Meeting report

The MLD initiative face-to-face meeting 2023

Moving the MLD field forward: academic preparations for therapeutic access

Amsterdam

September 28 & 29, 2023

Minutes

In vivo gene therapy

Caroline Sevin presented the study results of the in vivo gene therapy and addresses the issues that arose from the trial. She concluded that results were disappointing in the human clinical setting. Possible explanations were discussed. After that, Marjo van der Knaap elaborated on the experiences with the AAV-based in vivo gene therapy in MPSIIIA/Sanfilippo A Disease. In this trial, unexpected intracerebral lesions at injection site appeared months after injection. It is hypothesized that the overexpression of a lysosomal enzyme causes damage to the brain. Concerns were also expressed regarding the probably very limited extension of the gene therapy throughout the brain since the lesions stayed localized.

Newborn screening

Stephan Kemp presented the development of the newborn screening program for X-ALD in the Netherlands. Challenges were discussed regarding the cut-of values used and the interpretation of the so-called ‘grey zone’ describing cases with borderline levels of very long-chain fatty acids. Also the rationale behind and approach used for the sex-specific screening, i.e. only boys are screened,

was discussed. Marc Engelen elaborated on the clinical management and monitoring of newborn screening identified ALD patients. The monitoring is based on the natural history as it is understood now and includes regular brain MRI scans, neuro exam, and cortisol and ACTH levels in blood. Marc emphasized that the screening population inherently differs from the ALD population with clinical manifest disease. NBS will therefore likely provide insights that might lead to a broader disease spectrum.

Lucia Laugwitz and Daphne Schoenmakers presented the current situation regarding newborn screening MLD. With the authorized gene therapy, introduction of newborn screening in mLD has gained urgency. Currently pilots are going on in different countries. Biochemical detection of MLD patients in dried blood spots is possible and is based on measuring sulfatide levels, ARSA enzyme activity and genotyping. There are a lot of uncertainties on how to deal with newborn screening identified MLD patients, in terms of choice of treatment, timing of treatment and monitoring. Within the MLDi we started a real-time Delphi procedure to reach consensus on expert recommendations regarding the clinical management of newborn screening identified MLD patients. Using Mentimeter several topics of the Delphi procedure were discussed.

- **ACTION:** Describe identified cases, especially those with uncertain disease, as 'individuals with a certain biochemical characteristic at risk for developing symptoms.'
- **ACTION:** Change wording into 'symptom onset' instead of 'disease onset'
- **ACTION:** it was discussed that it is important that treatment is done before evident abnormalities on brain MRI.
- **ACTION:** Suggestions for the Delphi in MLD: skew the cut-off 80% predicted LJ and 20% EJ; change manage into 'treat'; make sure that combination of multiple parameters are considered in monitoring before treatment decision; decrease/increase/deteriorating etc. to monitoring for treatment decision
- **ACTION:** registration of all identified MLD cases and archiving biomaterial to generate evidence was considered crucial.

Long-term outcomes of ex vivo gene therapy

Francesca Fumagalli showed the newest follow-up results of the patients treated with ex vivo gene therapy. In short, long term outcomes so far >12 years follow-up are positive.

Access to innovative orphan medicines

Carla Hollak gave a presentation on the challenges in timely access to new medicines for orphan diseases. She stressed the importance of new ways of drug development and access programs to ensure that effective treatments are available for socially acceptable prices. It was discussed that a pro-active role for academia is needed. Besides being involved in clinical care, research and drug discovery, academia should be involved in the complete drug development pathway including access.

Reality of care in underrepresented countries

Kaiia Liiv presented the clinical care for an MLD patient in Estonia based on a case presentation. She shared experiences regarding the consultation of MLD experts and indicated that fast and easy contact has been really helpful.

Galina Stevanovic gave a presentation about the organization of care for MLD in Serbia. She emphasized that it is difficult to get access to basic aspects of care for pediatric neurology patients, which is illustrated by the fact that MRI scans and genetic testing has only become accessible

recently and supportive care is very difficult to arrange. Treatment with allogeneic stem cell transplantation is also not available for MLD patients.

- **ACTION:** It was discussed that there is a need for a central contact point to easily consult MLD expert for clinical care related questions, not only regarding treatment eligibility but also supportive care. Make proposal for central contact point on MLDi website.

Intrathecal baclofen pump

Maria Forsgren talked about her experiences with administering intrathecal baclofen treatment in Lund. This treatment is considered to be an effective treatment option to manage spasticity in MLD patients. It is however not widely applied in MLD patients in other countries. Differences in clinical practice between the Netherlands and Sweden were discussed, for example: in contrast to the Netherlands, late infantile patients are also eligible for ITB, no problems with the size of the pump in such small children have been experienced. Also, in the Netherlands the test intrathecal injection of baclofen is nowadays skipped because ITB was always effective in MLD patients.

- **ACTION:** Intrathecal baclofen treatment is considered a well-tolerated and effective method to treat severe spasticity in MLD patients of all ages.

Mild genotypes

Shanice Beerepoot presented an overview of phenotypes associated with variants c.256C>T, c.257G>A and c.542T>G. She described that some patients have long-term sparing of the central motor tracts on MRI and preserved motor function years after symptom onset. She emphasized the importance of characterization of clinical phenotypes associated with genotypes in measuring outcomes of treatment and also counseling in for example the newborn screening setting.

