Supplementary material to

Parent perspectives on complex needs in patients with MCT8 deficiency: an international, prospective, registry study

Ferdy S. van Geest, Stefan Groeneweg , Veronica M. Popa, Milou A.M. Stals, W. Edward Visser

Supplementary material

Registration in the International MCT8 Deficiency Registry

Upon registration, parents/caregivers (from here on: collectively termed parents) were asked to provide informed consent via a digital informed consent form (see section 'Informed consent form'). After providing full informed consent, the questionnaire for parents was made available to the parents (see section 'Questionnaire for parents'). Moreover, the parents received a unique token to provide to their caregiving physician. With this token, the caregiving physician was able to register in the system and received access to the questionnaire for physicians (see section 'Questionnaire for physicians') upon registration. Without this token, physicians were not able to enter the registry and to provide data, thereby preventing physicians from sharing data from their patient(s) without full informed consent from the parents. In case the parents did not provide full informed consent, no questionnaires were sent out and no data was collected. In case parents retracted full informed consent, data on the patient was deleted from the registry. With no formal patient organization existing when the registry was designed, we consulted several members of the parent community on the design of the questionnaires for parents and physicians prior to implementation in the registry, with the goal to capture relevant data as efficient as possible. The questionnaires for parents and physicians could be sent out periodically, to ensure data was updated. The informed consent form, questionnaire for parents and questionnaire for physicians were available in the English, Dutch and Italian languages.

Technical details of the International MCT8 Deficiency Registry

Questionnaires were developed in LimeSurvey (LimeSurvey GmbH, Hamburg, Germany). Audit tracking software monitored access patterns, machine locations and user IDs in the registry. This information enabled accurate tracking and identifying any illegal usage. The registry stored some user information so that it could act as a register of users, and logged the user's IP address (automatically recognised by the web server). The website and server logs were hosted by the IT Services at the Erasmus Medical Center using private, TLS-encrypted web browser sessions, and the IP information

was accessed through tools provided by Google Analytics. Cookies were not used for collecting user information from the site and did not collect any information about users except that required for conducting research using data gathered in the registry, enforcing privacy rules of the registry, or for system administration of the registry.

Access to all information in the registry was tightly controlled with passwords and logins set at multiple levels. User passwords were acquired and stored encrypted using a one-way hash function, ensuring that passwords could not be extracted from the password database. Access to the registry was limited to named people who have specific job responsibilities related to the registry. The registry was housed within the Erasmus Medical Center IT services and all project staff within the organization undertook training in the protection of data confidentiality.

Data handling, cleaning and validation

Data of patients of whom parents provided full informed consent and at least one answer to the questionnaire for parents was exported from the International MCT8 Deficiency Registry. Obvious erroneous data (e.g. age at diagnosis older than current age) was verified with parents or physicians and corrected if needed, prior to analyses. In case answers were provided in another language than English, answers were translated to English prior to categorization (using online available translation tools). Explicit consent of parents was asked and provided for all quotes. Patients with missing data were excluded from individual analyses to minimize confounding effect.

Sensitivity analyses

Analyses of median diagnostic delay were performed descriptively after stratification by continent of residence. Sensitivity analyses on diagnostic delay were performed after exclusion of patients born before the first report on MCT8 deficiency in October 2004 (1, 2).

Informed consent form

The informed consent form consisted of the following sections. Every item in the informed consent section requires choice of a preset answer ('yes' or 'no').

Patient identification

- First name patient
- Last name patient
- Date of birth patient

Informed consent

- I understand that my participation in the registry is voluntary and that I can change my mind and withdraw at any time.
- I understand and consent that the doctor will be asked to provide information from the patient's records.
- I understand that all attempts will be made to protect my privacy and my family's privacy. I understand that my personal information will be protected and saved in the registry using a code. However, there is a very small risk that my personal information could be revealed.
- I understand that by agreeing to participate, I will be contacted by the registry to update or correct my health information regularly.
- I understand that I will be contacted by e-mail.
- I am willing to provide my de-identified medical information to be used for clinical trials and other medical studies related to my disease.
- I understand that my de-identified information can be used for any approved research study including diseases that are not associated with my disease.
- I understand that my de-identified information may be shared with other databases such as the Global Rare Disease Patient Registry and Data Repository (GRDR).
- I understand that I may not personally benefit from participating in the registry or from the use of my de-identified medical information in any research study.
- I understand that I can withdraw from the registry at any time and remove my information. I also understand that any information given previously and already have been assigned to a specific study, cannot be removed.
- If permitted, I would like to know of any findings or results that may affect my child`s or family member`s health.
- I would like to be contacted of any future clinical trials or other studies that I can participate in.

Questionnaire for parents

The questionnaire for parents consisted of the following sections. The questionnaire includes closed questions (preset answer options: *yes*, *no*, or *no answer*; other preset answer options are shown in *italic* below, where applicable) and open questions. For some questions, multiple present answers can be chosen (indicated with o below). Explanatory information is provided in the system to further clarify questions. Parents can remark on their answers for a subset of questions. The sections 'Medical history', 'Current medication', 'Progression of symptoms' and 'Progression of symptoms' include user-friendly tables to enable easy data entry.

General information

- Date of birth of your child?
- Age at which MCT8 deficiency was diagnosed? (years and months)
- Are any other family members also affected?
- Please specify who and the family relation to your child.
- Is mother a known carrier of the MCT8 mutation?
  Yes; No; Not tested
- What is the highest education level of father?
  No education; Primary school; Secondary school (middle / high school); Community college; University
- What is the highest education level of mother?
  No education; Primary school; Secondary school (middle / high school); Community college; University

Pregnancy and delivery

- Gestational age at time of delivery? (weeks and days)
- Have any prenatal screenings been performed?
- Please specify the prenatal tests and describe abnormal findings (if applicable).
- What was the birth weight (in grams)?
- What was the birth length (in centimeters)?

Growth and development

- At what age did you first realize that something was wrong with the development of your child?
- What was/were the first sign(s)/symptom(s)?
- How did these signs and symptoms progress during the first year of life?
- What difficulties did you encounter in the diagnostic trajectory?
- Development of motor milestones (current situation). Please provide age when milestone was first reached (in years).
  - Slipps not through
  - Maintains head balance in sitting position
  - Turns head around

    - Lifts head while lying on his belly
    - Reach/slap to toys or things
    - Grasp to / hold toys or things
    - Turns from back to belly
    - Turns from belly to back
    - Sits in tripod
    - Sits without support
    - Crawls
    - Stands with support
    - Stands without support
    - Walks with support
    - Walks without support
    - Jumps
    - Cycles
    - None of the above
- Development of fine motor milestones (current situation). Please provide age when milestone was first reached (in years).
    - Fixates with eyes on object
    - Grasps object
    - Grasps objects and puts in his mouth
    - Moving object from one hand to the other
    - Drinks with a cup
- Is there progression in the abovementioned motor skills?
- Did your child loose the ability to do things he was able to do before?
- Development of social/communication skills (current situation). Please provide age when milestone was first reached (in years).
    - Cry
    - Smile
    - Monotonic sounds
    - Combination of sounds
    - Babbling
    - First words
    - Combination of words
- Is there progression in the abovementioned communication skills?
- Did your child loose the ability to do things he was able to do before?
- How do you predominantly communicate with your child?
- Do you have the impression your child has any visual problems?
- Do you have the impression your child has any hearing problems?
- Do you have the impression your child is able to taste different flavours?
- Is your child able to let you know whether he likes or dislikes something?
- Does your child respond to pain (e.g. during blood sampling, biting on his hand/lips)?
- How was your child fed during the first 0-6 months of life?
    Breast fed; With a bottle; Other way of feeding
- Were any feeding problems present at that time?
- Please specify what kind of feeding problems were present?
- Does your child currently aspirate any food?
- If yes, what kind of food does your child currently aspirate?
    Liquid; Smooth/pureed; Pieces/chopped; Solid
- How frequently does your child aspirates food?
    Multiple times a day; Once a day; Less than twice a week
- Does your child has a PEG tube / gastrostomy or an intranasal feeding tube?
    No; Intranasal feeding tube; PEG tube / gastrostomy

- Does your child have gastric reflux?

Sleeping

- Does your child have difficulties to fall asleep (takes > 30 minutes)?
- Describe your child's sleeping pattern at night?
  Sleeps whole night; Wakes up 1 x; Wakes up 2-5x; Wakes up more than 5x
- Time of awakening during the night (between 10 pm and 7 am)?
  Before 4AM; After 4AM; Both
- Describe the behaviour when your child is awake during the night?
- Does your child sleep during daytime more than 3 days a week?

Thyroid Hormone

- Does your child easily sweat during minor exercise?
- Does your child easily loose weight during periods of infections or increased stress?
- Does your child have difficulties to (re)gain weight?
- Does your child easily get agitated?
- Does your child have frequent stools (>4 times a day)?

Medical History

- Please list the medical history of your child (e.g. severe illness requiring hospital admission, surgery, recurrent infections etc.)?
- Health care use: please indicate which doctors you regularly visit.

Current medication

- Please indicate the current medication of your child.

Supporting care and devices

- Please check the supporting care your child gets at the moment and further specify your experiences.
  - Physical therapy
  - Horse riding therapy
  - Speech therapy
  - Music therapy
  - Dietary advice
  - Swimming
  - Other
- Please check what kind of supporting devices your child uses at the moment and further specify what your experiences are.
  - Wheelchair
  - Standing frames
  - Walkers and gait trainers
  - Tricycle
  - Other devices used to promote mobilization
  - Splints
  - Brace/corset
  - Speech computer
  - Eye gazer
  - Other devices used to promote communication
  - Other

General questions

- What is the living situation of your child?
  At home; Other; In an institution; Combination of both
- List the top 3 major problems you encounter in the daily care for your child due to the disease of your child?
- Where do you look for information on AHDS or MCT8 deficiency?
  Ask our doctor; Information flyers or leaflets; On the website mct8.info; On the Facebook group for family members affected by MCT8 deficiency; Other internet websites; Patient organization for MCT8 deficiency; A combination of all; Other
- What is your opinion regarding the availability of information about AHDS or MCT8?
  Very bad; Bad; Sufficient; Good; Very good
- What can be improved about the availability of information about AHDS or MCT8?
- How do you rate the level of knowledge about AHDS or MCT8 among medical professionals?
  Very bad; Bad; Sufficient; Good; Very good
- What can be improved regarding the knowledge of AHDS or MCT8 among medical professionals?
- Do you currently receive the AHDS or MCT8 newsletter?
- If yes, please provide your opinion about the newsletter?
- If no: Do you want to receive the newsletter in the future?

Progression of symptoms

- Please indicate the progression of the listed symptoms during the different age periods (in years) on a scale from 0-4. (at ages 0-1, 1-2, 2-3, 3-4, 4-5, 5-6, 6-10, 11-15, 16-20, 21-30 and +30)
  - Increased muscle tone
  - Seizures
  - Swallowing difficulties
  - Low body weight
  - Sleeping problems

Progression of development

- Please note if your child has improved in the development of these listed skills during the different age periods (in years) on a scale from 1-3. (at ages 0-1, 1-2, 2-3, 3-4, 4-5, 5-6, 6-10, 11-15, 16-20, 21-30 and +30)
  - Communicative skills
  - Social skills
  - Motor skills

Questionnaire for physicians

The questionnaire for physicians consisted of the following sections. The questionnaire includes closed questions (preset answer options: *yes*, *no*, or *no answer*; other preset answer options are shown in *italic* below, where applicable) and open questions. For some questions, multiple present answers can be chosen (indicated with o below). Explanatory information is provided in the system to further clarify questions. Physicians can remark on their answers for a subset of questions. The section 'Evaluation over time' includes user-friendly tables to enable easy data entry.

General information

- Date of birth of your patient?
- At what age has MCT8 deficiency been diagnosed (years and months)?
- MCT8 mutation
    - At DNA level:
    - At protein level:
    - Reference sequence that has been used:
- Have skin fibroblasts been collected?
- Has any data on your patient ever been published?
- If yes, please provide any of the following identifyers .
    - PMID:
    - DOI:
    - Reference:
- Are any other family members of your patient affected by MCT8 deficiency or carrier of the MCT8 mutation?
- If yes, please specify who en what the relation to the child is.
- Upload a pedigree (if available).

Perinatal information

- APGAR score of the child after 1 minute?
- APGAR score of the child after 5 minutes?
- Birth weight of the child?
    - Grams:
    - Percentile:
    - SD-score:
- Birth height of the child?
    - Centimeters:
    - Percentile:
    - SD-score:
- Head circumference at birth of the child?
    - Centimeters:
    - Percentile:
    - SD-score:

Feeding

- Does the child aspirate any food or drinks?
- If yes, please specify?
    - Liquid
    - Thickened liquid
    - Smooth/pureed
    - Pieces/chopped
    - Solid
- Is a gastric tube present?
- If yes, please specify what kind of feeding tube is present?
    - PEG tube/ gastrostomy
    - Intranasal tube
    - Other
- Since what age is this feeding tube present? (years and months)
- Remarks

Current situation

- Dystonia?
    - Treatment:
- Spasticity?
    - Treatment:
- Seizures?
    - Treatment:
- Drooling?
    - Treatment:
- Constipation?
    - Treatment:
- Gastric reflux?
    - Treatment:
- Urinary incontinence?
- Sweating without or with minimal exercise?
- Hip luxation?
    - Treatment:
- Scoliosis?
    - Treatment:

Evaluation over time

- Overview of body weight (in kilograms) and height (in centimeters) over time (in years). Measured at one timepoint within the indicated time frame. (0-1, 1-2, 2-3, 3-4, 4-5, 5-6, 6-10, 11-15, 16-20, 21-30, 30+)
    - Exact age (in years and months)
    - Weight
    - Height
- Please indicate the absence (0) or presence (1) of the symptoms below at indicated ages. If not known or not applicable, the field can be left empty. (0-1, 1-2, 2-3, 3-4, 4-5, 5-6, 6-10, 11-15, 16-20, 21-30, 30+)
    - Dystonia
    - Spasticity
    - Seizures
    - Scoliosis

Physical examination

- Examination date
- Body weight?
- Body height?
- Head circumference?
- Describe dysmorphic features.
- Pulse rate (bpm)?
- Muscle volume (relative to patients of the same age with intellectual disability)?
  Less; Similar; More; No answer
- Pectus excavatum?
- Tanner stage?
  I; II; III; IV; V; No answer
- Most important way of interaction with you?
  - Sounds
  - Eye contact
  - Signs / physical contact
  - Speech computer
  - Speech
- Nystagmus?
- Please describe.
- Truncal hypotonia?
- Head drop?
- Patellar tendon reflex (left)?
  No response; Slight but definitively present; A brisk response; Very brisk response; Pathologically brisk with clonus; No answer
- Patellar tendon reflex (right)?
  No response; Slight but definitively present; A brisk response; Very brisk response; Pathologically brisk with clonus; No answer
- Plantar reflux according to Babinski (left)?
  Dorsiflexion (pathological); Plantar flexion; Indifferent; No answer
- Plantar reflex according to Babinski (right)?
  Dorsiflexion (pathological); Plantar flexion; Indifferent; No answer
- Contractures?
- Dystonia?
- Other dyskinetic movements (dyskinetic movement disorders)?
- Please specify.
- Tonic neck reflex?
  Present; Absent; Unknown; No answer
- Glabellar sign?
  Present; Absent; Unknown; No answer
- Muscle tone forelimp (MAS score)? (left and right)
- Indicate which motor milestone have been achieved by your patient.
  - Holds neck
  - Slipps not through hands when lifted
  - Lifts head in prone position
  - Turns head in prone position
  - Rolls over (back to belly)
  - Rolls over (belly to back)
  - Sits without support
  - Gets to sit without support
  - Stands without support

    - Stands without support
    - Creeps
    - Walks with support
    - Walks without support
    - Rides tricyle
    - Jumps with both feet of the floor
- Select fine motor milestones that have been achieved by your patient.
    - Fixates with eyes on object
    - Grasps objects
    - Grasps objects and puts in his mouth
    - Moving object from one hand to the other
    - Stacks bricks or other objects (max 3)
    - Drinks from a cup
    - Paints
- Select the communicative milestones that have been achieved by your patient.
    - Crying
    - Smiling
    - Monotonic sounds
    - Polytonic sounds
    - Babbling
    - Words
    - Word combinations (max. 3 words)
    - Sentences
- Are already achieved skills regressing over time?
- Please describe.
- Remarks and other findings?

Historical diagnostics and evaluations

- Has an MRI-cerebrum been performed in the past?

422 **Supplementary table 1**

Exemplary quotes from parents
Daily care challenges
Mobility: *"He is like a newborn baby in a larger body and could not hold his head."*
Sleeping: *"He wakes up screaming and cries very loud. He often arches his back and his body seems very stiff. While crying it sometimes seems like he holds his breath too long."*
Communication: "*He makes it clear with facial expressions whether he likes something or not, in addition, communication with icons works well. Also mumbling/making noise when he doesn't agree."*
Challenges in diagnostic trajectory
Specialist care: *"…Unfortunately, a referral to genetics was the last step on our path when it probably should have happened much earlier. We had a diagnosis within three weeks of seeing a geneticist, but it took us over a year to get to that point."*
Thyroid function test evaluation: *"They knew pretty fast what the diagnosis could be when they saw the testresult of the thyroid hormones."*
Improving the diagnostic process
Disease awareness: *"Spread information directly to neurology and endocrinology specialists at the major pediatric hospitals all over the world. Because it's known that as soon they diagnosticate the disease better are the chances for improvements in cognitive and motor skills."*
Screening: "*In [European country] doctors don't know the disease so we need to have prenatal screening and be able to talk about the disease to pediatricians to explain symptoms and to test children early."*

423 Exemplary quotes from parents.

Supplementary table 2

	Patients on Triac	Patient not on thyroid medication
Transpiration with little exercise (fraction)	5/18	4/10
Weight loss at infections/stress (fraction)	16/20	5/8
Difficulty to regain weight (fraction)	12/18	5/9
Easily agitated (fraction)	9/18	7/10
Frequent defecation (>4/day; fraction)	4/20	4/9
Difficulty falling asleep (>30 minutes; fraction)	7/18	5/8

Report of thyrotoxic symptoms of patients on treatment with thyroid hormone analogue Triac *versus* patients who were not on any thyroid medication. Data are not expressed as percentage given the low number of patients included in the analyses.

Supplementary table 3

	Patients with data on specialist care
Specialist (n=32)	
(Paediatric) neurologist	21 (66%)
General paediatrician	16 (50%)
(Paediatric) endocrinologist	14 (44%)
Ophthalmologist	9 (28%)
(Paediatric) gastroenterologist	6 (19%)
Orthopaedic surgeon	6 (19%)
General practitioner	5 (16%)
Neuropsychiatrist	3 (9%)
ENT specialist	2 (6%)
Dentist	2 (6%)
Geneticist	2 (6%)
(Paediatric) specialist in metabolic diseases	2 (6%)
Revalidation specialist	2 (6%)
(Paediatric) cardiologist	2 (6%)
Osteopath	2 (6%)
Nutrologist	2 (6%)
Specialist for patients with intellectual and motor disability	1 (3%)
Developmental paediatrician	1 (3%)
(Paediatric) surgeon	1 (3%)
Multidisciplinary team	3 (9%)

Data are n (%). Abbreviations: ENT, ear nose throat medicine.

Supplementary table 4

Specialist	Role & areas of attention	Frequency
(Paediatric) endocrinologist	- Follow-up of peripheral thyrotoxic signs - Follow-up of weight and growth - Initiation and follow-up of thyroid hormone analogue treatment - Follow-up and treatment of adverse events	- Every 2-4 weeks during treatment initiation - Bi-annually on stable or no treatment
(Paediatric) neurologist	- Follow-up of brain development - Follow-up of movement disorders - Follow-up and treatment of epilepsy (by EEG) - Follow-up and treatment of drooling	- Bi-annually
General paediatrician, general internist or general practitioner	- Coordination of complex needs	- Bi-annually
(Paediatric) cardiologist	- Monitoring of cardiovascular abnormalities (specifically: PACs, bundle branch blocks and extended QTc by 24h Holter; aortic root size by TTE) and blood pressure	- Annually
(Paediatric) gastroenterologist	- Follow-up and treatment of (treatment-resistant) gastro-esophageal reflux disease - Follow-up and treatment of (treatment-resistant) constipation - Installing feeding tube when appropriate	- Annually
Orthopaedic surgeon	- Follow-up and treatment of scoliosis (patients >5 years) - Follow-up and treatment of hip luxation	- On indication
Physical therapist	- