center, Zagreb, Croatia, Reference Center for Neuromuscular Disease Croatia

[2] Department od Pediatrics, University Hospital Split, Split, Croatia

Spinal muscular atrophy (SMA) is a neuromuscular disorder that affects approximately 1 in 6000 to 1 in 11,000 live births in the United States with a high carrier frequency of 1 in 40 to 60.[1] Incidence of all SMA in Croatia, is 4-8/per year. SMA is an autosomal recessive disease, classified into several types related to the age of onset of the disease and the degree of motor function achieved by the affected individual. Approximately 50% of patients have SMA type I with onset until 6 months of age; these infants usually do not survive beyond the first 2 years without respiratory support. It is the most severe form of SMA with extensive muscle weakness, children are never able to sit without support, have respiratory difficulties, and increasing difficulty over time with swallowing and feeding.Very severe SMA Type 0 manifest with prenatal signs and neonatal onset. Type I patients are further categorized into three subtypes: type Ia, with neonatal onset (head control never achieved) as well as in type I b); type Ib, with onset after the neonatal period as well as in type Ic while head control is being achieved in SMA tpe I c. Patients with SMA manifest clinical signs of disease between the age 7-17 months, children are mostly able to sit without support

and some may stand, but they are never able to walk independently. SMA type II patients manifest with variable severity of scoliosis, swallowing or chewing difficulties, and respiratory problems. The survival rate of type II patients is higher than type I. Patients with type III SMA have less intense symptoms and are able to walk and reach the major motor milestones, but often lose the ability to walk over time as the disease progresses. These patients require wheelchair and could develop scoliosis, obesity, hip pathology and other problems related to loss of ambulation. Because symptoms for type III SMA appear later in childhood, type III is, usualy, diagnosed later than type I or type II SMA. The type IV SMA category includes those patients with mild disease and who are diagnosed in early adulthood, between 10-30 years of age (on average ≥18 years).[1]

The gene responsible for SMA is the survival motor neuron 1 gene located in a complex duplicated region of around 500 kb. In this region, at least four genes are duplicated (SMN, NAIP, SERF1 and GTF2H2), each of which has a telomeric and a centromeric version. The centromeric copy of SMN1 is the SMN2 gene. SMN1 and SMN2 differ in only five nucleotides. The transition c.840 C>T located in exon 7 of the SMN2 gene leads to the alternative splicing of this exon. As a consequence, most SMN2 transcripts lack exon 7 (D7-SMN2), leading to a truncated and unstable protein that is rapidly degraded. SMN2 copies are present in all patients and produce around 10% to 50% of full-length SMN protein.[2]

95% of the SMN1 gene mutations are the homozygous mutations. The remaining 5% of cases are generally compound heterozygous mutations (deletion in one allele and a point mutation in the other). The SMN2 copy number is considered as phenotypic modifier of the disease and can vary from 1 to 5 copies. Most type I SMA patients have two SMN2 copies whereas most chronic type II and III forms have three SMN2 copies. [1, 2] More recently, a nucleotide variation in the SMN2 gene (c.859C>G) has been proposed as a positive phenotypic modifier found in SMA children with a lower SMN2 copy number than expected considering their phenotype. Two other genes located in the 5q13.2 region, NAIP (neuronal apoptosis inhibitory protein, currently BIRC1) and SERF1A (small EDRK-rich factor 1A), have been postulated as possible modifier genes, since they are deleted in around half the patients with severe SMA. However, their role is not prognostic for the course of disease. *De novo* mutations occur in 2% of all.[2]

Early diagnosis is essential for spinal muscular atrophy treatment strategy and outcome.[1, 3]

Standard of care in spinal muscular atrophy involve five areas: diagnostic/new interventions, pulmonary, gastrointestinal/nutrition, orthopedics/rehabilitation,

and palliative care. Consensus was achieved on several topics related to common medical problems in spinal muscular atrophy.[3] Care for children with SMA is best achieved in team based approach of many specialists and primary care providers. Parents are key members of this team and are encouraged to participate as much as possible.[4] The number one problem for SMA patients are respiratory or breathing difficulties. It is the most common cause of death among infants and children with type I and II disease.[4] The compromised respiratory muscle function results in: impaired cough, in poor clearance of lower airway secretions, hypoventilation during sleep, chest wall and lung underdevelopment; and recurrent infections that exacerbate muscle weakness and the integrity of the lung parenchyma.[4,5] Respiratory care of SMA patients is essential for survival and quality of life. SMA type I and II patients develop chronic progressive restrictive pulmonary disorders. Since respiratory care planning is so important, discussions with a pulmonologist, familiar with SMA management issues, should be done as soon as possible. Regular assessment of respiratory functions is required by pulse oxymetry (for oxygen saturation) as well asn polysomnography and chest X-ray especially for type I and II. Depending on disease severity, tools that may help are:

- manual or mechanical cough assist devices
- non-invasive ventilatory support such as bi-level positive airway pressure devices (BiPAP)
- mechanical or invasive ventilation with tracheotomy.

Invasive ventilation refers to the placement of a tracheostomy tube and use of mechanical ventilation. Tracheotomy is usually not an acute intervention for SMA patients and is controversial for SMA type 1. Tracheotomy is usually not indicated in SMA type 2. Frequent episodes of respiratory instability when off NIV may benefit from tracheostomy and mechanical ventilation. Placement of a tracheostomy tube and mechanical ventilation in children with SMA type 1 typically results in the inability of the child to tolerate time off mechanical ventilation and lack of vocalization.[5] Very important is parents-medical cowork, especially to develop a care plan for use during acute respiratory illness such as a cold or flu. Regular immunizations and flu shots are also recommended.[4]

It is very important to monitor child's growth on a growth chart and develop a individualized feeding plan. Major problems are swallowing difficulties, gastric reflux and constipation.[4,5]

Muscle weakness, as the dominant clinical sign in SMA patients, is depending on SMA type and disease severity. Orthopedic assessment for scoliosis is necessary as well as bone densitometry due to the role of SMN1 protein in bone growth and remodeling , its deficiency resulting in severe osteoporosis.[3,4]

Until last year, no disease modifying treatment was available for SMA. Management consisted of supportive measures directed at providing adequate nutrition, respiratory assistance, and treating or preventing complications of muscle weakness. Currently, a new therapeutic option became available for patients with SMA. [6,7, 8] New therapeutic products can be classified broadly into two major categories:

- genetic based therapies, such as SMN1 gene replacement therapy or SMN2 upregulation or modification
- non-genetic type therapies, such as neuroprotective strategies or altering downstream motor unit function.

Importantly, treatment considerations and care standards are dramatically altered by the development and clinical implementation of nusinersen (Spinraza, Biogen, Cambridge, MA), the first disease modifying therapy approved for SMA to treat pediatric and adult patients with SMA.[7] But historical turning point was when FDA approved that it is possible to treat patients also outside the clinical trial. Spinraza is an antisense oligonucleotide, which, administered intrathecally, is able to increase exon 7 inclusion in the majority of the SMN2 mRNA and increase the production of fully functional SMN protein. It has received the U.S. Food and Drug Administration approval in late December 2016 after initial clinical trials showing that it is safe, well tolerated and effective. Until August/2017 with nusinersen 400 patient, until max age of 15, was treated in 18 countries (67 medical centers).[6,7,9] Due to poor transport across the blood brain barrier it must be given via intrathecal injection for four initial loading doses; the first three loading doses are given at 14-day intervals, while the fourth loading dose is given 30 days after the third. Thereafter, a maintenance dose is given once every four months. Due to intrathecal injection it doesn't affect other organs for which SMN protein also has important role. In the study of infants with type I SMA (ENDEAR), the risk of death or permanent ventilation was reduced by approximately half over a 13 month period. There were also improvements in motor milestones, a standardized motor score, and electrophysiology biomarkers (ulnar and peroneal compound muscle action potential) compared to decline in these measures in placebo treated infants. Among infants with spinal muscular

atrophy, those who received nusinersen were more likely to be alive and have improvements in motor function than those in the control group. [9,10] The recently published results of ENDEAR trial showed significant improvement in motor milestones among 40% of the patients treated with nusinersen, 8 % of them were able to sit and 1 % was able to stand unasisted while all untreated patients consistently deteriorated[10]. In the phase 3 study of nusinersen in later onset SMA, or children with SMA type 2 at age 2–7 years, the results were similarly striking at end of study analysis at 15 months. Nusinersen treated children improved by four points on a standardized motor scale for SMA compared to a one point decline for the placebo group.[9] No significant major adverse events occurred secondary to the administration of this drug except for few reported cases of respiratory tract infections and constipation. Long time side effects and long life survival are unknown.[7,9] Despite its cost (84.000 Euro/dose), treatment with Nusinersen is recommended for most patients when available since it can prevent worsening of the disease and avoid respiratory failure and death.[7] The current regulatory approvals in these jurisdictions do not have any restrictions or criteria for access (e.g., such as start/stop criteria) and minimal post marketing safety mandate beyond standard pharmacovigilance.[9] The scientific and medical importance of this advance is marred by a pricing policy by the corporate sponsors that may complicate accessibility of the drug for some desperate patients. [11]

There have also been small molecules therapeutics aimed at increasing SMN2 protein levels. One strategy has been to target the SMN2 splicing pattern to include exon 7. Both PTC Therapeutics (South Plainfield, NJ)/F. Hoffmann-La Roche Ltd (Roche, Switzerland) and Novartis AG (Switzerland) have developed such molecules. The PTC Therapeutics/Roche partnership has produced another candidate molecule that started phase II trials in SMA types I–III in 2016. All these drugs are orally administered, so if safety issues can be resolved and efficacy established they offer an attractive alternative to more invasive drug delivery methods (such as needed for Spinraza). [9]

Gene therapy to replace SMN1 is an obvious candidate strategy. In fact, gene therapy with *AAV9* virus and full length SMN1 has been attempted via intrathecal delivery in a phase

1 clinical trial in infants with SMA type I. Encouraging results and a favorable safety profile have been presented at recent academic forums; all 15 study participants are still surviving and do not require 16 hr or more of ventilation per day. [12]

Other strategies for treating SMA are:

- beta-adrenergic medicines (salbutamol/albuterol) although their precise mechanism of action is not well understood, results with salbutamol or albuterol have been encouraging.
- olesoxime, a non-specific neuro-protective drug (i.e., a drug aimed at preventing neurodegeneration and apoptosis (neuronal death) that acts at the mitochondrial permeability transition pore to mitigate cell stress reactions (phase 3 placebo controlled clinical trial in type II and III SMA patients)
- CK-2127107, a cytokinetic agent that enhances muscle contractility at the actin myosin interface (phase 2 studies for SMA, is a small molecule that alters the interaction of calcium and troponin resulting in improved myofibres contractility).[9]

It has to be concluded that SMN protein related monotherapy is not sufficient for the whole life therapy strategy and such treatment should be combined with non- SMN targeting drugs.

Of note, one key challenge to any treatment for SMA is the likely presence of a therapeutic window for the disease. Data from animal models of SMA provide strong evidence for the presence of a critical 'therapeutic time-window' for delivery of SMN-targeted therapies. [7-10]

Early treatment may be necessary to maximize the benefit of the drug, with better outcomes and suggests that an earlier diagnosis, particularly for type I and II patients, will be immensely helpful to increase the chance of survival using optimal care and supportive interventions.

Ongoing creative trial design, and thoughtful regulatory consideration for rare diseases such as SMA becomes even more important.

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Spinalna mišićna atrofija – standardi liječenja i suvremena terapija

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Hrvatsko društvo za dječju neurologiju HLZ

Proksimalna / infantilna SMA

- SMA 1-proksimalna SMA: najčešći tip
- Najčešći genetski uzrok smrti dojenčadi AR
- Druga genetska bolest (AR) po učestalosti iza CF

- Podjela proksimalne (tipovi) SMA = spektar težine bolesti tipovi SMA ≠specifični sindromi
- SMA učestalost
- 1:6000-1/11.000 živorođene novorođenčadi (Mercuri, Lancet Neurology, 2012)
- Tip I 2-4/ godinu/HR (obzirom na broj živorođene djece tj do 50% od ukupnog broja SMA
- Sve SMA incidencija/godinu : 4-10 svih tipova
- Broj prenosioca u populaciji 1:47 do 1:90

Proksimalna SMA

Slabost proksimalnih mišića

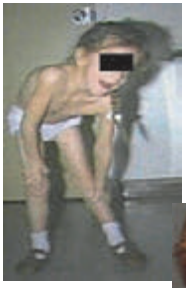
80-90% SMA

- SMA 0- < rođenja, artrogripoza, e.l.
- SMA I A (do 2 tj);B (do 3 mj) ne kontroliraju držanje glave;C do 6 mj (kontrola +)
- SMA I 50% SMA
- *Non sitter, non walker*

- SMA II 7 do 17 mj,tremor
- *Sitter*

- SMA III A(<3g) i B(>3g),
- (Kugelberg Welander)
- *Walker*

- <u>SMA II i III –plato faza do 4g</u>
- SMA IV >10-30 g ili >30 g adultni oblik (Farrar 2017)
- preklapanje pojedinih tipova SMA



SMAIII

SMA IV

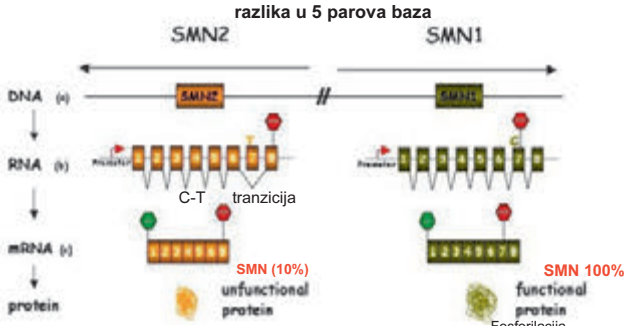
SMN gen, kromosom 5q11.2-q13.3

SMA – homozigotna disrupcija *SMN1* -95%

2%- složeni heterozigoti del+intragenska mutacija drugog alela

9 egzona i 8 introna, 20 kb, protein SMN 294 ak

Težina bolesti inicijalno u funkciji količine SMN proteina

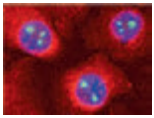


SMNΔ7 (90%) ekson 7 isključen iz prepisivanja

Fosforilacija
Kardiogeneza
Mašinerija za vezivanje

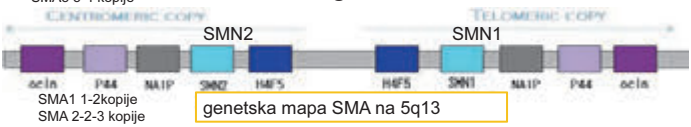
Uloga SMN proteina

- SMN se nalazi u svim stanicama: u citoplazmi, razvojnim pupoljcima neurona, ekstenzijama, Cajalovim tjelešcima i tz gemini –gemovima
- Ima regulatornu ulogu u neuronima –RNA metabolizam, ribonukleoproteinima i citoskeletu
- Važan za funkciju aktina, ubikvitina
- **Značajan za funkciju neuromuskularne spojnice i aksona**
- Transport mRNA, bioenergetske puteve, oslobađanje sinaptičkih vezikula



Nuklearna tjelešca - gemini

SMN2 i ostali genski modifikatori SMA



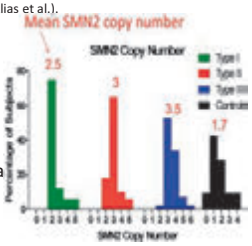
- ***SMN2*-**biomarker težine bolesti – broj kopija –tip SMA (ne određuje funkciju- i nemaju prognostički značaj)
- Osobe s homozigotnom del SMN1 + 5 i više kopija SMN2 : SMA 3 ili asimptomatski
- 8 kopija humanog *SMN2* – normalan fenotip u *Smn*$^{-/-}$ miša
- 10-15% zdravih osoba- SMN2-0 kopija

- modificirajući geni *NAIP*, c.859G>C
- Homozigotne mutacije SMN1- asimptomatske-u djevojčica - plastin –epigenetski faktor (F-aktin ↑)

Genetika proksimalne/ iSMA

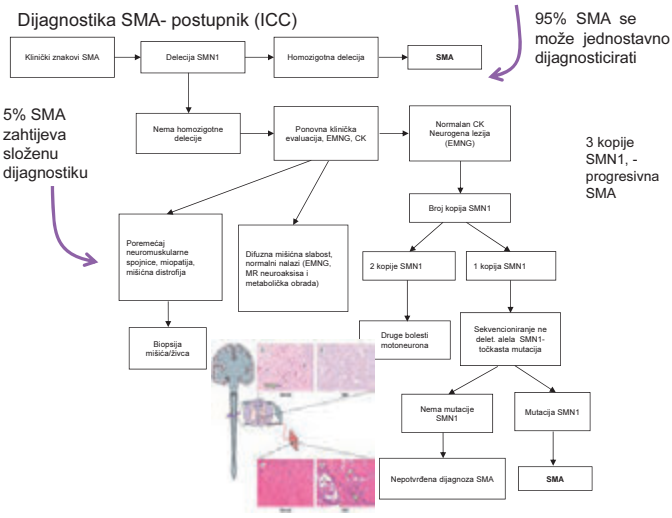
- SMN protein- značajno smanjena produkcija
- Genski modifikatori: plastin , i c859G>C
- NAIP /BIRC1 egzon 5- u 75 % odsutan u SMAI
- SERF1 (small EDRK rich factor 1A)- u 35% odsutan u SMAI

- SMN1 egzon 7 i 8, kromosom 5q11.2-q13.3 u telomernoj regiji –najčešće u 90% homozigotna delecija SMN1 gena (ekson 7 +8)-
- 5% homozigotna del ekson 7 (ne ekson 8)
- 5% složeni heterozigot s intragenskom točkastom mutacijom na drugom eksonu ili alelu (ne na 7,8, ili 5) (Wirth et al., Parsons et al., Alias et al.).
- Vrlo rijetko su obje mutacije točkaste

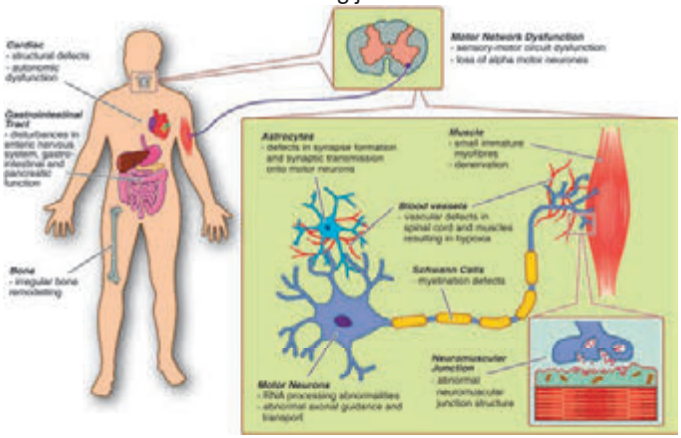


- De novo 2% (roditelji nisu prenosioci)

- Broj SMN1 kopija : 2 i > = normalan
- 1 =prenosioc ili bolesnik
- 2 kopije na 1 krom. : 2+0= prenosioc u 4 % slučajeva
- Određivanje prenosioca (visoka učestalost1:45-70)
- - određivanje doze SMN –a – za prenosioce
  (oko 6% roditelja- **normalan nalaz** 2+0 +de novo)
- - vezna analiza u obitelji (u slučaju 2+0 konstelacije)



Patofiziologija SMA



Farrar et al: Therapies and Challenges in SMA AnnNeurol 2017

SMA I

- Najteži oblik, 50% SMA
- Prvih 6 mjeseci,
- Oskudni fetalni pokreti
- Bulbarni simptomi (sisanje, gutanje, dišni put, fascikulacije jezika) i slabost interkostalne muskulature
- Paradoksalno disanje (abdominalno)
- Aritmije, srčani blok i dilatativna kardiomiopatija(rijetko)
- ASD, VSD (češće s 1 kopijom SMN2)
- Rizik ranog smrtnog ishoda smanjuje se u rođenih poslije 1995 –posebno vezano za neinvazivnu ventilaciju
- vjerojatnost preživljavanja 32 % do 2 g, 18% do 4 g i 8% do 10g (Zerres, Rudnik Schoneborn u 197 djece)
- U prosjeku smrtni ishod do 2. god**-.Δ 9- 13,5 mj, NIV>16h:Δ10mj**
- **e.l.50 % <12 mj, 90% <24mj**
- CK može biti blago povišen, autonomna disfunkcija
- EMG i biopsija mišića sukladni u 98%

Standardi zbrinjavanja bolesnika sa SMA

- 5 glavnih točaka
  - Dijagnostika i zbrinjavanje novootkrivenih bolesnika
  - Pulmološki pristup
  - Gatrointestinalni / prehrana
  - Ortopedski problemi, rehabilitacija
  - Palijativna skrb

International Clinical Coordinating Committee (ICC), svibanj 2010

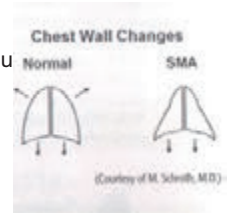
Dijagnostika
Timski pristup zbrinjavanju novootkrivenih bolesnika

- **Potvrđena Dg. SMA I**
  - Razgovor s obitelji, multidisciplinarni tim
  - Pedijatrijski neurolog, pulmolog, ortoped, gastroenterolog, fizijatar, dijetetičar, psiholog, genetičar
- Kontakt s drugim obiteljima radi potpore,udruge roditelja
- Provesti razgovor o prognozi,
- Psihološka podrška članovima obitelji

Pulmološki pristup

- Plućne komplikacije, najveći uzrok morbiditeta i mortaliteta bolesnika sa SMA
- **Kronična progresivna restriktivna respiratorna bolest**,
- Održavanje dišnih puteva
- Redovite kontrole plućne funkcije
- Rane intervencije produlju život i poboljšavaju kvalitetu života

- Pulsni oksimetar, pO2
- Rtg pluća
- Polisomnografija (OSA)



•Slabost interkostalnih mišića, toraks u obliku zvona, pectus excavatum, i u nekim slučajevima nedovoljno razvijena pluća

Cilj uvijek treba biti povećati kvalitetu života, ne isključivo (samo) produljenje života već za život vrijedan življenja

- Prohodnost dišnih puteva je važna
- Redovita oksimetrija tijekom noći, naročito ako je reduciran VC (<65%) ili s kliničkim znakovima noćne hipoventilacije
- Polisomnografija- noćne hipoventilacije,OSA
- Spirometrija (nakon 5. g), FVC >6 g
- kontrola skolioze svaka 6-12 mj (tip II),

- <u>važno -smanjena učestalost infekcija i trajanje hospitalizacija</u> (Mercuri,Lancet Neurology 2011)
- U sitters/walkers: imunizacija i profilaksa respiracijskog sincicijskog virusa, influenze, pneumokoka (II/III)
- Infekcije s RSV- VC ↓, mortalitet ↑do 5% (inače 0,2%)

Pulmološki pristup i zbrinjavanje

- Respiratorna fizikalna terapija i
- Aparat za potpomognuto iskašljavanje ima ulogu u prevenciji infekcija i u skraćenju trajanja terapije
- Rana neinvazivna ventilacija može spriječiti promjene oblika prsnog koša-od 2. mj života
- poboljšati razvoj pluća, i usporiti gubitak rastezljivosti prsnog koša
- Neinvazivna ventilacija
- Ventilacija Bi-level pozitivnim tlakom može biti provedena i kod kuće uz masku
- Inspiratorni pozitivni tlak (IPAP) i niži ekspiratorni pozitivni tlak(EPAP) za lakšu respiraciju.
- Čak i u neonatalnom periodu
- Indikacije:

  -Dnevna hiperkapnija

  -Poremećaji disanja tijekom sna

Photo credit: http://www.nbnrespiratory.com/images/machine/save_coughassist.jpg

Photo credit: Jackie Montes, SMA Clinic, Columbia University Medical Center

Standardi skrbi i korištenje neinvazivne ventilacije povećali preživljenje i kvalitetu života

Mehanička ventilacija

Traheotomija, invazivna ventilacija

Izbjeći ukoliko je moguće, raspraviti s roditeljima

U nekim slučajevima doživotna (tip I), neka djeca polaze školu unatoč meh.ventilaciji

Kućna ventilacija, (+humidifikacija i nebulizacija)

Odluka o održavanju života u djece ovisne o mehaničkoj ventilaciji- odluka roditelja

Novorođenče/dojenče koje je ovisno o meh. ventilaciji, nepokretno bez mogućnosti verbalne komunikacije i bez mogućnosti značajnijeg oporavka- teška odluka za roditelje i liječnike

http://www.fsma.org/,http://www.mda.org

Gastrointestinalni sustav i prehrana
Otežano hranjenje i gutanje

- GI tegobe bolesnika sa SMA
  - Aspiracijska pneumonija
  - Rast, pothranjenost, preuhranjenost
  - Hranjenje i gutanje
  - Piti vodu poslije obroka
- Praćenje
  - Rast
  - Unos hranjivih tvari
  - Osmisliti plan prehrane

- Slabost bulbarno inervirane muskulature

- Sprječavanje aspiracije hrane:
- Tekuća i polutekuća hrana

Metode:

- prehrana nazogastričnom sondom
- gastrostoma (PEG)

GER i opstipacija

- Klinički znakovi
  - Učestalo povraćanje nakon obroka
  - Nelagoda u trbuhu i u prsima
  - Zadah
- Liječenje GER
  - antacidi
  - Inhibitori sekrecije želučane kiseline
  - Laparoskopska anti refluksna terapija (Nissenova fundoplikacija)
- Opstipacija
  - Prokinetici (metoklopramid)

- AKUTNA BOLEST

- Slaba tolerancija gladovanja
  - hipoglikemija
- Izbjegavati gladovanje
  - Pogoršavanje znakova SMA
  - Započeti s pravilnom prehranom unutar 4-6 sati od prijema na odjel
  - Postoperativno – paziti na zadovoljavanje kalorijskih potreba

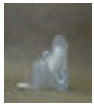
Ortopedska skrb i rehabilitacija

- Očuvati mobilnost i dnevne aktivnosti
  - Kontrakture
  - Deformiteti kralješnice
  - Otežana mobilnost
  - frakture - bol
- Zbrinjavanje:
  - Procjena ortoze
  - Procjena skolioze (rtg)
  - Rtg kukova
  - Denzitometrija

SMA I

SMAII

- Ortoza za sjedenje i stajanje (parapodiji)
- Ortoza za kralježnicu- mogu komprimirati prsni koš i imati negativan učinak na respiratornu funkciju
  - SMA III
- Invalidska kolica samo za veće udaljenosti i ako često pada
- ukoliko se bolesnik (SMA III) brzo umara kolicima, preporučaju se **motorna kolica**; u nekim slučajevima motorna kolica dovoljna samo za boravak u školi
- Regulacija ručnom tehnikom ili glasovnim putem omogućuje neovisno kretanje
  - Za adolescente sa SMA- adaptacija automobila (skupo ali moguće)



Korekcija skolioze

Nedostaju čvrsti kriteriji za liječenje skolioze
u djece < 5g
- U pacijenata s dobrom prognozom
- Što je ranije moguće, to su bolji rezultati

- Rastuće šipke - prije10g
- vertikalna protetička rebra od titana
  - Važno za rast prsnog koša i kapacitet pluća (učestali kolaps rebara)
- povećati prostor za širenje pluća i prilagodbu prsnog koša
- Fuzija kralježaka- tretman izbora
  - definitivna sfuzija kralježaka (optimalno nakon 10. g)

Osteoporoza

- Osteopenija –osteoporoza
- U SMA izraženija osteoporoza nego u DMD
- *Funkcija SMN proteina -sudjelovanje u remodeliranju kostiju i koštanoj patogenezi u SMA*
- Niska razina osteoblasta, visoka razina osteoklasta
- Denzitometrija/1x u 1-2 g
- Vit D3, kalcij

REGISTAR NMB u HR
Bolesnici s proksimalnom /infantilnom SMA
ukupno 45 od 1991

	0-4 godine		4-18 (uključujući i djecu koja su navršila 15)	
SMA I	**6** 2<7mj 2<2g	meh.ventilacija (MV): 2	8	m.ventilacija: 8
SMA II	1 (<2g)	/	8	m.ventilacija: 3
SMA III	0	/	**8**	/

SMA I ukupno: 14, bez MV 4
SMA II ukupno: 9 , bez MV 6
SMA III ukupno: 6 < 15 godina
SMA III:2 > 15 godina
Ukupno 34 (21 bez ventilacije)

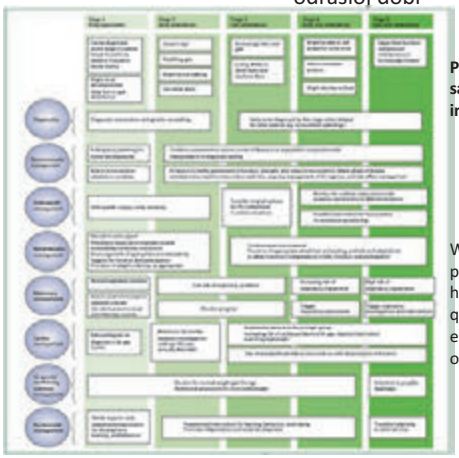
Savršenost je rezultat brojnih sitnih detalja (Michelangelo)

- Multidisciplinarni timski pristup zbrinjavanju bolesnika sa SMA prema protokolu o standardima zbrinjavanja ICC (International Care Consensus)

Tranzicija≠transfer/transport

- **Multidisciplinarni tim za dijagnostiku ,praćenje i liječenje bolesnika** s neuromuskularnim bolestima :
- neuropedijatar,neurolog, pulmolog, gastroenterolog, ortoped, fizijatar, kardiolog, ORL, genetičar, fizioterapeut, nutricionist-dijetetičar, psiholog, psihijatar, logoped, endokrinolog, ginekolog, anesteziolog
- Nedovoljan broj užih specijalista , nedovoljna edukacija
- **Registri** bolesnika su vrlo značajni kao izvor informacija o bolesniku (i prije i u tijeku tranzicije)

Preporuke za zbrinjavanje
NMB: bolesti koja se očituju u djetinjstvu ali se nastavljaju i u odrasloj dobi



Pedijatrijske bolesti nisu više samo problem pedijatara već i internista

Walton Report (UK) “a growing population of adults who… have a right to continuing, high quality support to ensure they enjoy the best possible quality of life”

Kronična ventilacija (mehanička i neinvazivna) u najvećem porastu upravo u NMB –(najviše u UK)

- Najčešći su neplanirani primici na odjel za intenzivno liječenje
- u 66 % je uzrok respiratorno zatajenje u tijeku respiratornih infekcija , 6x češće u tijeku gripe, naročito u nepokretnih bolesnika
- NIV smanjuje broj hospitalizacija i produljuje životni vijek napr u bolesnika s DMD i SMA.
- Pozitivan je stav roditelja u odvajanju tj ekstubaciji nakon mehaničke ventilacije pomoću NIV i nastavak ventilacije u kućnim uvjetima
- Roditeljima treba omogućiti donošenje odluke za ili protiv kućne mehaničke ventilacije
- Veliki problem nastaje pri tranziciji tih bolesnika u skrb internista koji nisu spremni niti educirani u liječenju tih bolesnika

Edukacija roditelja

- **edukacija roditelja bolesnika s** NMB /NMS-
- **iz reanimacije-neophodna** uključujući i one s djecom sa KMS, na NIV-u ili traheostomijom i MV, i treba biti dostupna za sve roditelje djece s NMB
- **Potreban plan zbrinjavanja u akutnim pogoršanjima-** aspiraciju dišnih puteva i priključivanje na NIV te kontakte sa specijalistima (posebno pulmolozima i intenzivne/urgentne medicine)

80% bolesnika s pedijatrijskim NMB > 18g
važnost uključivanja bolesnika i njihovih obitelji pri tranzicijskim postupcima

- troškovi za mehaničku kućnu ventilaciju do 50.000-100.000 USD/g
- Pomagala za opremu kućanstava/domova za nepokretne bolesnike s NMB-dizalice, prilagodba automobila, gradskog prijevoza
- Neujednačenost dostupnosti pomagala i razine zbrinjavanja u pojedinim zemljama EU

- Tranzicija nije samo medicinski već je **i društveni problem**
- **Tranzicija je često u praksi samo transfer bolesnika**
- Za bolesnike i njihove obitelji je bitan kontinuitet i stabilnost razina zbrinjavanja pri tranziciji

Prijelazno razdoblje (tip III b i IV)-adolescencija

- Izolirani, nezreli, ovisni o roditeljskoj skrbi

Pacijenti s SMA III i SMAIV trebaju biti educirani i pripremljeni za samostalan život

Planiranje obitelji i potomstva =vrlo rijetko u praksi

- Genetičko savjetovanje
- status prenosioca bolesti
- Skrining novorođenčadi i postavljanje prenatalne dijagnoze
- in-vitro fertilizacija (donori), moguća prenatalna dijagnostika (4 zdrave djece u 5 analiziranih obitelji, Liss, 2010)
- Asimptomatska djeca imaju 50 % šanse da su nositelji
- Testiranje asimptomatske djece je kontroverzno

- Trudnoća :smanjena pokretljivosti za vrijeme trudnoće-pogoršanje bolesti u 80%
- Češći prijevremeni porod i potreba za carskim rezom
- MgSO4 može uzrokovati paralizu (kao i kod miotone distrofije

- Opća anestezija – veći rizik respiratornih komplikacija za bolesnike kojima je potrebna ventilacija

NMB edukacija i zaposlenje

Odrastanje = postizanje neovisnosti/samostalnosti temeljem edukacije i mogućnosti zaposlenja i uključivanje u društvo

- Invalidne osobe imaju iste želje kao i neinvalidne ali se suočavaju s frustracijama ne postižući svoj cilj:
- invalidne osobe s **18g 3x vjerojatnije ne** postižu željenu edukaciju, s **26 g 4x vjerojatnije** od neinvalidnih osoba su nezaposlene (UK 2008)
- Vjerojatnost zaposlenja veća :ukoliko je viša razina edukacije, u prosjeku oko 57% bolesnika sNMB je zaposleno posebno ako se radi o mlađim muškarcima
- Zamaranje- veliki problem na poslu- potreba prilagodbe radnog vremena

Zaposlenje i problemi vezani uz zaposlenje bolesnika s NMB

- Za bolesnike sa SMA tip II-IV, BMD, MG i KMS te CMT osim fizičkih (motoričkih) ograničenja nema drugih ograničenja za zaposlenja koja zahtijevaju višu ili visoku razinu edukacije
- Progresija bolesti neminovno utječe na ostanak na radnom mjestu (napr mogu asistirati uz razumijevanje nadređenih) i odlazak u prijevremenu mirovinu
- bolesnici s MG imaju 6 puta manju vjerojatnost zaposlenja i 9 puta veće šanse za duga bolovanja (dulja od 9 tjedana). – posebno žene
- Bolesnici s polineuropatijom koji su zaposleni imaju u pravilu niske plaće i visoke troškove liječenja (>12,500 USD) u odnosu na ostalu populaciju
- 16% odraslih bolesnika s **DMD** je zaposleno u Danskoj i Njemačkoj!! u dobi od 24-30g, a **0%** u Istočnoj EU

Prilagodba okoline za potrebe bolesnika s NMB

- Čak 60% odraslih DMD žive samostalno ili s partnericom (Danska), 7% u UK, 13% u Njemačkoj , 0%u Istočnoj EU
- Forsirati funkciju ruku -važno za samostalnost: gubitak funkcije ruku-prosjek 26 g ali i do 41.g.!
- Kognitivni problemi u djece s DMD su česti napr verbalni, zatim vještine tj motorički, oko 50% imaju razvojnu disleksiju , probleme s pamćenjem.
- asistent u nastavi - posebno bolesnicima s DMD – pojednostavniti upute za zadatke prema mogućnostima, za SMA zbog motoričkog deficita

Kvaliteta života bolesnika i psihološka podrška bolesnicima i članovima obitelji

- Procjena kvalitete života **zanemarena**- pogrešan stav da bolesnici s invaliditetom procjenjuju kvalitetu života nižim rezultatima od bolesnika bez fizičkog invaliditeta- ovisnost o prilagodbi bolesnika invaliditetu, redovitim kontrolama, i pozitivnom stavu zajednice prema bolesnicima
- Procjena kvalitete života treba se rutinski provoditi u svih bolesnika s NMB kao način procjene odgovarajućeg stupnja zbrinjavanja – nije primarno vezana za reduciranu funkciju mišića ili probleme ventilacije- **paradoks invaliditeta- duljim trajanjem bolesti -bolja prilagodba**
- **Važno za QOL-** različite aktivnosti **izvan kuće**
- Psihološka/psihijatrijska podrška i psihoterapija i bolesnicima i roditeljima- mogu utjecati na raspoloženje i time na KŽ
- i roditeljima- doživljavaju stres prilikom progresije simptomatologije, potrebna je i organizacija i informacije za samopomoć

Priprema za terminalnu fazu

- treba biti iskren u komunikaciji s djecom
- Treba razgovarati s roditeljima i bolesnicima o tome da li pristupiti reanimaciji ili ne u hitnim stanjima (dakle prije prijma u JIL)
- prema literaturi o tome se uopće ne razgovara/ili se premalo razgovara niti u obiteljima niti s bolesnikom
- **Povod -neplanirani prijem na intenzivno liječenje**
- 95% bolesnika **ne** smatra (previše) stresnim takav razgovor, žele razgovarati o tome kako i po čemu će ih se njihove obitelji sjećati
- Treba biti pripreman na gubitak đaka u razredu s neuromišićnom bolešću
- Žalovanje je normalan proces i treba ga omogućiti i nastavnicima i drugim učenicima u razredu

Primjena respiratorne terapije i nutritivne podrške može značajno produljiti život

Važne su informacije koje roditelji dobiju o mogućoj terapiji (različitim oblicima respiratorne potpore) i smrtnom ishodu tj približno očekivanom vremenu smrtnog ishoda- o čemu je važno informirati roditelje što je važno za odluku u daljnjoj terapiji ali i za psihičko zdravlje roditelja

Važno je za : **odluku roditelja o odabiru mjesta (dom/bolnica) kad se očekuje smrtni ishod**

Važna je i **psihološka podrška starijoj braći i sestrama koju rijetko dobiju**

Također je važno **jasno tj razumljivo objasniti terapijske mogućnosti**
(EJPN 2016)

Palijativna skrb

- Palijativna skrb cilj :povećanje kvalitete života i dalje ima krivu definiciju da se treba primjenjivati samo u finalnim stadijima bolesti posljednjih nekoliko dana prije smrti
- Palijativna skrb se može primjenjivati paralelno s aktivnim liječenjem u tijeku zbrinjavanja bolesnika čija je životna dob skraćena zbog osnovne bolesti poput DMD, SMA I/II

Palijativna skrb- izbor između interveniranja i palijativnog zbrinjavanja nije uvijek jednostavan

- Upoznati obitelj s mogućim životno ugrožavajućim stanjima i smrtnim ishodom
- Uputiti obitelj na odgovarajuću instituciju (hospicij), potpora u terminalnim fazama bolesti
- Olakšavanje terminalne faze bolesti i za pacijenta i za njegovu obitelj
- Pravo na odluku o prekidanju životne potpore u Jednicama intenzivne skrbi
- Kućna mehanička ventilacija u SMA pacijenata otprilike 100.000 USD (Neurology 2012)

Pristup bolesnicima u terminalnoj fazi Hospiciji-nedostatak

- izuzetno mali broj publikacija o liječenju terminalne faze u bolesnika s NMB- malo iskustva
- **Terminalna faza - najbolje zbrinjavati u hospicijima**
- Potrebno je **planiranje terminalne** faze što predstavlja izuzetno osjetljivo i teško područje za tim
- Treba poticati mlade ljude da donesu odluku o postupanju u terminalnoj fazi (napr odluka da se prekine zbrinjavanje u terminalnoj fazi bolesti)
- Napredni plan zbrinjavanja ne predstavlja legalni dokument niti naređenje o tome da se ne pristupi reanimaciji, može biti dio plana za hitna stanja

Edukacija liječnika o tranziciji

- U tijeku edukacije liječnika (i u dodiplomskoj nastavi) posebno u okviru specijalizacije (pedijatrije, neurologije, opće /obiteljske medicine) i sub/specijalizacija (pulmologija, intenzivna, kardiologija,gastroenterologija, neuropedijatrija) potrebno je da liječnici dolaze u kontakt s bolesnicima u procesu tranzicije što može olakšati savladavanje samog problema
- U primarnoj razini zbrinjavanja: prevencija te zbrinjavanje akutnih interkurentnih bolesti
- Složeniji bolesnici zahtijevaju pisani plan tranzicije
- već u dobi bolesnika od 12 godina treba planirati i razvijati proces tranzicije a svakako od 16. godine

Problemi vezani za tranziciju: nema idealnog modela

Bitno: održati kontinuitet i stabilnost skrbi

•(Jedan) **dijagnostičko-terapijski /neuromuskularni centar** na razini države (Danski model) za redovito praćenje/kontrole bolesnika od postavljanja dijagnoze u djetinjstvu do terminalne faze, uz edukaciju roditelja, za kardiorespiratorne probleme /respiratornu potporu, op. zahvate-skolioza

Odrasli bolesnici nemaju adekvatnu skrb u odnosu na pedijatrijske

•Danski model bolji od UK (efikasniji za odrasle s DMD)

•regulacija tranzicije legislativom- Zakon o sprječavanju diskriminacije invalidnih osoba, propisi Ministarstva zdravstva

•razina države- zakonska regulativa i planiranje razvoja unaprijed

• koordinator za mnoge specijalnosti i komisije za nadzor

•Značajan je doprinos **obiteljskih i udruga bolesnika**

September 30. 2017.
SMA Awareness day

Znati nije dovoljno, znanje se mora primijeniti. Željeti nije dovoljno moramo raditi. (JW Goethe)

Suvremena terapija proksimalne /iSMA

„SMN"

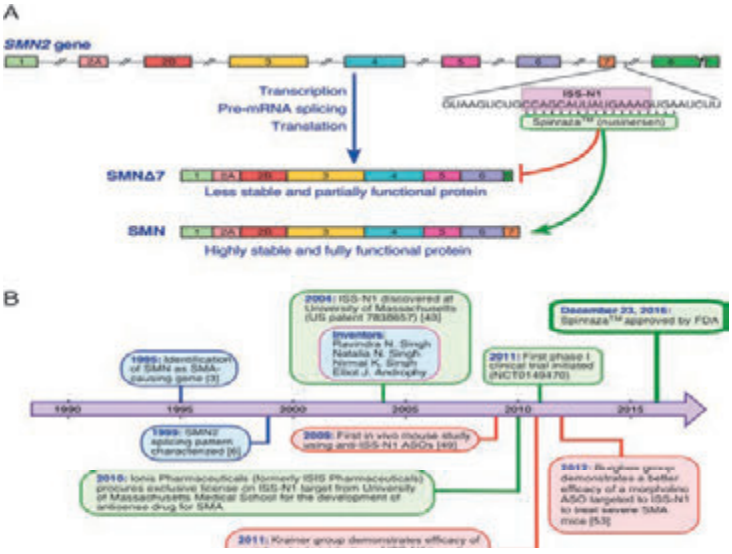
- **Nadoknada SMN (SMN1 genska terapija)**
- **Modificirajuća SMN2 terapija-modulacija SMN2**

„Non SMN"

- **Neuroprotekcija**
- **Terapija perifernih tkiva i organskih sustava** (mišića)

(Farrar Ann Neurol 2017)

- Intratekalna terapija protusmjernim oligonukleotidima (inkluzija eksona 7 u SMN2 gen- nusinersen) odobrena je od FDA i EMA
- Značaj prenatalne dijagnostike- th najdjelotvornija ako se primjeni u prvih 6 mj života (zbog degeneracije motoneurona)
- Genska terapija još je uvijek u fazi kliničkog ispitivanja



Uzrok SMA- niska razina SMN proteina

Uloga SMN proteina- DNK biogeneza reparacija translacija,promet, sinteza

SMA je jedinstvena bolest u kojoj postoji kopija (SMN2) mutiranog gena SMN1 ili backup za SMN1

ISS-N 1- glavni inhibitor/glavna kontrola izrezivanja i spajanja (prekrajanja) te uključivanja eksona 7 u području introna istog eksona

ISSN1 -15 nukleotida
ASO se sastoji od fosfotioata i metoksi 2 MOE komponent

Nusinersen omogućuje inkluziju eksona 7
mijenja prirodni tijek bolesti tj SMA I u SMA II
„orphan drug" - lijek za rijetke bolesti

Nusinersen IONIS ASO 10-27
Natječe se s ISS-N1 koji sprječava produkciju SMN2 u cjelovitoj duljini transkripta i SMN protein

ISS-N1 = intronski utišavač/supresor prekrajanja
glavna kontrola prekrajanja SMN2

- Nusinersen- ASO- protusmjerni oligonukleotid
- Vezivanje na RNA –(komplementarnih baza)
- Modificira splicing (izrezivanje i vezivanje)
- Povećava ekspresiju proteina

- Kemijske prilagodbe ISS N1 ASO –(nusinersena)

Fosforotioat-sprječava degradaciju ASO endonukleazama, smanjuje afinitet hibridizaciji i povećava citotoksičnost (aktivacija kaskade komplementa,poremećaj koagulacije), alveolarna st tip II i bronhalna toksičnost) nefrotoksičnost

2 MOE (metoksietil)-smanjuje citotoksičnost i povećava hibridizaciju

Outcome	Sham procedure control	Nusinersen
Death or permanent ventilation, n (%)	28 (68%)	31 (39%)
Alive and no permanent ventilation, n (%)	13 (32%)	49 (61%)

Nusinersen – ASO koji djeluje na ribosome – tako da ih prevari i ponudi im DNK kod prema kojem se u ribosomima stvaraju aminokiseline u SMN proteinu

Inkluzijom eksona 7 u SMN2 gen stvara se manje vrijedan SMN1 gen tj umjesto 100% produkcije kod nedeletiranog gena stvara se 90% maksimalno

ASO se nakuplja u neuronima leđne moždine te u kortikalnim neuronima ovisno o dozi
Spori klirens omogućava rijeđe doze održavanja

SMN je značajan i za druge organske sustave i periferna tkiva izvan SŽS-a ne samo za NMS
Stoga problem nije riješen djelovanjem samo na 1 sustav

Dokazano je da SMA uzrokuje promjene na :
krvnim žilama
Srcu,
Jetri, slezeni
Pankreasu
Skeletnim mišićim,a
Schwanovim stanicama

znači da primjena SMN proteina tj povećanje SMN proteina s AON

ne rješava problem u ostalim tkivima posebno u SMA I u tipu u kojem su nepoznate posljedice niske razine SMN proteina u tkivima izvan SŽS-a na njihovu funkciju nakon dojenačkog razdoblja

i.t. primjena nusinersena zaobilazi ostala tkiva i organske sustave

Nusinersen je odobren nakon 442 dana primjene u tijeku kl. Ispitivanja u kontroliranim studijama u prosjeku na 261 dan za tip I
odobrenje nakon primjene na 52 bolesnika od kojih je primjena u 40% bila uspješna

Do 08/17 ukupno 400 bolesnika na terapiji u18 zemalja /67 centara

- ne znamo dugoročni učinak niti dugoročno preživljavanje
Ne sprječava razvoj simptoma(znakova) dugotrajne bolesti

Odobren je za djecu i odrasle ali za odrasle nema kl. Ispitivanja već samo nekontrolirane studije ali za dob do 15 g??

Morrow: New Therapy for Spinal Muscular Atrophy Offers Modest Bang for Pharmaceutical Buck MANAGED CARE February 2017

Kriteriji za uključivanje u liječenje nusinersenom (SMA I) (Biogen)

•početak kl.znakova SMA <6 mj
•genetska dijagnoza 5q SMA homozigotne del ili heterozigotne del (složeni heterozigot)
•≤7 mj prilikom postavljanja dijagnoze
•2 *SMN2* kopije

Kriteriji za isključivanje
•znakovi SMA prisutni pri rođenju ili unutar < od tjedan dana po porodu
•neliječena ili liječena aktivna infekcija
•prethodna uporaba lijeka za terapiju SMA u istraživačke svrhe

Doza- 4 inicijalne doze 12 mg (0,15,30 d i nakon 30 d) zatimsvaka 4 mj

Klinička ispitivanja nusinersena

- NURTURE-
- u presimtpomatskoj fazi je najuspješniji-sa 6 mj sjedi hoda s 2 g Bertini
- 100% uspješna u 17 bolesnika (E.L.=0, Resp.=0)

- ENDEAR U dojenčadi <od 7 mj s 2 kopije

- CHOP INTEND- Childrens Hospital of Philadelphia Infant test for NMD (>4 značajno poboljšanje)
- HINE – Hammersmith Infant neurological exam

- Sva djeca uključena u SHINE studiju –djeca koja su dovršila studiju nusinersenom ranije - tj kontinuiranom primjenom po protokolu svaka 4 mjeseca

Klinička ispitivanja nusinersena (2)

- CHERISH – dvostruko slijepa – faza 3- u tipu II i III (starija od 2-12 g u kojih bolest počinje s > 6 mj (Mercuri) ispitivanja u djece i odraslih
- (najstariji pacijenti (3 ukupno) –pri zadnjoj dozi imali 18 god!!)
- Hamersmith motor scale expanded (33 boda)- svi su kasnije uključeni u
- SHINE otvorena studija
- Placebo pokazuje u početku uspjeh ali nakon 6 mj se razlika značajno povećava razlika između bolesnka na nusinersenu u odnosu na placebo
- RULM(revised upper limb) skala i Hammersmith scale za starije od 2 godine
- nuspojave uglavnom blage
- Značajno poboljšanje-HFSE , RULM skale

Za nastavak terapije i procjenu uspjeha potrebno je poboljšanje od 2 stupnja motoričkog razvoja maks 26 bodova
Stupnjevi su prema **H**ammesmith **I**ntend **N**eurological **E**xam

-Odizanje (kontrola) glave
-Odizanje donjih ekstrmiteta vertikalno i horizontalno
-Okretanje
-Sjedenje
-Puzanje
-Stajanje
- hodanje

Prema CHOP – 63% je imao poboljšanje u odnosu na 3% u placebo skupini
Za tipI, a pogoršanje samo u4% liječenih u odnosu na 40% placebo

6 minutni test hoda za pokretne bolesnike

Nuspojave-
Trc↓
Proteini/urin↑

Nesiguran pristup /mogućnost liječenja djece sa SMA u Eu i USA – zbog cijene

- Cijena nusinersena ugrožava njegovu vrijednost/znanstveni i medicinski značaj onemogućavajući primjenu djeci sa SMA I kojoj je neophodna a nije dostupna iz financ razloga

  .. Nevertheless, the scientific and medical importance of this advance is marred by a pricing policy by the corporate sponsors that may complicate accessibility of the drug for some desperate patients.

Friedmann I. Gene Ther. 2017 Jun 22. Gene therapy for spinomuscular atrophy: a biomedical advance, a missed opportunity for more equitable drug pricing.

(marred)- to mar: ruin/spoil the beauty of perfection

Cijena spinraze uvjetuje pitanja o opravdanosti iste, transparentnosti i odgovornosti
Velike razlike u cijeni lijeka i mogućnostima plaćanja/pokrivanja troškova-nejednakost u mogućnostima tj u dostupnosti lijeka bolesnicima

Nusinersen ima veliki značaj za liječenje SMA
ALI
Nejednakost u dostupnosti lijeka
+ cijena je galaktičkih razmjera

- Cijena je ekstremno visoka – i izgleda da ipak nema opravdanja niti matematičkog rezona niti za to nema jasnog objašnjenja od Biogena
- Rijetke bolesti= skupa istraživanja (velika cijena) +mali broj bolesnika,

- Izračun troškova zbrinjavanja u odnosu na cijenu spinraze

- ČINJENICE-Proračun- treba obuhvatiti zbrinjavanje- ortopedsko, fizikalna th, pomagala i prilagodbe stambenog prostora, boravak u boln ustanovama zbog upale pluća/resp. insuficijencije, (pulmologije, JIL-ovi), trošak respiratora, odsustvo tj bolovanje roditelja , liječenje osteoporoze, palijativnu skrb
- Prijevremeni porodi-nedonoščad (tip IIIb i IV)
- Kvaliteta života bolesnika i obitelji i zajednice

Jedina modificirajuća terapija za bolesnike sa iSMA-

- Biogen –monopolistički pristup u liječenju izazov/poticaj za daljnja istraživanja – za lijekove koji nisu slični N(S) ali su superiorniji
- DA-Biogen je uložio sredstva u istraživanja i razvoj, ali sve drugo - obustava kl. Istraživanja i postupak odobrenja za tržište-bio je beneficiran/ubrzan i jeftiniji prije registracije uz jasnu podršku javnih i regulatornih institucija
- U financiranju istraživanja su sudjelovali: pacijenti/udruge.neprofitne i privatne tvrtke te Ionis, Biogen pokrio razvojne i troškove licenciranja
- EAP započeo u rujnu 2016.
- Mogućnost javno-privatnog parnerstva /profitno-neprofitnih organizacija da omogući dostupnost lijeka bolesnicima
- Evaluacija lijeka/cijene-ne samo isplativost već u evaluaciji sudjeluju i liječnici,pacijenti te proizvađači i države koje plaćaju lijek
- Ravnoteža se može postići ako se udruže države/unije u zajedničkoj nabavi lijeka

Nesrazmjer cijene i mogućnosti plaćanja lijeka na tržištu crna i/ili Pandorina kutija ? Potrebno je opravdati donošenje teških odluka za državne institucije (i još težih za liječničku profesiju i najtežih za bolesnike i njihove obitelji)

- Cinjenica je da bez suradnje farmaceut. kompanija i istraživača s bolesnicima ne bi bilo niti nusinersena
- Pravo na patent su prvo prenesena na neprofitne organizacije i potom u konkrentom slučaju na Biogen koji je razvio monopol i cijenu „sky is the (only) limit"-
- Izazov je Biogena da omogući dostupnost lijeka pacijentima koje predstavlja organizacija Cure SMA izvan EAP
- Biogen nema objašnjenja za tako visoku cijenu osim da je u rangu sa lijekovima za druge rijetke bolesti

Market access of Spinraza (Nusinersen) for spinal muscular atrophy: intellectual property rights, pricing, value and coverage considerations S Simoens and I Huys
Gene Therapy (2017) 24, 539–541; doi:10.1038/gt.2017.79; published online 7 September 2017

Status u zemljama EU
Rezultati analize sadašnjeg statusa u EU
Izuzetci Francuska, Danska

Zemlja	Kriteriji uključenja Tipovi SMA	Primjenu pokriva zdravstveno osiguranje (ZO)	Primjenu spinraze Ne pokriva ZO
Slovenia	Tip I (EAP)		√
Njemačka	I, II, III Djeca na respiratoru	√	
Italija	Samo Tip I (država)	-	√
Austrija	I,II, III	Samo SMAI	√
UK	Samo Tip I (uključuju i djecu na respiratoru) EAP	-	√
Mađarska			√
Rumunjska			√
Nizozemska			√
Belgija	EAP samo tip I	-	√
Švedska	Preporuka vlade-samo tip I (zbog životne ugroze)	-	+, vjerojatno će ZO pokrivati liječenje od 11 mj/17 za sve tipove

EAP expanded/early access program - compassionate use –Biogen/ionis
Omogućava primjenu dok još lijek nije odobren u zemlji (ili nije na listi) a u drugim je zemljama odobren
Izvan kliničkog ispitivanja ? Ili open access Drugi izvori?

Motoneuroni su primarni cilj terapije u SMA
druga tkiva (somatske stanice) su zahvaćene klinički i/ili subklinički

Najveća potreba za SMN proteinom je u tijeku realizacije strukturnih neuromuskularnih poveznica-dobno ovisna
u fetalnom i dojenačkom razdoblju dakle za tip I

Veće količine SMN proteina (vjerojatno) **nisu dovoljne/potrebne** za zaustavljanje sporog procesa degeneracije u blažim oblicima bolesti,

bolesnici mogu postati vulnerabilni za odgođene simptome ako je pristup neuromuskularnom sistemu nepotpun

Veliki broj starijih bolesnika ne ispunjavaju kriterije za inkluziju u terapiju pomoću ASO i vjerojatno neće imati koristi od povećanih količina SMN-a
Therapeutic strategies for spinal muscular atrophy: SMN and beyond
Melissa Bowerman1, Catherina G. Becker2, Rafael et alDisease Models & Mechanisms (2017) 10, 943-954

Riješenje problema

Vrijednost SMN AON/genske terapije najveća je i najviše provjerena za SMAI

za ostale tipove učinak genske SMN terapije je nejasan i nesiguran potrebno je kombinirati terapiju sa učinkom koji ne djeluje na povećanje SMN protein (non SMN)

Kombinacija- tzv koktel terapija koja povećava količinu SMN proteina i lijekovi tzv non SMN modifikatori

Eksperimentalni modeli **nisu ekvivalentni za procjenu dugotrajnih učinaka** terapije u djeteta jer SMN- miš umire brzo (život je nespojiv s mutacijom jednog alela tj za tip II i III
Već samo za SMN I
Postoje modifikacije eksperim. modela sisavaca ali je adekvatniji
riba Zebra

značajna rana dijagnoza- novorođenački skrining iz suhe kapi krvi –PCR-RFLP
(Brain & Development 39 (2017) 774–782)

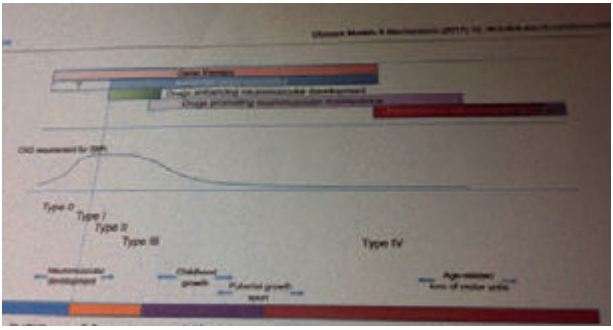
Primjena SMN terapije =neadekvatna dugoročna terapijska strategija za SMA

- Pluripotentne matične stanice- u tijeku su ispitivanja
- Genska terapija
- Nereplicirajući AAV+SMn1 i.v. –koja prelazi HEB (AveXis)
- Genska terapija AAV9 SMN i.v.- ovisna o dozi (Faza II)- vrlo uspješna djeca prohodala nakon 4-10 mj
- 1x i.t. možda dovoljna- eksperiment. rad (Meyer 2015)
- PROBLEM –IMUNOGENOST i PATOLOGIJA (ne SŽS komplikacije- tm itd tj bolesti koje nisu vezane sa SMA

Stoga treba istraživati potencijalne terapeutike koji djeuju u kroničnoj fazi bolesti nadopunjujući SMN terapiju i omogućujući poboljšanje i održavanje integriteta i funkcije neuromuskularnog sustava u kroničnoj fazi

Činjenice :Terapijski prozor-kritičan za uspjeh terapije
Rana korekcija razine SMN proteina je potrebna

- SMN bitan za razvoj motorne jedinice ali se time ne izliječuje bolest već se smanjuje težina bolesti za tip I
- **Potreban cijeloživotni terapijski pristup i postupci (ovisni i neovisni o SMN proteinu) usmjereni ne samo na SŽS već i ostala tkiva i stanice**



budućnost u neinvazivnoj primjeni – ne i.t. već **i.v. ili per os** ASO slijedeće generacije

PMO (fosfodiamidat morfolino) molekule prolaze sve membrane , kemijski neutralne (također ISS-N1 PMO)

Targeted small molecule that suppresses alternative splicing of *SMN2* mRNA, thus "rescuing" the full-length mRNA and increasing SMN protein levels

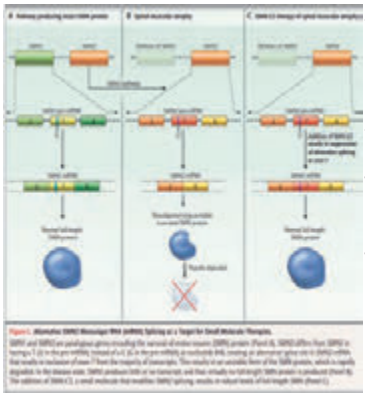
- small-molecule therapy may provide an effective and orally available therapy for SMA
- promote the inclusion of exon 7 into *SMN2* mRNA transcripts
- three orally available compounds identified :SMN-C1, SMN-C2, SMN-C3
- ↑↑ **SMN u mozgu, krali, moždini, mišićima i u serumu**

modifying the transcriptome

Naryshkin NA, et al. Motor neuron disease. SMN2 splicing modifiers improve motor function and longevity in mice with spinal muscular atrophy. Science 2014;345:688—93

Kathryn J. Swoboda, M.D .**Romancing the Spliceosome to Fight Spinal Muscular Atrophy**.n engl j med 371;18 neim org october 30, 2014

radically alters transcriptome
precedes motor neuron degeneration and loss , reversing downstream effects

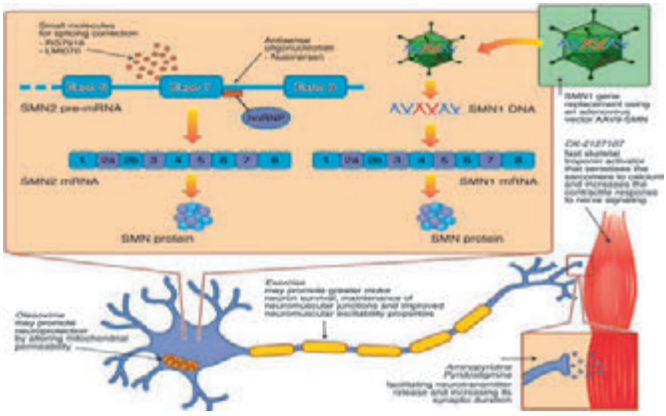


- all three compounds modified *SMN2* splicing and increased SMN protein
- High selectivity and specificity of gene modifiers
- Hoffmann La-Roche is currently recruiting 48 SMA patients (aged 2—55 years) in a double placebo randomized Faza II (tip II i III)
- Phase II study orally aplicable Novartis SMA type I 22 pts

Press release-SUNFISH study in Type 2/3 SMA patients -dose-dependent increase in SMN2 full length/Δ7 mRNA ratio of ~ 400% versus baseline, as measured in whole blood. No ADR (7/17)
Faza II za tip II i nepokretne tip III

Nadomjesna „non SMN" terapija

Farrar Ann Neurol 2017

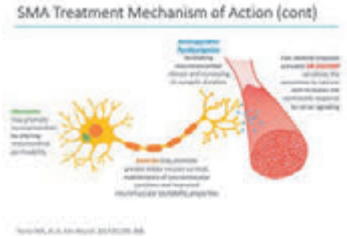


Olesoksim – najdulja i najveća kontrolirana dvostruko slijepa studija u bolesnika sa SMA (Bertini et al, Lancet Neurol. 2017 Jul;16(7):513-522.)

JEDINA U POTPUNOSTI PROVEDENA KLINIČKA STUDIJA NON SMN TERAPIJE

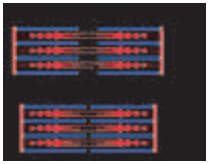
Djeca < 6 g –**dominantan je razvoj i poboljšanje motorike**
U Djece > 15 g uz olesoksim dolazi **do stabilizacije u trajanju 2-3 g**
(iako nije bilo uspjeha u primarnim mjerilima ishoda- tj razvoju motorike)

Ali većina pacijenata smatra da je uspjeh prisutan time što 2-3 godine nije došlo do motoričkog pogoršanja
Interindividualna varijabilnost je bila velika



Olesoksim – mala molekula koja djeluje na vanjsku **membranu mitohondrija** djeluje na **otvaranje tranzicijske pore** kao odgovor na oksidativni stres (Roche, GenenTech)
Djeluje **neuroprotektivno,zaštićuje od apoptoze**- sprječava oslobađanje citokroma C koji uzrokuje apoptozu
Postignuta stabilizacije bolesti u SMA tipu II i III- stabilizacija u trajanju od 2 g
SLABO DO UMJERENO USPJEŠNA TERAPIJA
uključeno 22 centra – 168 bolesnika dob 3—25 g(10mg/kg), razdoblje ispitivanja:3g-tip II i III
Nuspojave blage -respiratorne, GER
Ishod- značajan učinak u odnosu na placebo- bez pogoršanja kroz 2 g dakle održavanje motoričke funkcije bez sigurnog poboljšanja motoričkih funkcija no u komparaciji s placebom učinak je bio jasan nakon 6i 18 mj primjene olesoksima i tendenciju motoričkog poboljšanja posebno za skupinu od 6 g-15 g
Dakle u razdoblju u kojem je (u tijeku puberteta pogotovo) najznačajnije motoričko pogoršanje-
Posebno snažan je efekat olesoksima u odnosu na placebo u tom razdoblju od 6-15 g ali ne prije niti ne za > 15 g

Drugi terapijski ciljevi



AKTIN

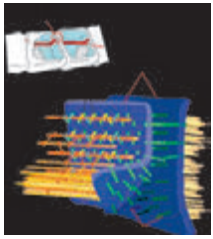
Modulacija aktivacijskog puta RhoA-ROCK značajno može produljiti život

serin-threonin i ROCK su glavni modulatori dinamike aktina

put koji je aktiviran i **stimuliran u neuronima kojima nedostaje SMN, kralješničnoj moždini i mišićima** u eksper. modelima za SMA

Inhibicija RhoA-ROCK puta produljuje život

djelotvorna u ostalim neuronima, fibroblastima i gliji (FASUDIL)



NEUROMUSKULARNA SPOJNICA

PTEN je tumorski supresor protein koji putem i značajan je za rast i migraciju stanica-
Reguliran je (fosforiliran) s RhoA ROCK pri čemu je rezultat skraćenje (inhibicija) života neurona

Suprimiranje PTENA dovodi do **poboljšanja funkcije neuromuskularne spojnice** i produljenja života
uloga modulatora aktina u produljenju života je značajna

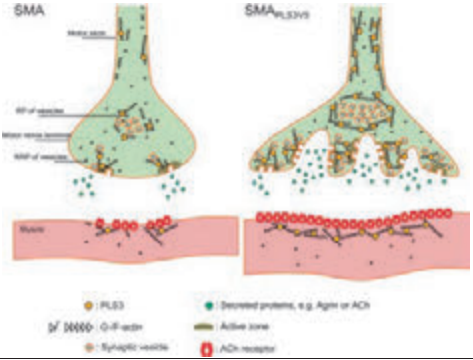
SINAPTIČKA REGULACIJA

stasimon -stimulacija
važan za **sinaptičku regulaciju** i njegovo smanjenje uzrokuje poremećaj prekrajanja- hiperekspresija dovodi do normalizacije

CDK (ciklin dependent kinase) 5– odgovoran za hiperfosforilaciju tau proteina u SMN defic. neuronima i smrt neurona,
aktivnost povećana u SMA modelima –jedan od potencijalnih non SMN ciljeva

Ubikvitinu sličan enzim (Uba1) i beta katenin signalizacijki efektor enzima- glavni non SMN ciljevi za uspostavu funkcije neuromuskularnog sustava i sistemsku patologiju – beta katenin se nakuplja zbog nedostatka UBA 1u aksonima SMA modelima njegova inhibicija poboljšava funkciju NM sustava

Aksoni i NMS



From: Plastin 3 ameliorates spinal muscular atrophy via delayed axon pruning and improves neuromuscular junction functionality
Hum Mol Genet. 2012;22(7):1328-1347. doi:10.1093/hmg/dds540

AKSONI

modulator funkcije aktina je i

plastin 3- protein koji je modifikator težine bolesti :
Stimulacija/Hiperekspresija plastina 3 značajno **spašava aksone** i njihov rast u zebra ribi –moduelu SMA, uz to smanjene vrijednosti SMN1 (SMN proteina) smanjuju razinu plastina3, poremećaje funkcije NMS

studije na SMA miševima pokazuju da povećana ekspresija plastina 3 sprječava degeneraciju aksona i omogućuje normalnu funkciju NMS i produljuju život ali:

Međutim-brojne studije na drugim modelima i humanim modelima nisu sukladne navedenim tvrdnjama- naime učinak je vjerojatno ovisan o težini bolesti tj tipu SMA

Kondrolektin- transmembranski protein nalazi se na aksonima , modifikator integriteta **aksona**
Stimulacija/ povećanje ekspresije spašava aksone

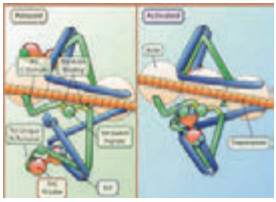
Važan je RNA regulacijski sustav – nedostatak SMN proteina uzrokuje smanjenje aktivnost kompleksa spliceosoma –

Therapeutic strategies for spinal muscular atrophy: SMN and beyond BowermanM et al Disease Models & Mechanisms (2017) 10, 943-954

MIŠIĆI

Troponinski aktivator djeluje na kontraktilnost mišića (faza II) Istraživan je na eksperiment. modelu zatajenja srca (štakor) ali ne i na modelima SMA , ali da na modelima ALS, MG, nemalinske miopatije- usporava oslobađanje kalcija iz troponina-NAVODNO ODLIČAN EFEKT

Miostatin- folistatin- negativni regulator rasta **mišić**a- povećava mišićnu masu- stoga je aktivan u hipotrofiji mišića u SMA + DMD (kl. Ispitivanje)



Neki dostupniji i (unatoč tome) efikasni terapijski pristupi

Piridostigmin- tip III > 3 g

3,4 DAP (diaminopirid) tip III dob 18-50 g

Salbutamol –omogućuje inkluziju eksona 7
Albuterol 1-2 x dnevno 2 mg

Quinazolin –povećava količinu SMN

Vježbanje značajno poboljšava funkciju NMS i kontraktilnost u SMA bolesnika

Dugoročna strategija -monitoring uspješnosti terapije

Uključuje

Kognitivne sposobnosti
Rast i razvoj
Autonomne funkcije i
Nuspojave

Mogućnosti efekta stresa pri reinervaciji preostalih neurona- „postpolio like" sindrom

Kombinirana terapija će vjerojatno omogućiti najbolji rezultat liječenja

Potrebno definiranje terapijskog prozora

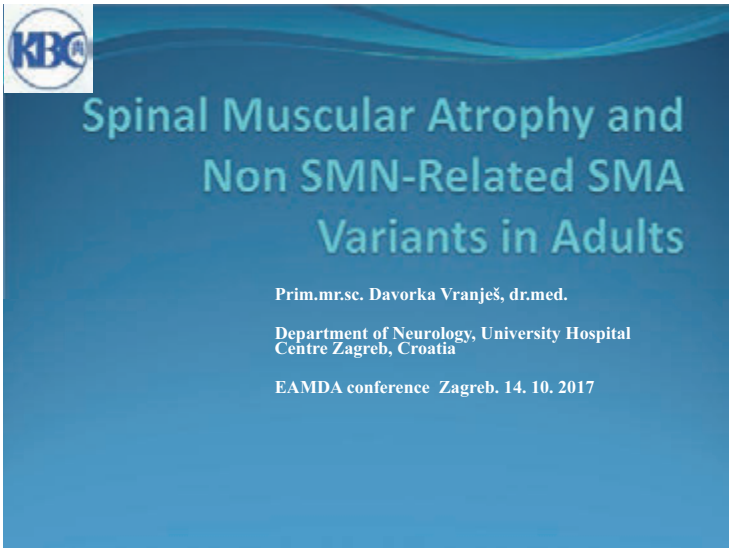
I usmjeravanje istraživanja na nove terapijske pristupe

HVALA NA POZORNOSTI

Mr sc **Davorka Vranjes** *MD*
Clinical Hospital Centre Zagreb - Department of Neurology, Centar of neuromuscular disorders and clinical electromyography.

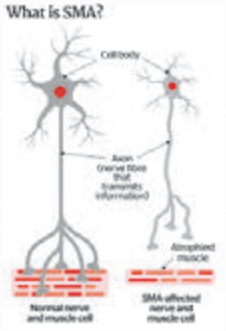
10000 Zagreb, Kišpatićeva 12 Croatia
Tel. +38512376377
E-mail: davorka.vranjes@zg.t-com.hr

The narrowest field of professional interes are neuromuscular disorders and clinical electromyoneurography, employed as neurologist at Department of Neurolgy, Sections for neuromuscular disorders University Hospital Center Zagreb and collabrators in scientific project in neuromuscular disorders at Medical School University of Zagreb.



Spinal muscular atrophy

- Spinal muscular atrophy is a rare neuromuscular disorder characterised by loss of motor neurons and progressive muscul wasting.

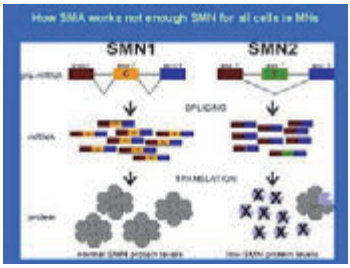


SMA types

- SMA type 0 (prenatal)
- SMA type 1 (Werding –Hofman) before age of six month
- SMA type 2 (intermedial form 3-15 month)
- SMA type 3 (juvenil form, Kugelberg-Welander) 18 month-adulthood
- SMA type 4 late onset about 30 year.

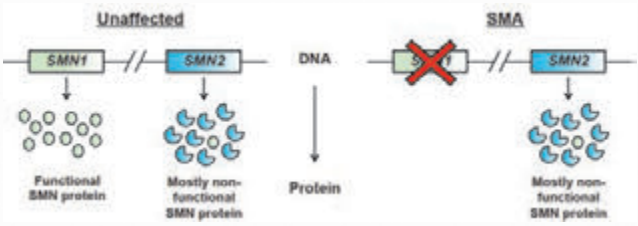
GENETICS

- Spinal muscular atrophy is caused by deletions or point mutations of the survival motor neuron 1 (SMN1) gene on chromosome 5q13.2 which encodes SMN, a protein widely expressed in all eucariotic cells and necessary for survival of motor neurons.



Genetics

- SMN2 gene - differs from SMN1 gene by single cytosine to thymidine transition in exon 7, which results in its exlusion during transcripton (functional absence of exon 7), which means low level production of truncated, rapidly degraided, unstable SMN protein



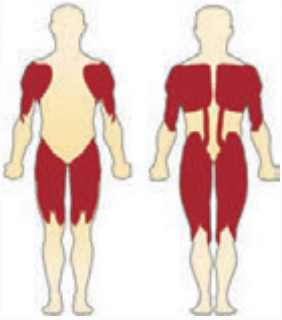
Genetics

- The differences between types of SMA are related to how well the *SMN2* gen can make up for the loss of function of *SMN1* gen.
- This is related to the number of *SMN2* gene copies present on the chromosome.
- Healthy individuals carry two *SMN2* gene copies.
- The greater the number of *SMN2* copies - milder the disease severity.

  Most SMA type 1 babies have one or two *SMN2* copies; people with SMA II and III usually have at least three *SMN2* copies; and people with SMA IV normally have at least 4-10 copies

SMA type 3

- Type 3a and 3b
- 18 month- adulthood
- Proximal weakness afecting the legs more than arms (often falls, truble climbing stairs)
- Pulmonary function is normal, most do not develop scoliosis
- Slow progresion with long plateua periods
- Wheelchair dependent at age 25-30
- Some of them ambulatory at age 40 (type 3 b) - foot deformity



SMA type 4

- Onset of muscular weaknes in adult life (mean age of onset 30y)
- The patern of weaknes is similar to that of LGMD (difficulty getting up from floor, rising from chair, going up steps)
- Fasciculations in the limb muscules (df.dg. ALS)
- Pulmonary involment, dysphagia , scoliosis are absent
- Patients with SMA 4 tend to remain ambulatory.

Non SMN-related variants SMA

- Reare disorders with very simillar phenotypic feature as SMA, caused by mistake of other genes

In adult populations:

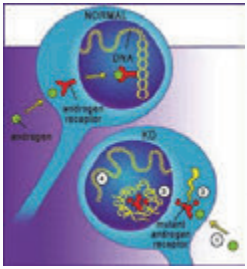
- Adult Proximal SMA (Finkle type)
- X-linked recesiv Bulbospinal Muscular Atrophy (Kennedy Disease
- Monomelic amyothrophy (Hyrayama Disease)
- Late-onset spinal motor neuronopathy

Adult Proximal SMA (Finkle type)

- Approximately 30 % of adult-onset SMA are autosomal dominant disorders not linked to the SMN protein.
- same phenotypic features as autosomal recessive form
- slowly progressive weakness and atrophy of the proximal leg muscles with later involvement of the arms muscles. Generalized areflexia and fasciculations are typical.
- The disease has a benign course.
- Linkage to chromosome 20q13.3 and missense mutation in vesicle-associated membrane protein .

X-linked recesiv Bulbospinal Muscular Atrophy (Kennedy Disease)

- X-linked recesive disorder caused by mutation with in the first exon of androgen receptor gene
- Men between 30 and 50 years

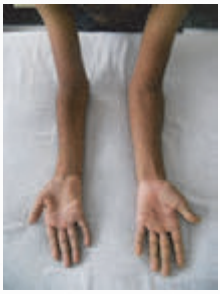


X-linked recesiv Bulbospinal Muscular Atrophy (Kennedy Disease)

- Facial fasciculation (around mouth and chin), tongue fasciculations, atrophy of facial muscles
- Dysphagia
- weaknes of proximal muscle, first lower limbs with asymetric distribution, later upper limbs.
- Hand tremor, cramps
- Gynecomastia

Monomelic amyothrophy (Hyrayama Disease)

- Etiology unknown (ishemia of the spinal cord especially the anterior horn cells)
- 18-22 years old
- Male: female 5: 1
- Unilateral weakness and atrophy of hand muscles (C7-Th1 myotomes)
- Progress over 1-3 years and than stabilizes



Late-onset spinal motor neuronopathy

- It is caused by a mutation in CHCHD10, and it is inherited in an autosomally dominant patern.
- usually after age of 40.
- muscle cramps and muscle twitches affecting the upper and lower limbs
- slowly progressive disease and it results in weakness and mild muscle atrophy specially distal muscles. The disease does not reduce life expectancy.

Instead of a conclusion…

- SMA and and non SMN-Related SMA variants in adults are slow progresive hereditar degenerativ diseases which are present with relativlly mild weakness of the limb muscles, without a pulmonary the involvement, heart complications and scoliosis.
- A certain number of patients remaind unrecognized or misdiagnosed
- Patients usually stay mobile for a lifetime.
- Regular physiotherapeutic treatment is necessary


Thanks for your
attention !

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I am a pediatrician working in the field of pediatric neurology. I am particularly interested in novel therapeutic options for children with neurological diseases. The topic of my PhD were neuroprotective treatments for neonatal hypoxic-ischemic brain injury, such as treatment with hypothermia, erythropoietin and xenon. I am currently focusing in novel therapies for neuromuscular diseases (NMD) in children. We have organized a dedicated team of doctors that has managed to improve the clinical care of NMD patients. We have introduced a registry in which we have enrolled all children with NMD in Slovenia. We started to treat the first patients with spinal muscular atrophy with nusinersen and the first patients with Duchenne muscular dystrophy with ataluren. Our goal is to continue to improve the standards of care for our NMD patients. We became a member party of the European Reference Network for rare NMD (ERN-NMD). We are also engaged in scientific research in the field of NMD.

The registry of children with neuromuscular disorders and the new approach to their holistic treatment

Neuromuscular disorders (NMD) are rare and as yet incurable genetic conditions that can also affect children. The disease inflicts an enormous burden on the affected children, their families and the whole society. Usually the disorder is of progressive nature, so the primary disease is soon accompanied by numerous associated difficulties that further deteriorate the child's health and quality of life.

Modern medicine has drastically changed the natural progress of NMD. The Division of Paediatrics of the University Medical Centre Ljubljana has already started to provide treatment with the drug nusinersen for children with spinal muscular atrophy (SMA) and ataluren for children with Duchenne muscular dystrophy (DMD). Both drugs regulate gene expression and thus slow down the progression of the primary disease. Similar treatments are anticipated for other types of NMD. Moreover, future medical development is expected to completely remove the genetic disorder.

To this end the Ljubljana clinic of paediatrics would like to modernise the approach to treating children with NMD. The treatment has become child-focused. Each year, a child with NMD is hospitalised for two days and examined by various specialists. Once all the tests are performed the child's medical condition in summed up in a single report. All changes in the medical condition are recorded in the NMD registry. The accurately kept registry provides a good overview of the situation of children with NMD in Slovenia and at the same time enables us to respond to the initiatives for participation in various researches that offer new forms of treatment to the patients.

Treatment of SMA patients with nusinersen: the Slovenian experience

Damjan Osredkar, MD PhD

Department of Pediatric Neurology
University Medical Centre Ljubljana, Slovenia

[Zagreb/ Oct 2017]

Introduction

- Slovenia: population ~2 million
- University Childrens's Hospital Ljubljana:
  the sole tertiary centre treating children with NMD

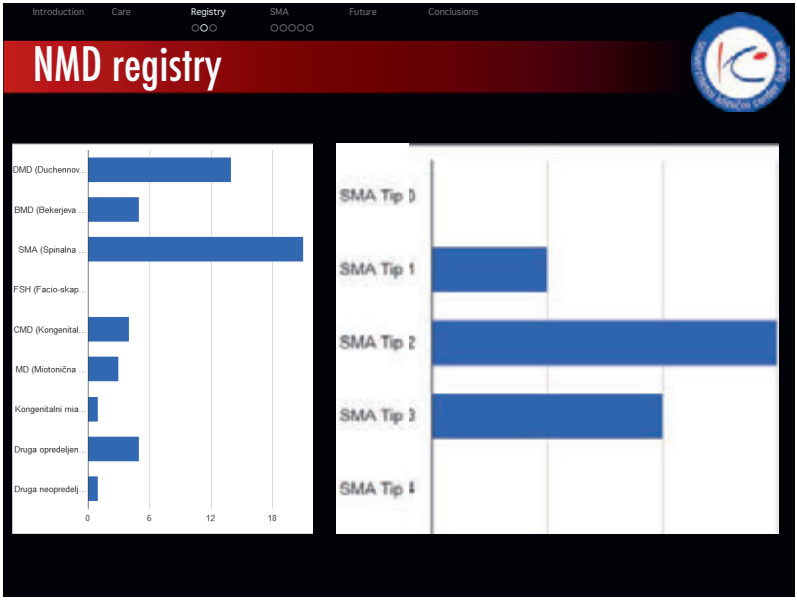
- New opportunities:
  1. Better care for NMD patients
  2. National registry
  3. New treatment options:
     nusinersen (nusinersen), ataluren (DMD)

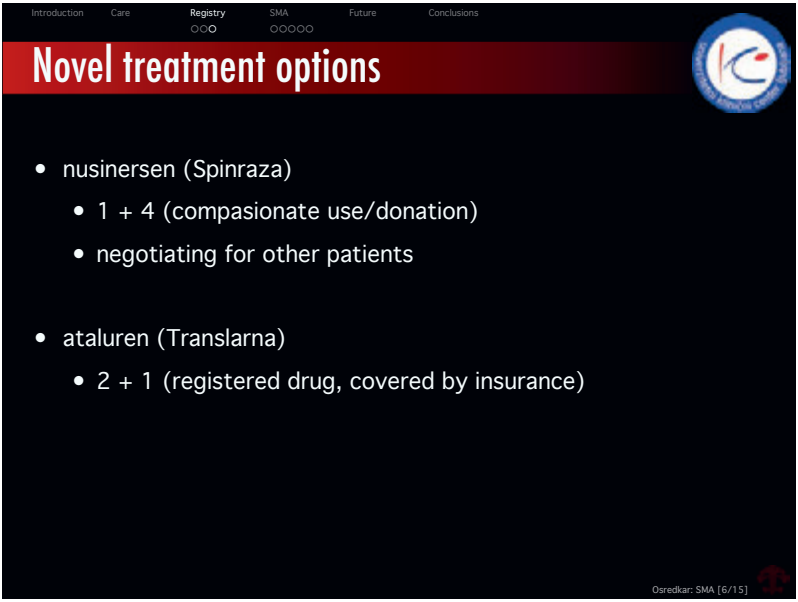
NMD yearly evaluation

- Annual two-day inpatient program
- Medical professionals come to the patient
  - Pediatric neurologist
  - Pediatric pulmonologist
  - Pediatric gastroenterologist
  - Pediatric cardiologist
  - Pediatric endocrinologist
  - Psychologist
  - Physical therapists
  - Dietitian
  - Nurse
  - Coordinator

Osredkar: SMA [3/15]

NMD registry


Introduction
Care
Registry
SMA
Future
Conclusions
NMD registry
DMD (Duchennov...
BMD (Bekerjeva ...
SMA (Spinalna ...
FSH (Facio-skap...
CMD (Kongenital...
MD (Miotonična ...
Kongenitalni mia...
Druga opredeljen...
Druga neopredelj...
0
6
12
18
SMA Tip 1
SMA Tip 2
SMA Tip 3

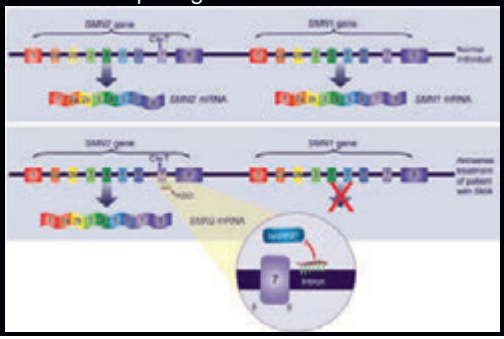

Introduction
Care
Registry
SMA
Future
Conclusions
Novel treatment options
• nusinersen (Spinraza)
• 1 + 4 (compasionate use/donation)
• negotiating for other patients
• ataluren (Translarna)
• 2 + 1 (registered drug, covered by insurance)
Osredkar: SMA [6/15]

SMA

- 1 / 10.000 children
- Mutation in the survival motor neuron 1 gene (SMN1)
- SMN2: produces only 10-20% of functional SMN protein
- Number of copies not always related to clinical type
- Type 0, 1, 2, 3, 4

SMA: treatment with nusinersen

- Antisense nucleotide
- Intrathecal application
- Alternative splicing: functional conversion SMN2 → SMN1



Introduction Care Registry SMA Future Conclusions

SMA: treatment with nusinersen

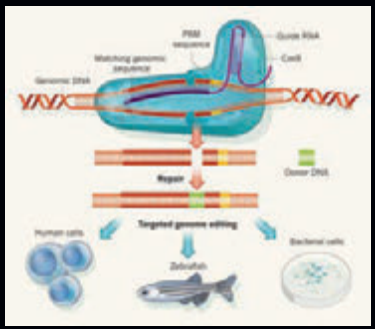
- Stops the progression of the disease
- Best effect in presymptomatic patients, but helps all
- In 60% patients with SMA type 1:
  improvement compared to initial state
- Side effects: post limbar punction problems postpunkcijske težave, blood cloting, infections of the respiratory system, hypoglycemia
- 0, 2, 4, 8w, than every 4m
- Lifetime therapy

Osredkar: SMA [9/15]

Introduction Care Registry SMA Future Conclusions

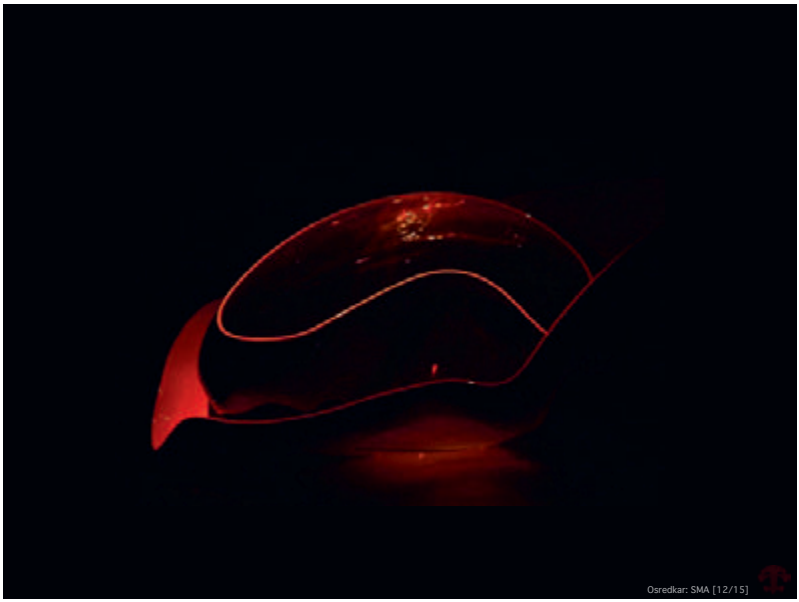
SMA: future therapies

- RG7916: alternative splicing, oral (Firefish / Sunfish, SMA 1-3)
- Avexis: viral vector – gene transfer (SMA 1)
- Gene editing: CRISPR / Cas9



Osredkar: SMA [10/15]


Introduction Care Registry SMA Future Conclusions
Conclusions
• Better patient care
• Nobody “left out”
• A medical team dedicated to NMD patients
• Collaborating with international registries (Treat-NMD)
• Fast response to novel treatment options
• Participation in international studies
• Orphan drug use
• Future challenges await
Osredkar: SMA [11/15]


Osredkar: SMA [12/15]

Danijela Petkovic Ramadza
Department of Pediatrics

Division for Medical Genetics and Inherited Metabolic Diseases

University Hospital Center Zagreb
Kišpatićeva 12, 10 000 Zagreb, Croatia
e-mail: dramadza@gmail.com

I graduated at School of Medicine Zagreb in 2004. In the following years I was research fellow and later pediatric resident at Department of Pediatrics, University Hospital Centre Zagreb. Since February 2012 I work as a pediatrician at Division for Metabolic Diseases. Currently, I am on metabolic medicine sub-speciality training. Since January 2017, I am teaching assistant at Deparment of Pediatrics; Medical School Zagreb. I actively participated at numerous national and international scientific congresses and symposia and I am author or co-author of several scientific papers. I participated in organisation of several national and international congresses, symposia and teaching programs and also contributed to several European registries for rare metabolic diseases. My special area of interest is metabolic myopathies.

POMPE DISEASE

Pompe disease is an autosomal recessive inherited glycogen storage and lysosomal storage disorder. Due to mutations in the GAA gene, deficiency of acid a-glucosidase (GAA) results in massive glycogen accumulation and cellular dysfunction, with prominent involvement of cardiac, smooth and skeletal muscles. Incidence is approximately 1 in 40 000. Clinical spectrum ranges from infantile-onset to late-onset disease. Complete deficiency of the GAA enzyme (activity <1% of normal controls) causes infantile-onset disease. Newborns typically present within the first months of life with hypotonia, feeding difficulties, cardiomyopathy and respiratory insufficiency. Without treatment, cardio-respiratory failure leads to death within the first two years of life. Later onset disease (LOPD) is clinically heterogeneous and associated with some residual enzyme activity

(2% to 40% of normal controls). Main features are proximal myopathy, with predilection of lower limbs, paraspinal muscle involvement and respiratory weakness. Respiratory involvement doesn't necessarily correlate with skeletal muscle involvement. Other problems are feeding difficulties, malnutrition and osteopenia. Patients usually have elevated serum CK. Muscle histology shows glycogen accumulation and vacuolar myopathy, but up to 20% of LOPD patients may have normal or unspecific finding. Urinary tetrasaccharides may be used as a biomarker, although excretion may be normal in LOPD patients. Assays of GAA enzyme activity in whole blood or dried blood spots are reliable for diagnostics, but the diagnosis must be confirmed by gene sequencing or enzyme assays in different tissue (fibroblasts of muscle). Enzyme replacement therapy (ERT), available since 2006, has markedly extended ventilator-free and general survival and improved cardiac function in infants with Pompe disease. Approximately 20% of infantile Pompe patients produce no endogenous GAA enzyme (CRIM-) and develop high levels of IgG antibodies to ERT. High sustained antibody titers (HSAT) have been correlated with poor response to ERT and clinical decline. Different immunomodulation protocols were designed to prevent or eliminate immune responses to ERT. Immunomodulation in CRIM negative patients is of major importance for improving outcome. In patients with LOPD ERT improves motor function and stabilizes or slightly improves respiratory function. ERT is well tolerated and most adverse events are mild or moderate, although development of HSAT in a subset of patients with LOPD may as well have potentially negative impact on clinical response to ERT. Therapies under investigation (ERT with improved uptake by muscle cells, small molecule therapy and gene therapy) could overcome disadvantages of current ERT. One of the most important aspects of management is a close monitoring for respiratory failure with timely interventions that include aggressive treatment of infections, immunizations, respiratory therapy, non-invasive or invasive ventilatory support. Other interventions include regular physiotherapy, maintaining weight with balanced diet, tube and/or enteral feeding, etc. As patients with infantile-onset disease survive longer, a new phenotype is emerging. It includes dysphagia, hypernasal speech, osteopenia, perceptive hearing loss, arrhythmias, anterior horn cell involvement, etc. In both in infantile and LOPD patients small- and medium-vessel arteriopathy and small-fiber neuropathy are occasionally reported. Considering rareness and complexity of the disease, it is recommended that these patients are followed in specialized metabolic centers by a multidisciplinary team.

EAMDA 46th Annual General Assembly, Zagreb, October 14th, 2017

Pompe disease

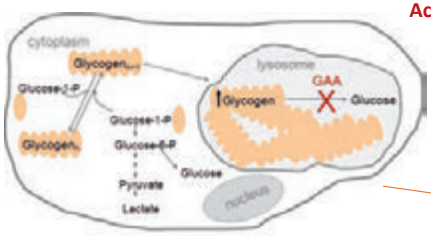
Danijela Petković Ramadža
Department of Pediatrics, University Hospital Centre Zagreb
University of Zagreb, School of Medicine

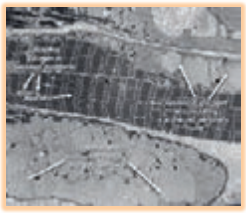
1

Pompe disease

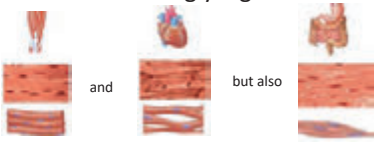
lysosomal and glycogen storage disorder

Acid alpha glucosidase deficiency





Accumulation of glycogen in:



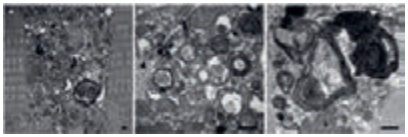
skeletal and cardiac but also smooth muscles

... and neurons

2

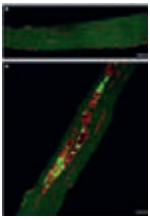
Pompe disease
pathophysiology

... **glycogen buildup**, but also:



Autophagic buildup in skeletal muscle from a GAA-KO mouse

dysregulation of autophagy



Conofocal microscopy images of fibers from WT and GAA-KO mice

accumulation of undegradable material (lipofuscin)

Autofluorescent lipofuscin inclusions in a muscle biopsy from a patient with a childhood form of Pompe disease

oxidative damage

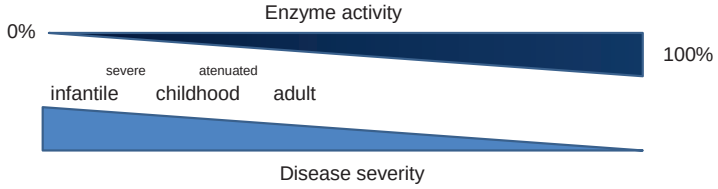
Pompe disease
epidemiology, inhertiance and genetics

- Combined incidence 1: 40 000
- Autosomal recesive inheritance
- GAA gene located on chromosome 17
- Almost 300 mutations, some common →
- No clear genotype-phenotype correlations

Mutation	Ethnic Group	Allele Frequency	Subtype
Asp645Glu	Taiwanese	0.8	Infantile
Arg854X	African-American	0.5	Infantile
del525T	Dutch	0.34	Infantile
del exon 18	Dutch	0.23	Infantile
IVS 1-13 t>g splice	Caucasian	0.46-0.67	Late

Hirschhorn R, et al. In: The Metabolic and Molecular Bases of Inherited Disease. 2000.

Pompe disease
spectrum of severity



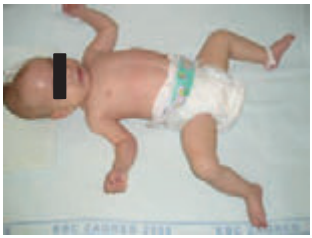
1. **Classic infantile** (first moths of life with cardiomyopathy)
2. **Childhood** (from birth to adolescence, without progressive cardiomyopathy)
3. **Adult form** (from adolescence to late adulthood)

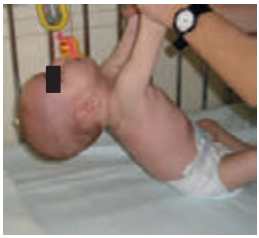
5

Pompe disease
classic infantile form

Onset in the first months of life

Severe hypotonia, delayed motor milestones





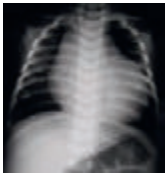
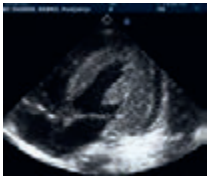
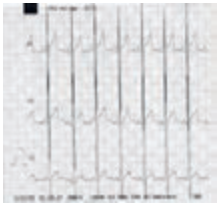
Feeding difficulties,
Failure to thrive

Macroglossia,
Moderate hepatomegaly

6

Pompe disease
classic infantile form

Cardiomegaly/cardiomyopathy

Respiratory insufficiency

If untreated:
Progressive deterioration
Cardio-respiratory failure and death within first two years

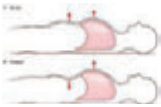
Atypical infantile – onset in the first two years, no progressive cardiomyopathy, somewhat better prognosis

7









Pompe disease
late onset forms

Onset >1 yr. to 7th decade

Muscle weakness (proximal, lower limbs more affected, paraspinal and neck muscles involved, ptosis)

Respiratory difficulties (morning headaches, exertional dyspnea, sleep apneas, resp. infections, resp. insufficiency)

Scoliosis, contractures (childhood/juvenile)

Osteoporosis

Fatigue, myalgias

GI problems (difficulty chewing/swallowing, dysmotility, malnutrition)

Death due to respiratory insufficiency

Respiratory involvement doesn't necessarily correlate with skeletal muscle strenght!

van der Beek et al. Orphanet Journal of Rare Diseases 2012;7:88

9

Pompe disease
diagnosis

CK often elevated (4-10x) as well as AST and ALT

May be normal in LOPD

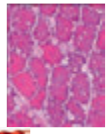
Urine GL4 - useful biomarker (HPLC, MS/MS)

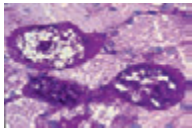
May be normal in LOPD

Vacuoles in lymphocytes

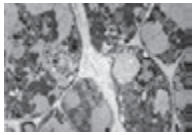
Less frequently seen in LOPD

Muscle biopsy





Up to 20% of children and adults with LOPD may have normal finding or nonspecific changes!



Vacuolar myopathy

IOPD – chest X ray, ECG, heart ECHO

EMNG: myopatic pattern,
also motor axonal neuropathy in IOPD

May be normal

9

Pompe disease
enzymatic and molecular diagnosis

- ENZYME ANALYSIS

DBS: minimaly invasive, low costs, rapid turn-around
Reliable for diagnosing and screening patients
Must be confirmed by another method

Lymphocytes, fibroblasts, muscle tissue

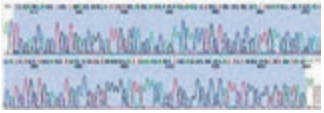
Be aware of pseudodeficiency!

Testing of high risk population:

Masumeci et al. JNNP 2015:
Age > 5 years, LGMW and hyperCKemia
1051 test – 21 positive, 17 diagnosed with Pompe (1.6%)

Spada et al. Mol Genet Met 2013:
Isolated hyperCKemia
137 test – 3 diagnosed with Pompe (2.2%)

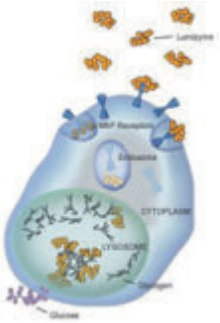
- GENE TESTING



10

Pompe disease

enzyme replacement therapy



Alglucosidase alpha, rhGAA (Myozyme®, Lumizyme®)
CHO-derived, available since 2006

- ✓Only disease specific treatment
- ✓Changes natural course of disease
- ✓Intravenous application, 20 mg/kg biweekly
- ✓Quite high price, lifelong treatment
- ✓Safe and well torelated
- ✓Immunogenecity (IAR, IgG antibodies)

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Enzyme replacement therapy

infantile onset Pompe disease


Recombinant human acid α-glucosidase

Major clinical benefits in infantile-onset Pompe disease

18 infants, <6 months vs historical control
Improved clinical outcome – markedly prolonged survirval and ventilator free surival, improved cardiomyopathy, improvement in gross motor skills

DRAMATICALLY IMPROVED NATURAL HISTORY!

Similar trends in extension studies

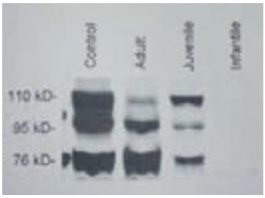
Some centers use weekly infusions in the first 12 weeks of treatment or 40 mg/kg biweekly

Factors affecting outcome of ERT: CRIM status, antibody production, age and degree of muscle involvement at start of treatment

12

Enzyme replacement therapy

infantile onset Pompe disease and CRIM status



CRIM negative

- 20% of IOPD
- No endogenous GAA
- Quick seroconversion
- High antibody titers
- Clinical decline

Immunomodulation protocols designed to prevent or eliminate immune response

Determination of **CRIM status** (Western blotting, fibroblasts, leukocytes) as soon as possible and prior ERT

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Pompe disease

new phenotype of IOPD patients on ERT

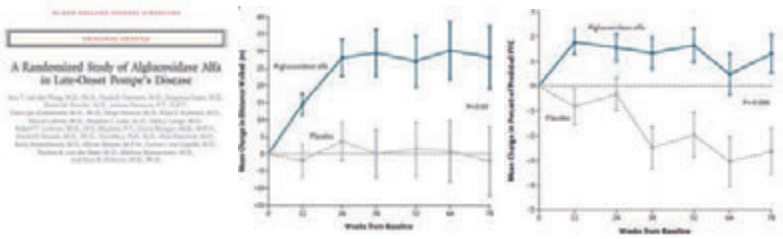
- Distinct from untreated historical controls and LOPD patients
- Dysphagia, GERD
- Speech disorders (hypernasal speech)
- Osteopenia, susceptibility to fractures
- Hearing loss
- Arrhythmias following anesthesia
- Anterior horn cell involvement

- Small- and medium-vessel arteriopathy (risk of cerebral aneurysms) and small fiber neuropathy – both in IOPD and LOPD

14

Enzyme replacement therapy

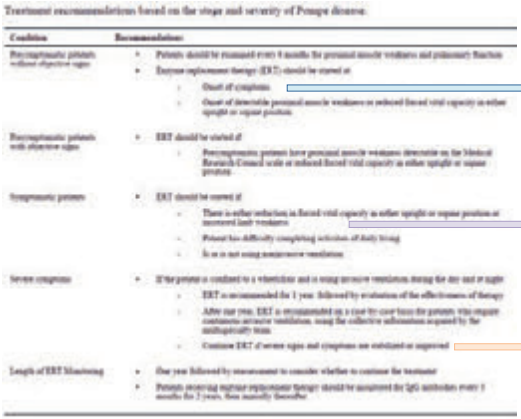
late onset Pompe disease



Better prognostic factors:
for muscle strenght - female gender
for pulmonary function - younger age, better clinical status prior ERT

Late onset Pompe disease

when to start treatment?



Presymptomatic patients - close monitoring until first symptoms then ERT

Symptomatic patients - as soon as the diagnose is confirmed

Patients with severe symptoms – one year trial then depending on therapeutical response

Cupler at al. Muscle Nerve 2012:45;319-333

Overall, ERT in LOPD is generally effective, stabilizes the course of disease and slows progression!

Toscano A, Schoser B. **Enzyme replacement therapy in late-onset Pompe disease: a systematic literature review**. J Neurol 2013

... twenty-one studies containing clinical data from 368 LOPD patients were analyzed...
At least two-thirds of patients were stabilized or had improved creatine kinase levels and muscular and/or respiratory function following treatment with alglucosidase alfa.

... but up to 1/3 NO IMPROVEMENT!!!

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Enzyme replacement therapy

disadvantages of current therapy and emerging treatments

Problems:

- **Stability**

rapid degeneration in blood

- **Targeting**

low uptake in muscles

majority of rhGAA not delivered to lysosomes

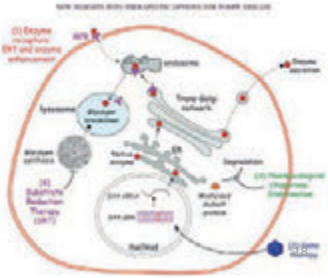
- **Immunogenecity**

IARs

high antibody titers affect treatment effect


Critical Review

New Insights into Therapeutic Options for Pompe Disease



Pompe disease

respiratory support

- The most important aspect of management
- Necessary regular monitoring (FVC, function tests, blood gasses, etc...)
- Agressive treatment of infections
- Regular immunisations (+ against influenza, and RSV in IOPD)
- Respiratory physical therapy, clearance of secretions
- Oxygen supplementation
- Non-invasive (CPAP and BiPAP) and invasive ventilation




Pompe disease

musculosceletal management

- Physical (submaximal aerobic excercize, gentle streching)
- Occupational therapy
- Orthotic devices, weelchair, etc.
- Screen for osteopenia – DEXA, vitamin D and Ca supplementation

GI aspects and management

- High protein and well balanced diet
- Growth parameters in children
- Videofluoroscopic swallowing assesment – if necessary tube feeding

Other speech therapist in children, audiology assesment, hearing aids, ...

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Pompe disease

management and follow-up

Cupler at al. Muscle Nerve 2012:45;319-333

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New perspectives in DMD management – Developing A Dystrophin Replacement Therapy

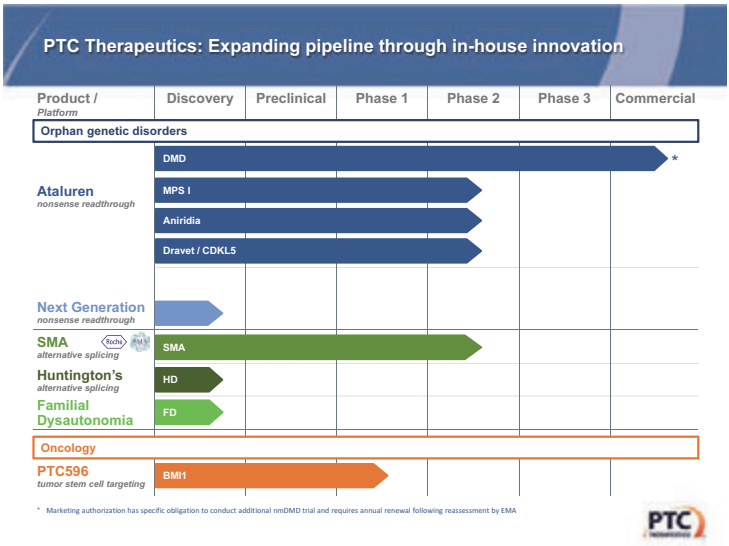
EAMDA 46th Annual General Assembly
October 14th , 2017 Zagreb - Croatia
Sunay Ozdas, MD
Medical Head of CEEMEA & APAC Region, PTC Therapeutics

PTC

Our Mission

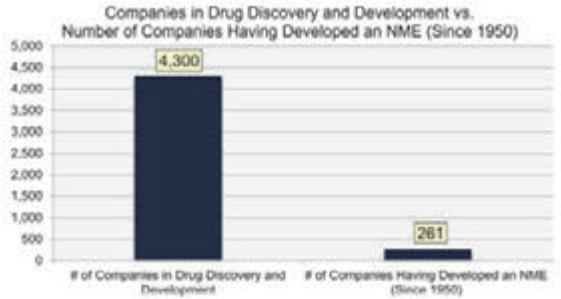
To leverage our knowledge
of **RNA biology** to bring
novel therapeutics to patients affected
by **rare and neglected disorders**

PTC


PTC Therapeutics: Expanding pipeline through in-house innovation
Product / Platform
Discovery
Preclinical
Phase 1
Phase 2
Phase 3
Commercial
Orphan genetic disorders
Ataluren
nonsense readthrough
DMD
*
MPS I
Aniridia
Dravet / CDKL5
Next Generation
nonsense readthrough
SMA
alternative splicing
SMA
Huntington's
alternative splicing
HD
Familial Dysautonomia
FD
Oncology
PTC596
tumor stem cell targeting
BMI1
* Marketing authorization has specific obligation to conduct additional nmDMD trial and requires annual renewal following reassessment by EMA


Drug Development – A long and challenging road
Discovery
PreClin /
Phase I
Phase II
Phase III
Approval
26%
13%
10%
6.2%
Idea to approval can take 10 – 20 years

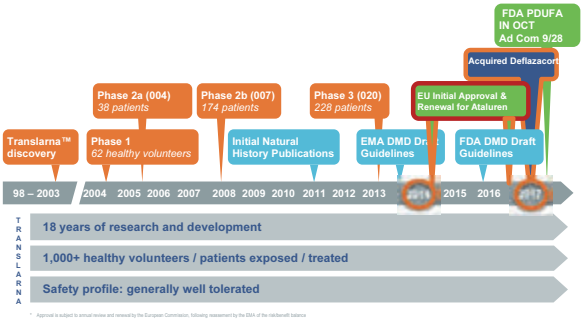
Drug development remains risky and challenging



Source: "Lessons from 60 Years of Pharmaceutical Innovation", Nature Reviews Drug Discovery 8, 959-968 (December 2009) | doi:10.1038/nrd2961

20

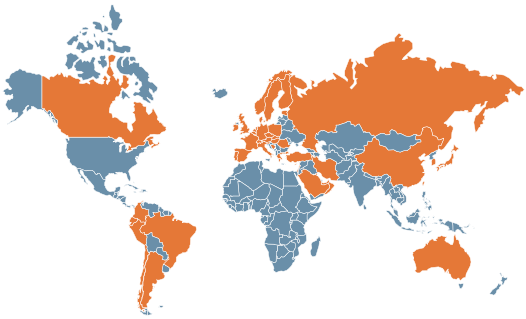
PTC Therapeutics: Committed to the Duchenne community for over 19 years



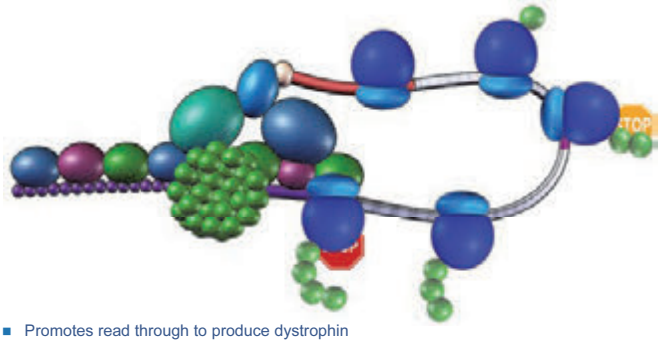
Development timeline for a novel dystrophin replacement therapy

Ataluren is available commercially in over 25 countries

- Approved in the EU for the treatment of Duchenne muscular dystrophy patients caused by a nonsense mutation that are over 5 years old and ambulatory
- Established footprint in 47 countries worldwide



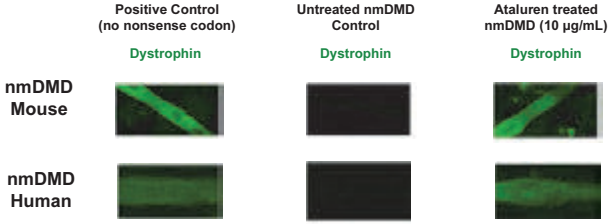
Ataluren binds to the ribosome and enables readthrough of nonsense mutations to produce functional dystrophin protein



- Promotes read through to produce dystrophin
- High specificity for nonsense readthrough without affecting normal termination codons
- Non-overlapping patient population from exon skipping drugs

PTC

Full-length Dystrophin Protein is Produced in nmDMD Myotube Cultures Treated with Ataluren



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European Medicines Agency approval of Ataluren for the treatment of nonsense mutation DMD patients – July 2014

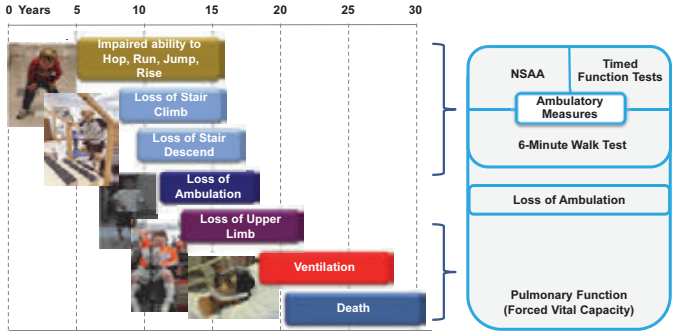
EMA, European Medicines Agency; nm, nonsense mutation
http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2014/05/WC500167540.pdf
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002720/human_med_001742.jsp&mid=WC0b01ac0580 01d124 (Both websites accessed 7 October 2016)

European Medicines Agency publication: ataluren treatment for patients with nonsense mutation DMD[1]

"… ataluren was considered to offer therapeutic innovation and relevant benefits for a rare disease with high unmet medical need. Whilst the effect was best measured in a sub-population of ambulatory patients in the decline phase of their disease, it was agreed that there should be **no scientific reason, nor any safety imperatives, to withhold ataluren from nmDMD ambulatory patients** aged 5 years or more who are at an earlier stage of disability progression."

EMA, European Medicines Agency; nm, nonsense mutation
1. Haas M *et al. Neuromuscul Disord* 2015;25:5–13

DMD is a complex heterogeneous disease requiring the use of multiple endpoints in clinical studies

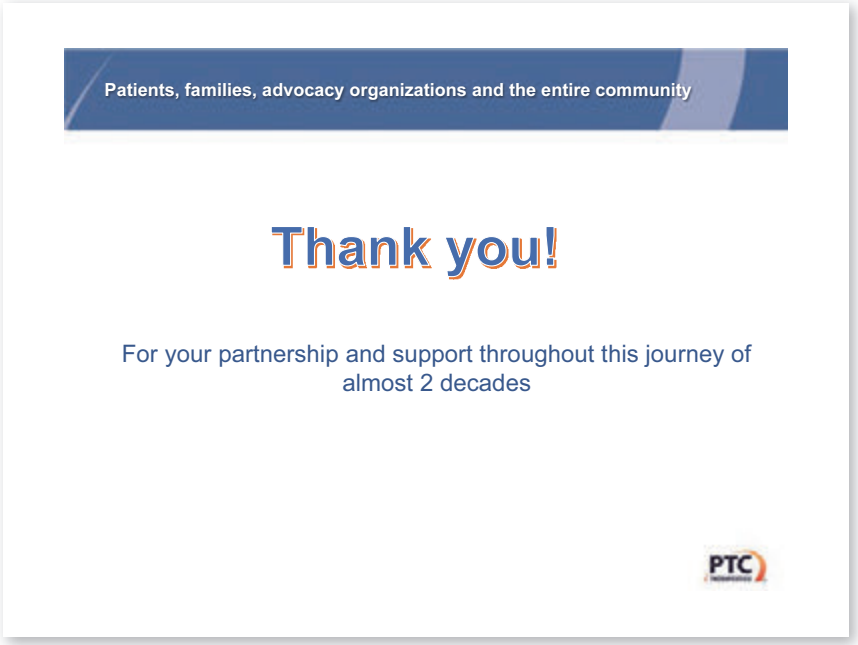


Active ataluren* clinical trials for nonsense mutation DMD patients

Details can be found at www.clinicaltrials.gov

- Trial 041
  - Global, multi-center, placebo controlled
  - Boys, 5 years and older that meet certain performance qualifications (at least 12 months under corticosteroid therapy)
  - 72 weeks blinded; All will receive ataluren for an additional 72 weeks
  - Details located on www.clinicaltrials.gov
- Pediatric (030)
  - Phase 2 Trial to establish safety and efficacy for label expansion
  - ≥ 2 to <5 years old
  - Fully enrolled
- Extension Trials (019 and 020e)
  - Transitioning to a new protocol (016)
  - Fully enrolled
- STRIDE Registry
  - Captures long term safety data
  - Available to those patients receiving commercial ataluren

*Investigational drug in the US


Patients, families, advocacy organizations and the entire community
Thank you!
For your partnership and support throughout this journey of almost 2 decades
PTC

NUTRITION CONSIDERATION IN NEUROMUSCULAR DISEASE

Prim MrSc Gordana Kovačević, MD, Goran Mitrović MD,

Slavica Ostojić MD PhD

Mother and child health care Institute of Serbia

Belgrade, Serbia

46th Annual General Meeting of EAMDA October 2017, Zagreb

Nutrition is a critical part in long term management in DMD and SMA

- Influence on:
  - Height and development
  - Muscle strength
  - Respiratory muscle strength
  - Immune response
  - Quality of life

Nutritional complication of NMD

frequent underestimated worsen with age

- Overnutrition
- Undernutrition
- Swallowing difficulties and dysphagia
- Gastrointestinal complication
  - Constipation
  - Delayed gastric emptying
  - Gastrooesophageal reflux (GER)

OVERNUTRITION

- Weight gain occurs in the early stages of disease (at 7-10 years)
- The greatest risk for obesity at 9-17.7 years
- 45-54% patients with DMD (Willing et al 1993, MsDonald et al 1995)
- ? % patients with SMA

OVERNUTRITION- CAUSES

Multifactorial

- ↑ appetite due to corticosteroid treatment
- ↓ caloric needs
- ↓ physical activity
- ↑ amount of food in attempt to increase body's production of muscle proteins
- Lack of food restriction by parents

OVERNUTRITION-CONSEQUENCES

- Progression of the disease
- Increase respiratory involment with worsening respiratory and cardiac function
- Agravation of sceletal malformation
- Increase need for orthopedic surgery and complication
- Insuline resistance, dyslipidemia,
- Hypertension, opstructive sleep apnea
- Impairment of quality of life

OVERNUTRITION- PREVENTION AND DIET

"Eat less do more"

"Eat less and slowly"

Avoid
Simple sugar
Sugar containing beverages
Trans fat

Eat
Complex carbochidrates
Legumes, fruits
Whole grain bred
Milk, fiber

Do not advice a strict diet - during fasting body will begin to break down muscle proteins which can result in the irreversible loss of muscle mass
Prevention better than cure!

UNDERNUTRITION

- With disease progression overnutrition ⇢ undernutrition
- Malnutrition is a predictor of a poor outcome
- 54 - 65% patients with DMD (Willing et al 1993, MsDonald et al 1995)
- ~50% patients with SMA (Mehta NM, 2016)
  - Significant muscle wasting
  - Progressive muscle weakness
  - Swallowing difficulties and dysphagia
  - Gastrointestinal problems

UNDERNUTRITION

- With disease progression overnutrition →undernutrition
- Malnutrition is a predictor of a poor outcome
- 54 - 65% DMD patients (Willing et al 1993, MsDonald et al 1995)

~50% patients with SMA (Mehta NM, 2016)

Significant muscle wasting

Progressive muscle weakness

Swallowing difficulties and dysphagia

Gastrointestinal complication

Swallowing difficulties and dysphagia

Causes

- Facial weakness, reduced mastication, poor tongue coordination
- Poor head control, ↓ in neck range motion

Impact on:

respiratory function

risk of chest infections (↑ episodes of choking, coughing)

weight loss (↑mealtime, ↓ food intake);

quality of life

Recommendation:

No weight loss → Small pieces, smooth food

Weight loss → high caloric diet, high energy drinks

UNDERNUTRITION

- With disease progression overnutrition →undernutrition
- Malnutrition is a predictor of a poor outcome
- 54 - 65% DMD patients (Willing et al 1993, MsDonald et al 1995)

~50% patients with SMA (Mehta NM, 2016)

Significant muscle wasting

Progressive muscle weakness

Swallowing difficulties and dysphagia

Gastrointestinal complication

Gastrointestinal complication

- Constipation
  - Immobility
  - Weakness of abdominal wall muscles
  - Inadequate fluid intake

  Recommendation:

  bulging agent, stool softener, osmotic, fibers, ↑ fluid intake

- Delayed gastric emptying and GER

  Recommendation:

  proton pump inhibitors, H2 receptor antagonists, prokinetics

Enteral nutrition
(percutaneous endoscopic gastrostomy-PEG)

Often required in patients with NMD

10% pts with DMD (Pane M, 2006)

0-98% pts with SMA1 (Davis RH, 2015; Tassie B, 2013)

Indication (Bushby et al, 2005)

- Undernutrition
- Difficulty in swallowing leading to aspiration pneumonia

Don't stop oral intake if the patient is able to eat without risk of aspiration!

> <
=

Nutrition recommendation:

Ambulatory DMD patients require 80% and non ambulatory 70% of the recommended calory intake for healthy children

Patients with SMA :

Calories 7-11cal/cm body height

Fat up to 30%

Proteins 1-2gr/kg

Fluids 115-135ml/kg body weight

Calory intake

Muscle activity

Devastating effects of excess weight gain on mobility

Muscle loss associated with Inducing negative energy balance

Increase muscle breakdown due to **overuse**

Increase muscle weakness from **disuse**

CONCLUSION

- *Nutrition is a crucial part of long term management in DMD and SMA patients*
- *Multidisciplinary team, with dietitian, gastroenterologist, swallowing therapist, plays a crucial role in the prevention and treatment of nutritional complications*
- *Significant progress has been made over the last few years towards developing therapies for DMD and SMA*

- *Waiting for an effective treatment of NMD, therapeutic and supportive intervention are necessary in preventing or delaying complications and preserving quality of life*

Thanks for your attention!

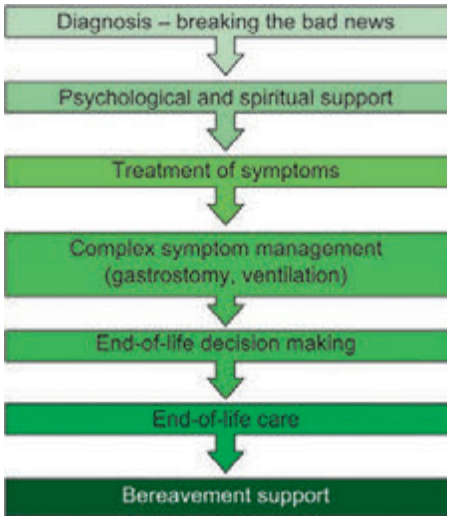
Different healthcare in different countries for patients with ALS/MND

Aleš Pražnikar
Department for Neurorehabilition
UMC Ljubljana

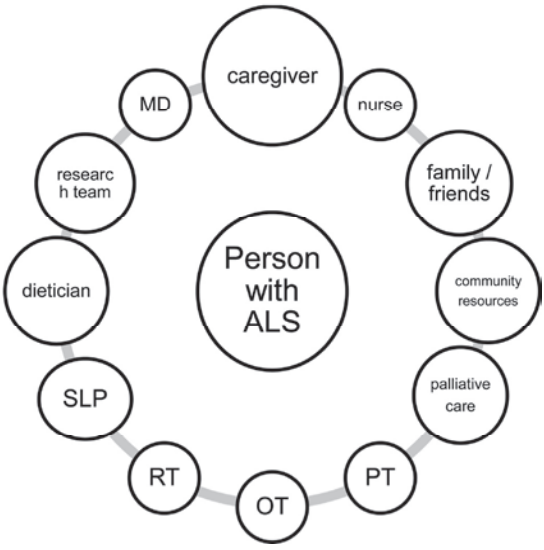
EAMDA, Zagreb, oct. 2017

Amyotrophic lateral sclerosis

- is a neurodegenerative disease that results in a constellation of problematic symptoms and a high patient and caregiver burden.
- prevalence estimated at 2,6 for women and 3,9/100000 for men (Baaumer B, Talbot K, Turner MR, 2014)
- The natural history of the disease is characterized by a progressive:
  - diffuse weakness and skeletal muscle wasting,
  - frequently dysarthria, dysphagia,
  - failure of the muscles that support ventilation (Brooks, 1996).
- A benign form of disease with about 10% of patients living 10 years or longer (Chio, Logroscino, et al., 2009).



Mitchell JD, Borasio GD,2007



Multidisciplinary care of symptoms in patients with ALS

Issue	Treatment options	Health care and support professionals involved
Disease progression	Riluzole	Neurologist/rehabilitation physician
Breathing difficulty	Assisted ventilation	Respiratory physician Respiratory therapist Nursing
Eating and drinking difficulties	Gastrostomy	Gastroenterologist Dietitian Speech pathologist Nursing
Saliva management	Medication	Neurologist/general practitioner/palliative care team
	Botox	Neurologist
Mobility	Mobility equipment	Physiotherapist Occupational therapist ALS association
Cognitive, behavior, and mood issues	Counseling and support for patient and family	Neuropsychologist Psychologist
Self-care	Assistive equipment	Occupational therapist Nursing ALS association
Communication	Alternative communication devices	Speech pathologist Occupational therapist ALS association
Grief and loss	Counseling and support for patient and family	Social worker Psychologist ALS association Palliative care team
Carer support	Counseling and support for patient and family	Social worker ALS association Palliative care team

Standard of care for patients with ALS

- a multi-disciplinary approach with highly integrated, comprehensive care is intrinsically “rehabilitative” and now considered standard of care.
- It results in:
  - in better quality of life,
  - increased utilization of supportive care services,
  - and possibly prolonged survival (Chio, Bottacchi, Buffa, Mutani, & Mora, 2006; Miller et al., 2009b; Traynor, Alexander, Corr, Frost, & Hardiman, 2003; Van den Berg et al., 2005; Zoccolella et al., 2007).

Access to multidisciplinary team

- Access to multidisciplinary team in different countries has not been studied.
- Different organization of health systems with economic, social, cultural, religious differences might cause differences in access of patients to the services.

- How available is the access to a multidisciplinary team, medical aids, and social/financial assistance for patients with ALS in different countries with a questionnaire sent to associations of patients with ALS through the International Alliance for ALS/BMN?

Questionnaire

1. accessibility of multidisciplinary team, technical aids / assistive devices (ambulation and transfer aids, adaptive equipment for ADL, communication and ventilation), social and financial compensation
2. the imposed limitations
3. who pays for it (reimbursement schedule)

Results

- Completed questionnaires were received from ***8 of 44 (18 %)*** of national associations of patients with ALS

No.	Organization	Country
1	Deutsche gesellschaft fur muskelkranke e.v. Germany	Germany
2	Motor Neurone Disease Association of Victoria	Australia
3	MND Association - England, Wales and Northern Ireland	UK
4	Miquel Valls Foundation (Catalonia)	Spain
5	ALS/MND Association Turkey	Turkey
6	The Israeli ALS Association	Israel
7	MDA/ALS Center of hope Drexel University College of Medicine Philadelphia	USA
8	Društvo distrofikov Slovenije	Slovenia

Access to multidisciplinary team

	Germany	Australia	UK	Spain	Turkey	Israel	USA	Slovenia
Access	complete	complete	complete	complete	partial	partial	complete	complete
Limitations	social worker	capacity, waiting list	/	payment (only fth.)	limited therapy, no OT	specialist, resp. th.	/	waiting list
Payer	IC, S, PO	IC, S, P	S	S,PO,P	IC	S,IC	PO	IC

Legend:
IC - insurance company
S - state
PO - patient organization
P - patient
OT – occupational therapist
fth - physiotherapist

Access to technical aids -ambulation

	Germany	Australia	UK	Spain	Turkey	Israel	USA	Slovenia
Access	complete	complete	partial	partial	partial	complete	complete	complete
Limitations	/	capacity	time	time, payment	/	patient wealth	payment	waiting list, rules of prescription
Payer	S	S, PO	S,PO,P	S, P*	IC	S,PO,P,IC	PO,P,IC	IC

1. canes, crutches, walkers
2. sliding board,
3. orthotics
4. wheelchairs

Legend:
IC - insurance company
S - state
PO - patient organization
P - patient
OT – occupational therapist
fth - physiotherapist

Access to technical aids - ADL

	Germany	Australia	UK	Spain	Turkey	Israel	USA	Slovenia
Access	complete	complete	partial	complete *	no	complete	complete	complete
Limitations	bathroom eq.	capacity, payment	time	payment	/	payment	payment	waiting list, rules of prescription
Payer	IC, P	S, PO,P	S,PO,P	S, P*		S,IC,P	PO,P,IC	IC

1. Meal preparation and self-feeding
2. Dressing
3. Grooming and personal hygiene
4. Reading and writing
5. Lifts
6. Beds, cushions

Legend:
IC - insurance company
S - state
PO - patient organization
P - patient
OT – occupational therapist
fth - physiotherapist

Access to technical aids - ventilation

	Germany	Australia	UK	Spain	Turkey	Israel	USA	Slovenia
Access	complete	complete	complete	complete	partial	complete	complete	complete
Limitations	cough-flator	capacity, payment	/	hospital capacity	no data	partial	payment	/
Payer	IC	S, PO,P	S	PO		S	S or P	IC

1. ventilator
2. coghflator
3. catheters

Legend:
IC - insurance company
S - state
PO - patient organization
P - patient
OT – occupational therapist
fth - physiotherapist

Access to technical aids - communication

	Germany	Australia	UK	Spain	Turkey	Israel	USA	Slovenia
Access	complete	complete	partial	complete	not within team	complete	complete	complete
Limitations	complex	capacity, payment	waiting list	payment	no data	/	payment	rules of prescription
Payer	S	S, PO,P	S,PO,P	PO, P(most)	no data	S,IC,P	PO,P,IC	IC

Legend:
IC - insurance company
S - state
PO - patient organization
P - patient
OT – occupational therapist
fth - physiotherapist

Access to social/financial help

	Germany	Australia	UK	Spain	Turkey	Israel	USA	Slovenia
Access	complete	not for disability compensation or TV	yes and no	not for TV and internet	TV, internet	partial	partial (no TV, internet)	complete
Limitations	yes for everything	help on home, different retirement schemes	home check	limitations in payment	10% off, early retirement	disability compensation	disability compensation	waiting list, rules of prescription
Payer	S and IC	S, IC	S,PO	S, P	no data	S,IC,P	IC, pension scheme	IC

1. TV and internet
2. disability compensation
3. early retirement
4. home help

Legend:
IC - insurance company
S - state
PO - patient organization
P - patient
OT – occupational therapist
fth - physiotherapist

Conclusion

Patient advocacy organizations should devote their attention to:

1. achieving and balancing the social and economic rights for patients with ALS,
2. supporting access to proper medical aids,
3. reducing the time of delivery of medical aids and
4. supporting access a standardized multidisciplinary treatment.

These endeavors are in line with the international clinical guidelines of care for patients with ALS.

The desired changes are important, yet neither complex nor difficult to achieve.

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Faculty of Medicine

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I am a neurologist involved in muscle biopsy diagnostics of neuromuscular diseases. My main research interests are muscular dystrophies and metabolic myopathies. My PhD thesis was „Dystrophin analysis in skeletal muscle“, under mentorships of scientific counsellor dr. Ida Eržen, Professor of biology, University of Ljubljana and Professor dr. Giovanni Salviati, Professor of pathology, University of Padova. I am responsible for the Tissue Biobank of neuromuscular disorders of the University of Ljubljana, a partner of EuroBioBank network. I am a member of various scientific societies, among Section for clinical neurophysiology, Section of child neurology, Society for medical genetics of the Slovenian medical association and TREAT-NMD.

Muscle biopsy and next generation sequencing

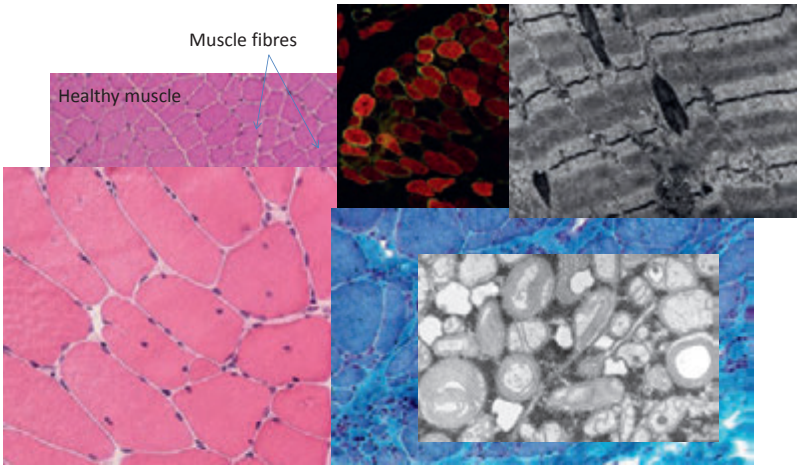
Marija Meznaric
University of Ljubljana, Medical faculty, Institute of anatomy

EAMDA Zagreb, 14.10.2017

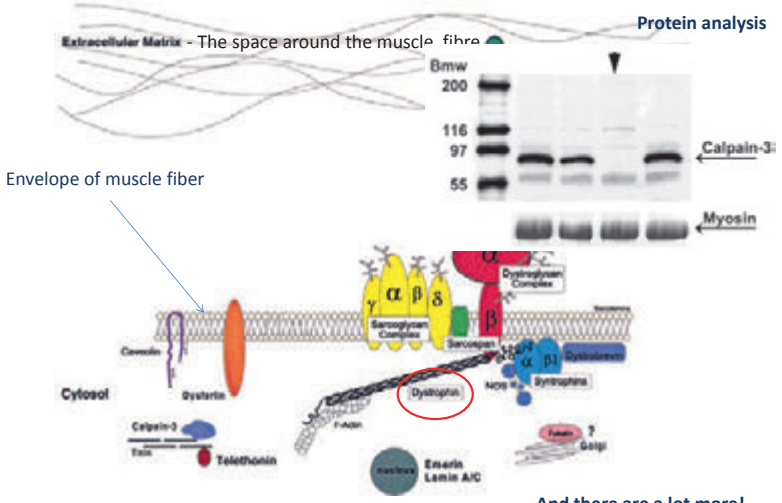
What is muscle biopsy?

- Analysis of the piece of muscle removed from the body in order to make a *diagnosis* of neuromuscular disease
- Is it painful to have a muscle biopsy? Unfortunately YES (injection of anaesthetic hurts, after some 5-10 minutes the physician can proceed and the person does not feel the pain any more)
-

Muscle under microscope



The new area after the discovery of dystrophin (Eric Hoffman and co-workers 1987)



Campbell K P J Muscle Nerve 23: 1456–1471, 2000

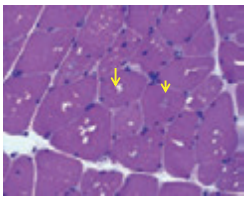
And there are a lot more! "daily" new ones…

Muscle biopsy – Conclusions I

- By muscle biopsy it might be possible to recognise type of abnormality: **is it nerve's fault?** (neuropathy) or **is it muscle's fault?** (myopathy)
- Sometimes the abnormalities are a more "**characteristic**" for example: Structural abnormalities (congenital myopathies), enzymatic defects (metabolic myopathies)

Vacuolisation "bubles"

Pompe disease



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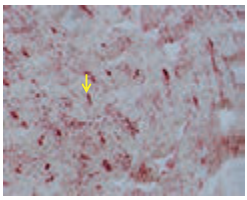
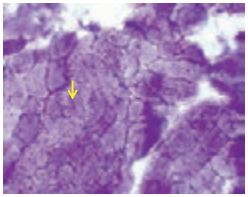
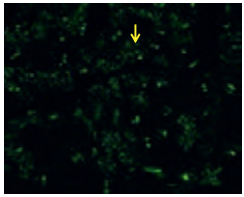


Acid Phosphataese



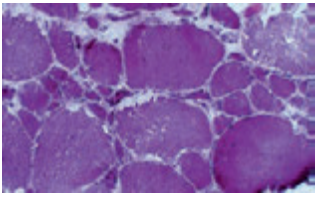
Gycogen



Lysosomal assosiated protein 2

Vacuolisation “bubles”

McArdle disease



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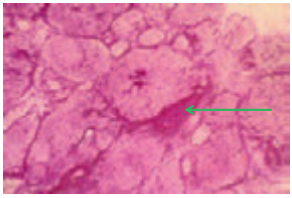
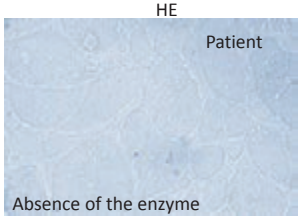
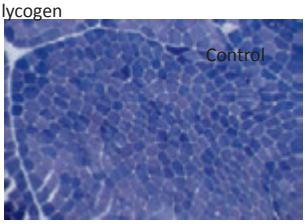


Glycogen



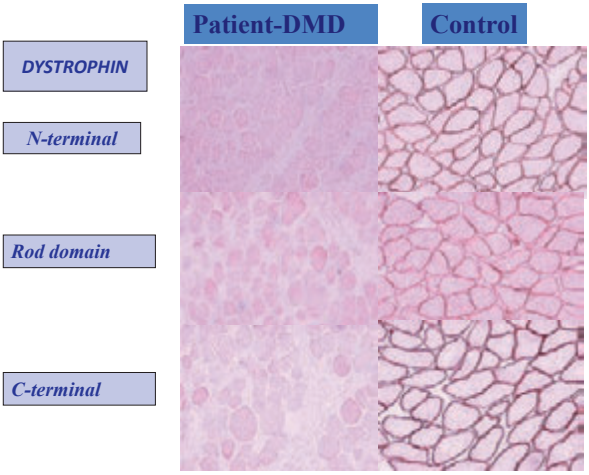


Myophosphorylase – enzyme which is necessary for glycogen degradation

Muscle biopsy – Conclusions II

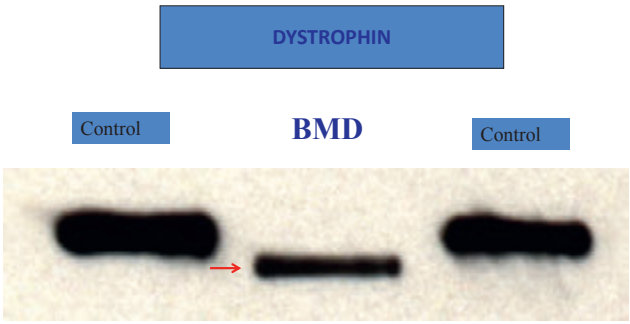
- **Protein abnormalities** (for example: *absence*, reduction, *abnormal molecular weight*) could be detected on muscle biopsy

Absence of protein by immunohistochemistry



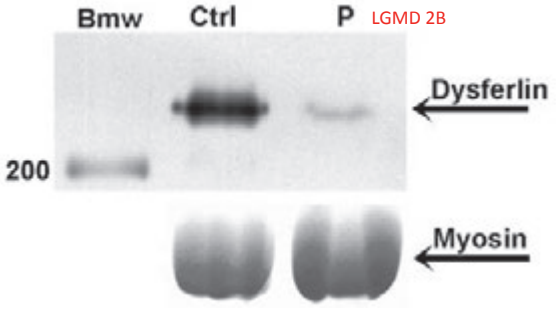
DMD= Duchenne muscular dystrophy

Reduced molecular weight of protein on Western blot



BMD= Becker muscular dystrophy

Reduction of protein amount on Western blot



LGMD= limb-girdle muscular dystrophy

Muscle biopsy – Conclusions III

- The conclusions from muscle biopsy could be important for further biochemical and genetic studies

Genetics say: Why not to perform the genetic analysis first?

We can do it from blood and we can give more information than muscle biopsy! It is less painful (less invasive)!

The investigation we are talking about is:

Next generation sequencing (NGS)

It seems it is rather obvious:

Since NGS is less invasive and possibly more informative, we shall not do muscle biopsy anymore! BUT is it through? Ask the experts!

QUESTIONNAIRE *MUSCLE BIOPSY* and *NGS*

- Sent to expert centres in Europe, USA, Australia
- The response rate not very high, but some responded and among them centres of excellence

Responders up to October 13 2017

- *Finland,* Tampere Neuromuscular Center (*Bjarne Udd*)
- *Italy*, Ospedale Maggiore Policlinico Milano (*Maurizio Moggio*) and Istituto Carlo Besta (*Marina Mora*)
- *Japan*, Tokyo National Institute for Neurology and Psychiatry (*Ishizo Nischino*)

Muscle biopsy first choice PRO et CONTRA

YES	NO
Tampere	**Tokyo** National Institute of Neurology and Psychiatry
Milano Istituto C. Besta	
Milano Granda Ospedale Maggiore policlinico	
3	1

Arguments **PRO** muscle biopsy

- Muscle biopsy is needed to clarify the many unclear variants from NGS
- … helps to indicate which type of panel of genes has to be used in NGS
- … is useful to validate NGS data at RNA level (is the source of mRNA)
- …. The residues from diagnostic muscle biopsies can be stored for future research (Bio Banking)

Answers collected from questionnaire *Muscle biopsy* and *NGS*

Arguments **CONTRA** the biopsy

- NGS is less invasive.
- If cost is low, NGS will be the first choice when patients suspect to have hereditary muscle disease.

Answers collected from questionnaire *Muscle biopsy* and *NGS*

Perspective

- General people will be having NGS testing in the near future. In such situation, we actually do not even have to order NGS but just need to look at their data.

Answers collected from questionnaire *Muscle biopsy* and *NGS*

Transition period (now and here)

- Genetic data are useful for the diagnosis only when genotype-phenotype* is well established.

* genotype = our genes (our "heritage")
phenotype = the symptoms and signs of the disease we have

Answers collected from questionnaire *Muscle biopsy* and *NGS*

Transition period (now and here)

- With more and more detailed genetic data becoming available by NGS, we actually realize that genotype-phenotype correlation is not well established for most muscle diseases. We are in the era of establishing this correlation.

Answers collected from questionnaire *Muscle biopsy* and *NGS*

Conclusion

- For muscle disease, muscle pathology is probably the most important part of phenotype as most muscle diseases, especially congenital myopathies, are classified or even defined by pathological features.
- Therefore, until *genotype-phenotype* becomes established, we will be needing muscle biopsy to *characterize the phenotype* in many cases except in certain diseases where *genotype-phenotype* has already been well established such as DMD, MYOTONIC DYSTROPHY, SPINAL MUSCULAR ATROPHY, FSH.

Answers collected from questionnaire *Muscle biopsy* and *NGS*

References

A comprehensive genomic approach for neuromuscular diseases gives a high diagnostic yield.
Ankala A et. al. Ann Neurol. 2015 Feb;77(2):206-14. doi: 10.1002/ana.24303.

Next generation sequencing on patients with LGMD and nonspecific myopathies: Findings associated with *ANO5* mutations.
Savarese M et al. *Neuromuscular Disorders*. 2015;25(7):533-541. doi:10.1016/j.nmd.2015.03.011.

M.D. **Sanja Malbasa Gosovic**

M.D. Sanja Malbaša Gošović, general practitioner, specialist. acupunturologist and cosmetologist, in 1990, has developed a method under the registered brand TEENLIFTING®, which continues to develop. On the world market this unique natural method of stimulation of the muscles of the body and face at the same time, or the stimulation of large muscle groups, for which are used in particular the newly formed electrodes with standard electrodes put in non-standard method to achieve better and more efficient results. TEENLIFTING® system is protected in Croatia, European Union, China, the United States and other countries. She has been investigating electrostimulation for the past 27 years and still continues to do so.

TEENLIFTING ELECTROSTIMULATION

Introduction:

TEENLIFTING® is the stimulation of all face, neck and body muscles. It is done using unique TEENLIFTING electrodes.

Parts of the body that are treated: head, spine, neck, shoulder belt, shoulder blades, armpits, upper arms, hands, palms, fingers, waist, hips, abdomen, breech, pelvis, thighs, knees, lower legs, ankle joints, feet.

TEENLIFTING stimulation is used for the purpose of rehabilitation for strengthening atrophic muscles, (myalgia) painful muscles, cramping muscles, (neuralgia)-painful nerves, nerve paresis, (arthralgia) pain in the joints, poor peripheral circulation, osteoporosis as result of poor physical activity, bladder incontinence, impotence, reducing edema, stress, very skinny person, obnoxious person.

Method:

Electrodes are put on the surface of the skin. Electrodes are made from different conductive materials and are in different shapes. Electrodes are then connected to the device for Neuro Muscular Electrical Stimulation.

Purpose:

Purpose of TEENLIFTING electrostimulation is:

- Achieving complete stimulation of larger or smaller group of muscles. E.g. round eyes and mouth muscles, pelvic diaphragm…
- decrease unpleasantness of tingling on the parts where electrodes are put with maximum results of the treatment
- achieve the pleasant feeling of electrostimulation, even when parts are stimulated with higher intensity
- adapt to the anatomy of the body and face while achieving synchronized contraction of all groups of muscles
- adapt to parameters of impulses of devices (stimulators) considering the purpose of rehabilitation, size, and shapes of electrodes

Types of exercises that are performed during TEENLIFTING electrostimulation:

- According to performance, there are passive, active assisted, active independent and active exercises with resistance or load.
- Exercises to maintain maximum range of motion in all joints
- Exercises for static stretching
- Exercise for strengthening, endurance, speed, and coordination:

1. Isometric – isometric contraction
2. Isotonic – concentric and eccentric contraction
3. Isokinetic

- Contraction of fast and slow muscle fibers

Contraindications for TEENLIFTING are: Pacemaker, Epilepsy and Pregnancy.

Dr. Sanja Malbaša Gošović

- M.D. Sanja Malbaša Gošović, general practitioner, specialist. acupunturologist and cosmetologist
- 27 years of experience with TEENLIFTING
- has developed method under protected brand TEENLIFTING®

On the world market this is unique **natural method of stimulation of all muscles of the body and face** at the same time, or the stimulation of large muscle groups. Electrodes for TEENLIFTING are the newly formed electrodes, combined with standard electrodes put in non-standard method, to achieve better and more efficient results.

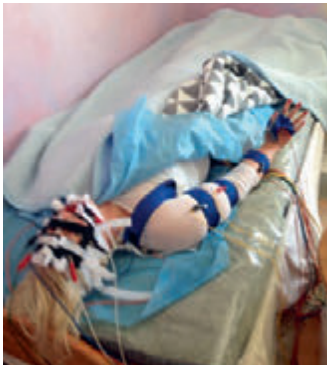
Experience from phisical therapy high school

- advice from experienced physiotherapist for treating Bell's Palsy: electrostimulation can cause myalgia and neuralgia, bite from current caused by small electrodes i.e. small area of stimulation zone
- own experience of electrostimulation for more than 35 years

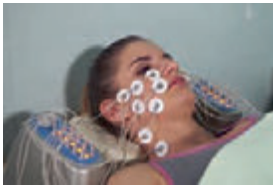
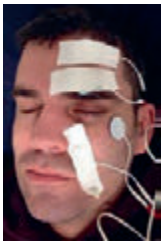
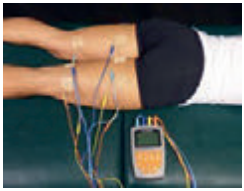
New shapes (forms) of electrodes that dr. Sanja Malbasa Gosovic has invented:

- circular electrodes used for stimulation of face circular, cervical vertebrae, gluteal zone
- band electrodes which are applied like whole scope e.g. lower leg, the shoulder gridle

TEENLIFTING® electrostimulation



Classical electrostimulation

- TEENLIFTING face stimulation (forehead, circular muscles, cheeks) is performed with two pairs of electrodes. Synchronized contraction of all muscle is achieved. It feels like one movement of entire face and you do not feel biting from current on any part.
- Goal of TEENLIFTING STIMULATION is strengthening all muscles (on any part that is treated) : agonist, antagonist and synergist muscles.
- When classical stimulation is preformed, face stimulation, it is done with numerous pairs of small electrodes. You feel “biting” on every area that this small electrode is applied on. Stimulated are is much smaller which means less intensity, smaller number of stimulated muscular and nervous fiber, greater discomfort during the stimulation and less effectiveness in rehabilitation.

Applying TEENLIFTING electrodes we achive numerous benefits:

1. With extension of stimulated zone, affection of motor end-plate increases, and we achieve higher amplitudes of motor response at lower stimulation level/point.
2. By extending stimulated area, we reduce importance of applying electrodes accurately and it becomes possible to simultaneously stimulate multiple outlying nerve branches.
3. By activating (nearby) cutaneous nociceptors, spinal inhibition of pain initiates/activates threw so called “gate control” located in the dorsal horn laminae of spinal cord.
4. By increasing electric stimulation to the point that doesn’t cause pain (yet), we enable/ensure to use stimulation at higher point, which increases/multiplies the number of stimulated nerves and muscle fibers, strength of stimulated muscle contraction and after all, the effectiveness of rehabilitation (process).

TEENLIFTING®

Body parts that are treated:

- face
- neck, shoulder, scapulas, armpits, upper arm, hands
- waist, hips, belly, breech, pelvis, thighs, knees, ankle joint, feet

TEENLIFTING® Rehabilitation of:

- all painful conditions of joints in locomotor system (cervical spine, shoulders, hands, scapulas, lumbar spine, hips, pelvic, knees, ankle joints, feet)
- cerebral paralysis, muscle atrophies, ALS, other paresis and plegias (with stimulating both face and neck
- **weak** peripheral circulation due to damaged venous, arterial and lymphatic blood vessels
- **osteoporosis** as a consequence after poor physical activity
- bladder incontinence and frequent urination, prolapsed uterus, impotence

TEENLIFTING® body electrostimulation for:

- Forming, shaming and firming body for:
  - extremely thin person
  - obese and extremely obese people
  - maintaining the ideal of weight
- Elimination of water and edema (swelling) of the body, lymphatic drainage of chest, armpit, abdomen, legs and joints
- Increasing blood circulation and oxygenation of tissues
- Detoxification of the body
- increased breathing capacity

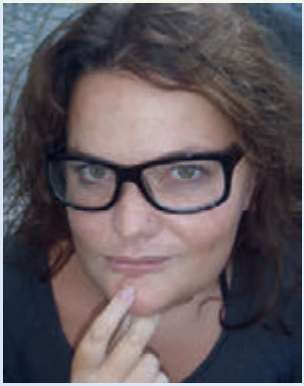
What and which types of exercise and contractions occur during body stimulation TEENLIFTING and bring it to the top of the effectiveness of exercise in the world?

According to performance there are: passive, active assisted, active independent and active exercises with resistance or load.

- Exercises to maintain maximum range of motion in all joints
- Exercises for static stretching
- Exercise for strengthening, endurance, speed and coordination:
  -Isometric – isometric contraction
  -Isotonic – concentric and eccentric contraction
  -Isokinetic
- Contraction of fast and slow muscle fibers

Impact of TEENLIFTING on the restoration of bone mass

- The composition and metabolic balance of the bone depends on the activity of the muscles, the point of maximum pressure and tendon insertions to bone.
- **Muscle activity slows down the process of osteoporosis** by constant stimulation of bone on its creation (of which the bone regeneration physiologically dependent), but it is also crucial at a young age.
- At the younger age when muscular activity increases “underlying principal amount of bones”, which are waiting for processes of osteoporosis and osteopenia. As the “principal” is greater, the “rest” of the bones is larger. Progressive bone loss begins at age older than 30 years of age, so that bone mass in this age is of decisive importance for the bone mass in old age.
- Intensive postmenopausal osteoporosis occurs at women 15 to 20 years after menopause.
- For this reason TEENLIFTING becomes one of the **key treatments for osteoporosis prevention** and rehabilitation of bones of the jaw and face.



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Tea Černigoj Pušnjak is a human resources manager. In 2011, she graduated from the »Faculty of Social Science« at the University of Ljubljana. From 2011 she works as a development coordinator at the Muscular Dystrophy Association of Slovenia. As a head of special social programs enables people with NMD actively participate in their daily life. In 2015 she also became a secretary general at the Rare Diseases Association of Slovenia. Within organization she is improving the quality of life of individuals with rare diseases in the field of health, social care, education and human rights promotion.

Teenlifting: an example of rehabilitation - person with SMA

I was diagnosed with spinal muscle atrophy (type II) when I was 2 years old. As a child I was able to sit alone and to stand by my own just for a few seconds. Doctors have been beaten in my head that my condition is irreversible, progressive and that it will never be better.

Although there is no cure that completely cures this disease it does not mean that there is no other effective ways of treatment that would at least partially stop its progression. From my experience, the best combination of therapies that have so far proved to be good are any kind of physical exercise on land, water therapy, especially in the see and breathing exercises.

When I first meet M.D. Sanja Malbaša Gošović, 3 years ago I was completely shocked by her directness, sincerity about my health, about my physical condition. She was trying to tell me that I don‘t do physical exercise enough and I am overweight. I admit I needed few months to process her suggestions and finally to visit TEENLIFTING® electro stimulation.

At that time only face TEENLIFTING® was available in Ljubljana. From functional and aesthetic point of view that part was the most disturbing for me, as it is the most exposed and visible. I remember that at the age of 22, when I started moving my lower lip, I began to tighten it to the side, and suddenly I can barely move it. This was a great shock for me, but I didn't tell anyone about it. At the same time I began to get a double chin, my face dropped, and I got a few kilograms.

After the first treatment with TEENLIFTING I started to feel the changes. They were barely noticeable at first, but priceless for me. I could at least partially master my lower lip. This was the moment, when I finally understood what M.D. Sanja Malbaša Gošović wanted to tell me when we met. At that time, I got hope that despite of my illness and the fact that no traditionally medical treatments are available, there is really something that works.

I had regular therapy scheduled at least twice a month and the results were significant. People around me began to notice changes, but they couldn't tell exactly what a difference was. I started to talk much more articulated and easier. My lips have no longer been strained in one direction. Not to mention visual effect of the therapy on the face that has completely changed: the forehead became fuller, my eyebrows and upper eyelids got healthy rose colour, my lips became fuller, my face tightened, my double chin started to disappear gradually.

For the past few years, I have had severe sinus problems that have clogged at least once a year. Every time I was forced to take antibiotics because I couldn't cough. Since then, I have no more problems. A few times I felt that they were clogging so, I went to therapy and the effect was immediate, I spit out the mucus at the end of the treatment, and I could normally breathed through my nose again.

In addition, I started using upper body TEENLIFTING® for my shoulders and arms, specifically. My muscles slowly began to wake up, for the first time I felt them and even tens them. At first I went to the treatment twice a week and the feeling was really phenomenal. After every 30-minute of treatment, I felt tired, but the feeling disappeared the next day. I felt very light, even better than after swimming in the see.

At that time, I wondered how it would have been if I would do it daily all over the body. I admit that I became addicted to TEENLIFTING®. For the first time in my life, something really works and that was really unimaginable and priceless for me.

Last October I finally went to Zagreb on body TEENLIFTING®. Every day I was strengthening my muscles all over the body for 30 minutes. After the initial treatments, I had a very strong pain in the muscles which is, of course, perfectly understandable, since the muscles were reactivated after many years. I have to admit that it was hard, but I didn't give up. Since then, I've been practicing it regularly. I have electrodes on my hands and feet at least 5 times a week. The feeling is great, because it stimulates muscles and consequently completely bleeds my body, specially my legs. I do not have cold legs anymore, they are even not swollen.

With body TEENLIFTING® I also electro stimulate my back and diaphragm. I started to notice that I can breathe easier and deeper. My lung capacity has increased, which is comparable to my clinical status from 15 ago. I also cough a lot easier. Now I can overcome cold as fast as almost any other people. In the last two years, when I seriously started with TEENLIFTING®, I have not been absent from my work because of a simple cold or other lung infections, which has been regular case before.

I pay also special attention to the neck muscles which I train at least once a day. After about a month of regular therapy, I have noticed that my double chin completely disappeared and I could tense neck muscles gradually. Now I am able to easier master my head, which is noticeable especially in the car, where I previously thrown it on each turn, but now I can hold it to the some point.

With body TEENLIFTING®, I'ye also lost some weight. I have more solid body and shape. This is especially evident on the thighs, abdomen and face. I also became much more self-confident, due to visual and psychological effects. For me it is the most difficult to observe how, regardless of the effort, my muscles weaken over time.

Every day I get up one hour earlier, so my assistant installs electrodes. I admit that I would rather skip all this and sleep because the procedure is long and monotonous. I admit I would quit long time ago if the effects were not so beneficial to my body. So now, at the age of 31, my physical strength, mobility and flexibility are comparable to those when I was 18 years old. I have achieved all this in a year, and I believe that the situation will only improve.

TEENLIFTING: AN EXAMPLE OF REHABILITATION - PERSON WITH SMA

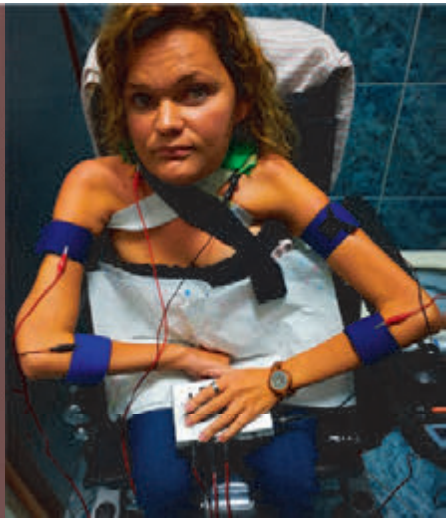
Tea Černigoj Pušnjak

My childhood...


Before using
TEENLIFTING®


Before and after...
2005
2010
2016

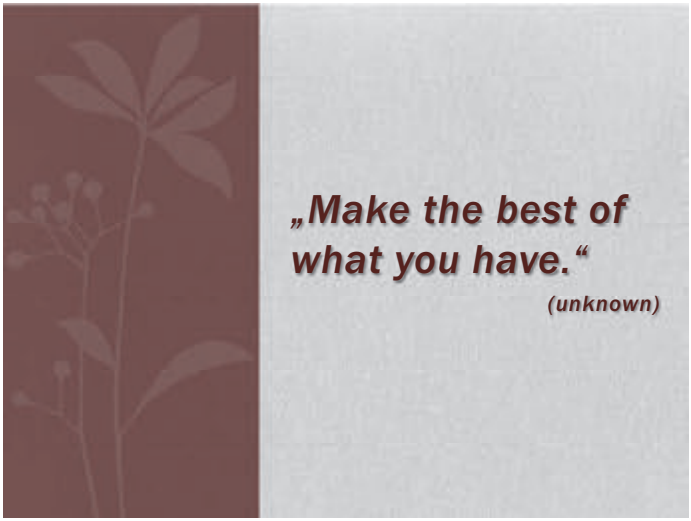
Upper body
TEENLIFTING®



No more
swollen legs...

BY EXERCISING, I NOTICE THE FOLLOWING POSITIVE EFFECTS:

- A feeling of flexibility, lightness in my arms and legs;
- Better lung capacity;
- Greater muscular strength;
- No more swollen legs;
- Higher self-confidence.



Jana Popova, *PhD student*

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Jana Popova is PhD student and freelance journalist. In 2014, she graduated from the Faculty of Journalism and Mass Communication at the University of Sofia - "St. Kliment Ohridski". In 2016, she got her master degree in "Book publishing" at the University of Sofia. Since 2011 she has been working as freelance journalist for different online media in Bulgaria. During 2011-2013 she worked as radio journalist in radio "Reaction", student's radio to Faculty of Journalism and Mass Communication. In 2016, she started her PhD program at Sofia University. She has interests in social policies, health system, education and different aspects of the daily life of people with neuromuscular disorders.

Article

Social aspects are very important part of the life. They are even more important, if you are a person with disability, because they can improve or aggravate the way you are living with your disability. It's very important to have an opportunity of living independent life and knowing that you can rely on an accessible environment, which is appropriate for your health condition. It always helps to know that your country has developed social policy in this area. Living with disability is quite challenging, but it's even harder when you don't get an adequate support from the social services in help of your decision to live an independent life and to develop your potential. In my article I will try to describe how disabled people in Bulgaria live and how they overcome some challenges and problems, related to different obstacles. The main purpose of my article is to show how people with restricted physical abilities in Bulgaria cope with the unfriendly environment and how they try to get better support for their needs, or with other words - what is it like to live with neuromuscular disorder in Bulgaria?

I will start my article with some numbers - the results from the last survey conducted by the National Social Security Institute. These numbers provide the exact information about the main problems of disabled people in Bulgaria and how social services are trying to improve their work. According to the survey's results published in March 2017, there are approximately 700 000 disabled people living in Bulgaria, which is about 10% of the Bulgarian population. This number includes people with different disabilities – some of them are caused by accidents, neuromuscular disorders, CNS disorders etc. In the research 55% of these people claim they often feel isolated and not fully supported by the institutions. Also the same percentage of people share that they are living restricted life. The lack of support from the social services forces these people and their families to search different ways of improvement and breaking the isolation. Following the results from this survey, the National Social Security Institute decided to publish a unified list with main requirements of disabled people in Bulgaria. This list includes 7 main problems evaluated as very important for disabled people. The problems are named as follows: bad condition of infrastructure and inaccessible environment, inaccessible public transport, gaps in the health system and lack of specialized hospital care for people with neuromuscular disorders, lack of accessible environment at public schools and universities, lack of job opportunities, absence of up-to-date register of patients with NMD and good training for personal assistants and extremely low value of social pensions.. In other words people are feeling alone with their disability, very often neglected and abandoned by social services. In this way they don't have an opportunity to live independent life and to accomplish their mental and physical potential. There is a reason behind each of these problems, but in the same time there are solutions to be taken into considerations. As a matter of fact in Bulgaria there is a good legislation about the rights of disabled people. Bulgarian laws do not neglect problems of disabled people, just in contrary – they are fully addressed and their rights are protected. The problem is lack of professional supervisory authorities in Bulgaria to observe if the law is implemented correctly. That's why we have good legislation fundament, but we don't have good results in the community and disabled people in Bulgaria feel that they are not supported and protected by the laws.

The inaccessible environment has been noted as the first problem for disabled people in Bulgaria. Bulgarian Law for Integration of Disabled People, Article 32 says: "The state of Republic of Bulgaria and its local authorities are obliged to organize and to build state institutions and departments, which are accessible for all groups of people, including disabled people". According to Article 33 of the

same law – “The Ministry of Regional Infrastructure Development has to create accessible infrastructure and architecture environment for all citizens, including people with disabilities”**.** Local administration in every Bulgarian city has a special budget be used for funding different projects aimed to improve the existing infrastructure. Unfortunately, the procedure in local municipalities for approval and implementation of these projects is extremely slow and basically these projects are never completed. Complicated system for approval and lack of fixed timelines for approval forces many local administrations to refuse participation in any projects related with an improvement of the current infrastructure. Speaking of which, there is a law for infrastructure development in Bulgaria. It is called Law of Territory Planning. Article 169, Chapter 2 of this law says: “All buildings constructions should be created and maintained in compliance with accessible environment for everybody, especially for people with disabilities”. Theoretically all buildings should be accessible for disabled people and the infrastructure environment should be friendly to their needs. Unfortunately, the reality is different. There are main streets, with sidewalks not appropriately designed and built up for disabled people, even in Sofia and other big cities in Bulgaria. The curbs are too high with very few or even no ramps at the street’s level, and quite often the surface is not flat due to damaged or missing tiles. If you want to move from the street on the sidewalk, you should rely on the help of your personal assistant. At the same time some Bulgarian drivers don’t respect parking rules and very often they park their cars on the sidewalks or even on special parking places marked with blue color and special sign, which are reserved only for disabled people. This situation is typical for the downtown of Sofia and other big cities in Bulgaria. One of the reasons for this is lack of strict control provided by the responsible services, which should observe this kind of law infringements. In addition to that, the number of parking places, reserved for disabled people in Sofia and other main cities in Bulgaria is relatively low. On the other hand, there are some areas of improvement in the last few years. For example, the building requirements of some new underpasses in Sofia and other big cities in Bulgaria have been aligned with the needs of disabled people and now they are fully accessible. Some underpasses located on central boulevards or in residential districts are equipped with modern elevators and ramps. Disabled people have full access to these facilities and they can use them alone, without the help of personal assistant. This is a good sign that the state takes actions to re-build and improve the infrastructure and to provide better access for people with special needs. Also in the last few years there is renovation to some public buildings in order to become more accessible. A lot of public buildings have been

designed with elevators and ramps in order to provide full access to wheelchairs. Unfortunately, there are still some buildings that are too old and they can't be modernized. But it is good to see that the state is making efforts to improve the surrounding environment and to make it friendly for NMD persons.

The next problem is access to public transportation. The access to old buses and street cars is very difficult and not possible without assistance or in some instances not possible at all. It's absolutely impossible to get on the old bus alone, if you have physical disability. That's why it is very good that in the last few years Bulgarian government has made a lot of remarkable efforts to provide new models of buses and streetcars in Sofia and other big cities in Bulgaria. In 2017 there are a lot of new buses in Sofia and other main cities, which are equipped with special ramps and internal space, especially designed for disabled people. Of course, the progress is good, but it will take longer to upgrade the entire system of ground transportation in Bulgaria. Fortunately, the Government announced a program to buy more new buses and streetcars for Sofia and for other main cities in Bulgaria till the end of 2020. This will improve the access to public transport for disabled people and they will become more active in their daily life. However, the situation with railway system is more complicated. Most of Bulgarian trains are very old, dirty and do not provide the required internal space and access. There are no ramps to get on the train and disabled person should climb some steep steps. There is special assistance service, available at some of the main Bulgarian railway stations, but it is not considered to be a good option though. The employees of these services put the person in the wheelchair on very old platform (the same used for transport of luggage) and it takes a lot of time and efforts to get on the train. The other problem is that when you finally get on the train, there is no special place in the cabins reserved for disabled people. Usually, the railway system is the cheapest way of travelling in Bulgaria, but it is definitely not the best option for transport for people with NMD. Actually, one of the most accessible public transportation systems in Bulgaria is the underground train system (the subway), which exists only in Sofia. There are new elevators at almost all underground stations and there are special places for wheelchair users inside the trains. Special assistance service at some underground station is also available – the employees operate with removable platforms for disabled people, helping them to get on and off the train. These ramps are very stable, the full access to train system is granted and the users are safe. Of course, there are still a lot of things, connected to the Bulgarian public transportation, which should be improved, but it is good to mark the progress achieved for now and to share expectations for gradual improvement of our life.

Another problem for people with neuromuscular disorders in Bulgaria is the access to healthcare system. Since year of 2000 Bulgaria has introduced a healthcare system, based on general practitioners (GP) and hospital treatment. This was intended to modernize the existing healthcare system and to introduce some positive effects on the treatment of patients. For this purpose, a National Health Insurance Fund (NHIF) was established as institution, providing funds for all hospital-based treatments. In spite of all these attempts to improve the existing healthcare system, people with neuromuscular disorders feel that they don't receive adequate health care for their health condition. According to the research of the National Social Security Institute one of the main problems for patient with neuromuscular disorders in Bulgaria is the lack of access to good hospital care and rehabilitation procedures. It's true that the rehabilitation of patients with NMD isn't well covered. According to the policy of National Health Insurance Fund patients with neuromuscular disorders are granted with one hospital admission for rehabilitation procedures once per year. The duration of this admission is only 10 days and it is usually provided at specialized hospitals and rehab centers in Bulgaria. If people with neuromuscular disorders want to do rehabilitation more frequently, they have to pay for that. This is one of the reasons why many patients with NMD feel that they are repressed by the existing healthcare system and they don't receive adequate cares for their needs. This is very important issue that should be solved soon.

The next problem is access to education. According to the research of the National Social Security Institute, 45% of disabled people in Bulgaria have experienced difficulties with their education. The main reason for that is lack of accessible environment at school buildings in Bulgaria. 18% of young disabled people in Bulgaria (below the age of 18 years) don't have the opportunity to finish their primary education and they leave school prematurely. In comparison, the average percentage for nondisabled and disabled people, who cease school prematurely, for the whole EU is 22%. According to EU strategy this percentage should decrease to 10% till 2020. In other words Bulgaria is far behind the successful execution of this EU strategy. Disabled people in Bulgaria are on the bottom of the classification and they don't have appropriate conditions to receive their school education. Another reason for these bad results is the Bulgarian teaching system. Every teacher has its own special classroom at school, which is specialized for the subject and students are expected to enter this classroom before the lesson. Between the lessons students have very limited time to go from one classroom to another. Every classroom is specialized for different school subjects – for example, geography, history, biology, etc. It is very difficult

for disabled students to go from one classroom to another and they experienced some obstacles due to lack of accessible environment.

Luckily, there are several opportunities for alternative education according to the Bulgarian Law for School Education. The first option is to participate in self-education and the second one is to participate in individual education. These opportunities have some specifics, which should be taken into consideration. For example, if disabled students decide to continue their education as self-educated students, they can continue studying at home and prepare themselves for different exams at school. At the end of every school term they should go to the school and pass exams on different school subjects. The individual education is quite different. Here disabled students have been visited at their homes by their teachers for private lessons. There are still some problems if you want to follow individual education. The first obstacle is that if the disabled student doesn't live close to the school, teachers would refuse to participate in teaching visits. The second problem is that according to the Bulgarian Law for School Education disabled students have the right to have only 12 hours per week for education with their teachers. These 12 hours includes work on different school subjects such as English, Bulgarian, biology, history, etc. Usually, this isn't enough to receive basic knowledge. That's why a lot of parents of disabled children try to pay to other tutors for private lessons in order to provide better education for their children. Unfortunately, many families can't afford that and they are obliged to rely on these 12 hours per week. In this situation there is discrimination against children with disabilities, because very often they don't receive equal opportunities for education with other children. At the same time the lack of accessible environment at schools forces disabled children to stay at home and stops their integration. Lack of accessible public environment continues to be one of the major issues for disabled people in Bulgaria and it's one of the main reasons why many people with disability refuse to apply for university education. The access to university education in Bulgaria is very difficult. The main reason for that is because most Bulgarian universities don't have accessible environment and they are located at very old buildings (quite often monuments of culture heritage), which can't be renovated. On the other hand, at the universities there are no special rooms equipped for particular subjects and lecturers can teach at every room. This provides better chances disabled people to be integrated in universities. Ironically, sometimes there is better integration for disabled people at universities than at schools, because there are many universities professors that have traveled a lot as guest lecturers. They have visited many European countries and they have seen how disabled people are part of the society. That's

why they try to adopt this good example in the Bulgarian university system of education.

According to the survey of the National Social Security Institute one of the biggest obstacles for disabled people in Bulgaria is to find a job. In the terms of legislation it looks like disabled people have equal opportunities to find a job as any other members of the society. Unfortunately, the reality is different. According to Article 22 from the Law for Integration of Disabled People in Bulgaria: "The state of Republic of Bulgaria and the Ministry of Labor and Social Policy are obliged to create and provide accessible and integrated working environment for disabled people". Article 23 from the same law says: "The Ministry of Labor and Social Policy and the State Employment Agency as official representative of the government create national programs to encourage the employers to hire disabled people and to provide equal opportunities for disabled people to participate on the labor market". According to the law there is no problem for disabled people to find a job and to participate on the labor market. Even more the state and the State Employment Agency will provide financial benefits for employers, who hired disabled people. The main purpose of all these clauses and articles is to provide better job opportunities for disabled people in Bulgaria, who are in active age. On theory everything looks OK, but the reality is different. In the research of the National Social Security Institute is declared that 55% of the disabled people in Bulgaria live in very bad social conditions. Barely 33% of them are working and have got permanent jobs. Almost 67% of the disabled people in Bulgaria are unemployed and they can't rely on finding permanent jobs in the near future. This leads to social isolation and impossibility to cover their basic needs. This is one of the reasons why disabled people are one of the poorest social groups in the country. On the other hand, almost 300 000 disabled people in Bulgaria are in active age and they have physical ability to work. Some of them are well educated and trained and could have successful careers in various professional areas. Unfortunately, very small percentage of these people are working and have permanent job they can rely on. What are the main reasons for this unfortunate situation?

There are many reasons why disabled people can't find permanent jobs in Bulgaria. I'm going to mark off three of them. The first one is that some companies are located in old buildings with no chance to modify current environment and to build up accessible solutions for disabled people. Even if these companies receive financial support from the social services and other related institutions, they still can't change the whole environment and can't provide enough facilities

for disabled workers. The main problem is that these buildings are too old and there is no chance to renovate them. At the same time nowadays even in some new office buildings the access to some areas in the office could be problematic for disabled people. For example, they can't use the toilets, elevators, kitchens etc. The second reason is that, although telecommuting policy (working from home) is adopted in Bulgarian Labor Code, it is still in development phase and should not be considered as a regular job opportunity. Regardless of the good level of communication services in Bulgaria (internet providers and telecoms covering worldwide standards), some employers are still not convinced that homebased employees are good decision for their business. At the same time there are many disabled people in Bulgaria, who are capable to work from home. This reserved attitude from many Bulgarian employers against homebased employees leads to limited job opportunities for people with disabilities. The third reason is connected with some stereotypes that are spread in the Bulgarian society. Many employers believe that disabled people have limited physical capacity and therefore would not be able to cover their professional standards, even as part time employees. They are concerned that disabled employees will be on sick leave very often and therefore would not be able to participate in long term projects. These affirmations aren't correct and institutions should take measures against these wrong stereotypes.

The next challenge for disabled people in Bulgaria is the absence of good program for personal assistance. The institution of social assistance is relatively new in Bulgaria – it was established more than 15 years ago. At the same time social assistance is already regulated in the Bulgarian legislation system. For example, according to Article 9 from the Law of Social Assistance: "The state of Republic of Bulgaria and the Social Assistance Agency are obliged to provide the help of personal assistants to people, who have more than 90% of disability.". According to the law the government and Social Assistance Agency are obliged to recruit candidates for the position of social assistant and to offer their services to disabled people. It is said in the law that the state will cover the expenses, related to this service and will grant a payment for social assistants. Unfortunately, the service of social assistance in Bulgaria needs improvements. The first problem is the fact that there is no professional register, where people who would like to do this job can apply. The government refuses to create and maintain such register and disabled people can't receive information from the social services about personal assistants. In other words, disabled people in Bulgaria should search different ways for finding personal assistant. They should search an appropriate candidate for this job on their own, because there is no

reliable source of this information. The second issue is that social services don't provide training to social assistants and such training should be provided by disabled people themselves. In addition to these problems, very often disabled people have to pay for personal assistance from their own pocket, because the salary for personal assistance in Bulgaria is very low. The underpayment and lack of motivation are the main reasons why a lot of people refuse to work as social assistants. Many families can't afford to pay extra money for personal assistance and one of the family members, mother or father (usually, the mother) stays at home to look after the disabled child. This situation continues even when the disabled child becomes disabled adult. Even when they are grown up, disabled people in Bulgaria don't have opportunity to pay for personal assistance and they should rely on their families. Lack of good service for personal assistance impedes life with disability.

Another obstacle for disabled people in Bulgaria is the extent of social pensions. According to Article 41, Addendum A from the Law for Integration of Disabled People: "Disabled people, who have more than 90% of disability, have the right to require financial support in the form of social pension from the state and its institutions according to their individual needs and health condition. The state, on the other side, is obliged to provide this financial support". It's true that disabled people in Bulgaria receive social pension, but the amount of this pension is extremely small. Usually, the social pension in Bulgaria for people, who have 100% disability in local currency is 120 leva, which is approximately 61 Euro. If you have less than 100% disability, your pension will be lower. The evaluation of the percentage of disability in Bulgaria is an expert opinion provided by special commission composed by different doctors and medical experts. This panel of experts is called Work Capability Assessment Commission and they are in charge of taking decision what is the percentage of patient's disability and based on this decision the amount of social pension is calculated. Even when disabled people have been assessed with 100% disability, their social pension remains very low and it is absolutely impossible to keep good standard of living. Low social pension turns out to be the main reason why many disabled people in Bulgaria live on the verge of poverty. According to the survey of the National Social Security Institute 55% of the disabled people in Bulgaria are not capable to cover their main needs. Their social pension isn't enough to pay their bills, medicines and to have good standard of living. In addition, they can't afford to pay extra money for personal assistance. The solution for disabled people is to work or to find another source of income.

In the spring of 2017 there was a big discussion in the Bulgarian National Assembly about the social pensions of disabled people. Some political parties wanted to change the law and to decrease the percentage of people who receive social pensions. This political proposal provoked very furious debate and it is still a topic of controversial statements. Many people share the opinion that this is discrimination against disabled people in the country. Even when they receive social pensions, disabled people in Bulgaria rely on the financial support of their families or they have to find permanent job. That's why it is impossible to decrease their social pensions, because this income is extremely small. This is one of the reasons why many people take actions against this injustice.

In the last few years the society of disabled people demonstrated that they will continue to participate in discussions with authorized institutions in order to improve the quality of life of disabled people in the country. The main purpose of these discussions is important improvements of social policy, feeling the gaps in the current legislation and granting disabled people with enough resources for normal life. The demonstrations and other related activities are just part of this negotiation process. In the last few years there are a couple of demonstrations of disabled people against some political decisions, which injure their social condition. The last demonstration of disabled people against some gaps in the current legislation took place on 17th of May 2017. This was the fifth demonstration, organized by disabled people themselves. The participants raise the slogan "National demonstration for adequate personal assistance of disabled children and people". There were a lot of disabled people and parents of disabled children who went in the streets and insisted on better social service and better opportunities for personal assistance. One of the main demands were to create Law for Personal Assistance, to develop internet register about disabled people and their diseases and to receive financial and medical help from the government, referred to single needs. During this demonstration parents brought black balloons with them as symbol of their righteous anger and despair. After the demonstration, the government promises to take measures and to focus on the needs of disabled people in the country. Some representatives of the government admitted that very often they neglect the needs of disabled people. At the same time the government and different social institutions promise to improve the standard of living of disabled people in the country.

In conclusion, I would like to underline that all these challenges and obstacles are important part from the life of disabled people in Bulgaria and I didn't describe them in order to search for sympathy. I was intended to comment the reality in

Bulgaria and to put together the real challenges that people with neuromuscular disorders are facing in my country. At the same time, I would like to say that I have been witnessing an improvement in the attitude towards disabled people in Bulgaria and I'm getting the feeling that finally the society realizes that disabled people are very important members of the community. Meanwhile disabled people also realize some things. They understand that they should fight for their rights and if they want to improve the situation in the country, they shouldn't be quiet and should raise their voices. Only in this way disabled people will get enough attention from the government and related institutions, which are responsible to take care of them. It isn't an easy task to fight against injustice. But disabled people in Bulgaria eventually have realized that we should stand together if we want to change our lives. Because the truth is that disabled people aren't actually disabled, they are just differently able and they deserve to live normal life in friendly and non-biased society.

The biggest challenges and obstacles for people with NMD in Bulgaria

Jana Popova

My house

My electrical wheelchair

Sofia University "St. Kliment Ohridski"

The Faculty of Journalism and Mass Communication

Friends from The Bulgarian Association for Neuromuscular Diseases

Living with NMD in Bulgaria – what is it like?

Current situation in Bulgaria:

- According to the National Social Security Institute there are approximately 700 000 disabled people in Bulgaria.
- 55% of these people claim they feel discriminated and not supported by the institutions.
- 55% of these people share they are living restricted life.

Link to the research:

http://www.cil.bg/%D0%9D%D0%BE%D0%B2%D0%B8%D0%BD%D0%B8/201.html

Main obstacles for disabled people in Bulgaria:

- Inaccessible environment + inaccessible public transport.
- Gaps in the health system and lack of profiled hospital care for people with NMD.
- Lack of accessible environment at public schools and universities.
- Lack of job opportunities.
- Absence of up to date register for personal assistants.
- Low social pensions for disabled people.

Inaccessible environment

- According to the Law for Integration of Disabled People, article 32: "The state of Republic of Bulgaria and its local authorities are obliged to organize and to build state institutions and departments, which are accessible for all groups of people, including disabled people".
  Link: https://www.lex.bg/laws/ldoc/2135491478
- Article 33 from the same Law: "The Ministry of Regional Infrastructure Development has to create accessible infrastructure and architecture environment for all citizens, including people with disabilities".
  Link: https://www.lex.bg/laws/ldoc/2135491478
- According to the Law of Territory Planning, article 169, chapter 2: "All buildings constructions should be created and maintained in compliance with accessible environment for everybody, especially for people with disabilities".
  Link: https://www.lex.bg/laws/ldoc/2135163904

(In)accessible environment

Sidewalks in the downtown of Sofia

Access to public transport

Old bus

New streetcar

Access to public transport (cont-d)

Trains in Bulgaria

Underground train system in Sofia

Healthcare system for people with NMD

- According to the policy of National Health Insurance Fund patients with neuromuscular disorders are granted with one hospital admission for rehabilitation procedures once per year.
- If people with neuromuscular disorders want to do rehabilitation more frequently, they have to pay for that.

Link to National Health Insurance Fund:
http://www.en.nhif.bg/

Access to education in Bulgaria

- 45% of disabled people in Bulgaria have experienced difficulties with their education.
- 18% of young disabled people in Bulgaria (below the age of 18 years) don't have the opportunity to finish their primary education and they leave school prematurely (22% for EU as a whole).
- Until 2020 should be decreased below 10% (according to EU strategy). Disabled people in Bulgaria are on the bottom of this classification.

Link to the classification:
https://www.vesti.bg/bulgaria/obshtestvo/55-ot-horata-s-uvrezhdaniia-sa-na-praga-na-bednostta-5452371

Alternative education in Bulgaria

There are several opportunities for alternative education according to the Bulgarian Law for School Education:

- Self-education
- Individual education

Link:https://www.lex.bg/bg/laws/ldoc/2136902456

Access to universities

Most of Bulgarian universities don't have accessible environment , because they are located at very old buildings, which can't be renovated.

Job opportunities

- According to Article 22 from the Law for Integration of Disabled People: "The state of Republic of Bulgaria and the Ministry of Labor and Social Policy are obliged to create and provide accessible and integrated working environment for disabled people".
- According to Article 23 from the same law: "The Ministry of Labor and Social Policy and the State Employment Agency as official representative of the government create national programs to encourage the employers to hire disabled people and to provide equal opportunities for disabled people to participate on the labor market".

Link: https://www.lex.bg/laws/ldoc/2135491478

Lack of job opportunities

- 55% of the disabled people in Bulgaria live in very bad social conditions.
- 33% of the disabled people in Bulgaria are working and have got permanent jobs.
- 67% of the disabled people are unemployed.
- 300 000 disabled people in Bulgaria are in active age and they have physical ability to work.

Link to the research:
https://www.vesti.bg/bulgaria/obshtestvo/55-ot-horata-s-uvrezhdaniia-sa-na-praga-na-bednostta-5452371

What are the main reasons?

- Some companies are located in old buildings with no chance to modify current environment and to build up accessible solutions for disabled people.
- Telecommuting policy (working from home) is adopted in Bulgarian Labor Code, but it is still in development phase and should not be considered as a regular job opportunity.
- Many employers believe that disabled people have limited physical capacity and therefore would not be able to cover their professional standards.

Personal assistance

According to Article 9 from the Law for Social Assistance: "The state of Republic of Bulgaria and the Social Assistance Agency are obliged to provide the help of personal assistants to people, who have more than 90% of disability".

Link:https://www.lex.bg/laws/ldoc/2134405633

Problems with personal assistance:

- There is no professional register, where people who would like to do this job can apply.
- Disabled people should rely on their own families and acquaintances if they want to find a personal assistant.
- Very often disabled people have to pay for personal assistance from their own pocket.

Social pensions

- According to Article 41, Addendum A from the Law for Integration of Disabled People: "Disabled people, who have more than 90% of disability, have the right to require financial support in the form of social pension from the state and its institutions according to their individual needs and health condition".
- The social pension in Bulgaria for people, who have 100% disability in local currency is 120 leva, which is approximately 61 Euro.
- There is panel of experts, which is called Work Capability Assessment Commission and they are in charge of taking decision what is the percentage of patient's disability.

Link : https://www.lex.bg/laws/ldoc/2135491478

Social pensions

- 55% of disabled people in Bulgaria are not capable to cover their main needs.
- In the spring of 2017 there was a big discussion in the Bulgarian National Assembly about the social pensions of disabled people.

Link to the research: https://www.vesti.bg/bulgaria/obshtestvo/55-ot-horata-s-uvrezhdaniia-sa-na-praga-na-bednostta-5452371

Demonstrations of disabled people in Bulgaria

- The last demonstration of disabled people against some gaps in the current legislation took place on 17th of May 2017.
- This was the fifth demonstration, organized by disabled people themselves.
- The participants raise the slogan "National demonstration for adequate personal assistance of disabled children and people".
- The corrective actions are still expected by the Government.

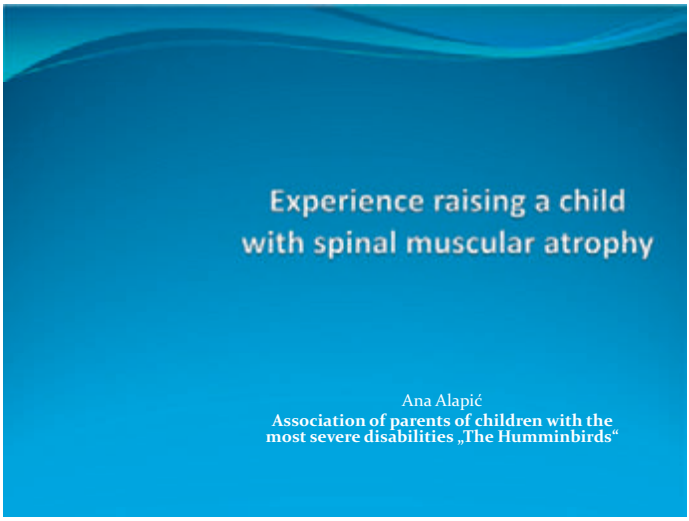
Link:https://nova.bg/news/view/2017/05/17/182494/%D1%85

Demonstration of disabled people on 17th of May 2017

Demonstration of disabled people

Thank you for your attention!

Questions


Experience raising a child
with spinal muscular atrophy
Ana Alapić
Association of parents of children with the
most severe disabilities „The Humminbirds“


Mate Bešlić
Spinal muscular atrophy type 1
8 years old
Breathes with the help of mechanical ventilation
Eats trough PEG tube
Cannot move or sit on his own
Communicates with the eye control, mimicry, eye flashing and unarticulated voices

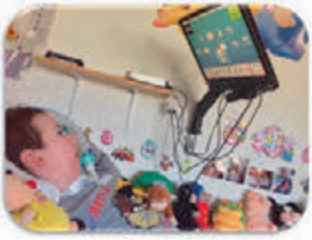
Preparation and evaluation for the school

Learning letters and numbers

The game „Name the fruit”

The game „Find a letter in a word”

Playing drums



Cuddling a dog

Playing a „Race car" game

Preschool "Galdovo"

Pastels painting with the help of a friends

Carnival in preschool

Preschool theater play for Easter

1. grade in school “Galdovo”

Home teaching

- With the help of Eyegaze
- The teacher prepares an individualized curriculum in Communicator 5 software
- 3 days a week

School teaching

- Monitors curriculum in school with other students
- 2 days a week full time
- Goes on school trips
- Participates in class activities

School teacher Kate Friš

Home teacher Martina Grđan

A circle in which they share their feelings

Walking and learning about the river Sava

Association of parents of children with the most severe disabilities „The Humminbirds" www.kolibrici.hr

Stella Franjic

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My life with SMA

I was born in 1995 as a healty child with no known previous cases of diagnose in family. When I was 1y/o having been expected to walk when I couldn‘t I was diagnosed with Spinal muscular atrophy type 2 (SMA II). Despite the diagnose I had very active, playfull and what would you call a „normal“ childhood. My parents enroled me in regular kindergrden and school. I finished primary and highschool and during that time went trough multiple surgerys neccesary for my condition. Operations I went trough put me in a life treathening states more than once and left consequences. Enroling in college and dealing with student obligations even only for a year was great expirience. As years went on the disease progresively took swing and left me with less and less ability to attend to. Being of impaired mobility and limited by the pain I‘m expiriencing I take what I can and make the most of it. I take a lot of time in the day having to rest and that‘s when I occupy myself with things I love that help me deal. I enjoy spending times with friends going out to concerts, theather, movies, restaurants, pubs. With selfless help and support from the people I‘m sorounded with I got trough the most hard times in my life. Having been asked the question how is my life with SMA my reply would be the best I can make it to be.