MRI in MLD

Samuel Gröschel talked about different MRI modalities in MLD. He discussed typical abnormalities on MRI and elaborated on the use of MRI and MRS as biomarker. He emphasized that cross-machine comparison (i.e. different scanners in different hospitals) is possible when assessing large effect sizes, like we anticipate in MLD. It was discussed that we should share data/MRIs with each other to enable research in larger cohorts.

- **ACTION:** Make a core MRI scan protocol for MLD patients that can be applied across hospitals. This will benefit the comparability across centers and foster research.

Treatment eligibility panel

Together with the ERN-RND the MLD initiative arranges panel discussions on treatment eligibility for individual MLD cases. Between 11-2020 and 08-2023 around 18 cases were discussed, of which 14 in the official MLDi-ERN-RND/CPMS panel. The panel recommendations for the cases were that treatment with HSCT or GT is not recommended (n=9), treatment with HSCT is recommended (n=3), treatment with GT is recommended (n=3), another advice was given (n=1), or no consensus could be reached (n=2). It was agreed on that we need to continuously learn from the discussed cases to evaluate the outcomes of treating/not treating and whether this was in line with the panel's recommendation and prediction.

- **ACTION:** Procedure of discussing patients using CPMS is complicated for referring physicians. It should be evaluated whether this process can be simplified.

- **ACTION:** all patients discussed in the panel should be monitored and registered in the MLDi registry, to evaluate the outcomes and the panel. An update on the cases should be provided at 6 months, 12 months and then yearly.

Definite program

Thursday September 28, 2023

Chair Nicole

11:00 – 11:30: Walk in, opening and coffee

11:30 – 12:00: Lessons learned from the in vivo gene therapy in MLD – Dr. Caroline Sevin

12:00 – 12:30: Experiences from in vivo gene therapy in Sanfilippo disease – Prof. dr. Marjo van der Knaap

12:30 – 13:15: Lunch break

Chair Mirjam

13:15 – 14:00: What can we learn from newborn screening in X-ALD? – Dr. Stephan Kemp

14:00 – 14:30: Monitoring of NBS-identified X-ALD patients – Dr. Marc Engelen

14:30 – 15-30: Consensus procedure on NBS in MLD – Lucia, Daphne, Nicole, and Samuel

15:30 – 16:00: Break + PHOTO OF THE GROUP

16:00 – 17:00: Long-term outcomes of Libmeldy – Dr. Francesca Fumagalli

Chair Nicole

17:00 – 17:30: Closure

17:30 – 18:30: Travel time

18:30: Dinner at Neni - Stadionplein 8, Amsterdam

Friday September 29, 2023

Chair Daphne

09:00 – 09:45: Innovative orphan medicines: how to improve access? - Prof. dr. Carla Hollak

09:45 – 10:45: Reality of care for MLD patients in underrepresented countries – multiple speakers: Kaia Liiv - Estonia & Dr. Galina Stevanovic – Serbia

10:45 – 11:00: Break

Chair Caroline Sevin

11:00 – 11:30: Intrathecal baclofen – Dr. Maria Forsgren & Dr. Erik Eklund

11:30 – 12:00: Mild genotypes leading to a cognitive presentation with motor sparing – Shanice Beerepoot

12:00 – 12:45: MRI in MLD – prof. dr. Samuel Groeschel

12:45 – 13:15: Lunch break

Chair Samuel

13:15 – 14:30: Evaluation of previously discussed treatment eligibility panel cases – Daphne Schoenmakers

14:30 – 15:00: Closure

Venue

Amsterdam UMC – location AMC

Emma Children's Hospital - Emma Theater – G8-143

Meibergdreef 9

1105 AZ Amsterdam

Accomodation

Hotel Casa Amsterdam

Eerste Ringdijkstraat 4

1097 BC Amsterdam

https://hotelcasa.nl/nl/

Attendees

Andreas Oberg (Norway), Annette Bley (Germany), Ayelet Zerem (Israel), Carla Hollak (Netherlands), Caroline Lindemans(the Netherlands), Caroline Sevin (France), Cecilie Videbaek (online, Denmark), Daphne Schoenmakers (the Netherlands), Dipak Ram (United Kingdom), Elise Saunier-Vivar (France), Enrico Bertini (online), Erik Eklund (Sweden), Eugenie Dekkers (RIVM), Fanny Mochel (online, France), Francesca Fumagalli (Italy), Galina Stevanovic (Serbia), Haniye Mehrabi (VWS), Hanka Dekker (the Netherlands), Janna Bredow (Germany), Kaia Liiv (Estonia), Lucia Laugwitz (online, Germany), Marc Engelen (Netherlands), Mareen Datema (Netherlands), Maria Forsgren (online, Sweden), Marjo van der Knaap (the Netherlands), Mirjam Langeveld (the Netherlands), Nicole Wolf (the Netherlands), Rose Maase (RIVM), Sabine Grønborg (Denmark), Samuel Gröschel (Germany), Shanice Beerepoot (the Netherlands), Sibren van den Berg (the Netherlands), Stella Reichmannová, Stephan Kemp (the Netherlands), Stefano Bruni (Orchard, only present during talk Francesca), Tom de Koning (online, Sweden), Valeria Calbi (online, Italy)

Organizing committee

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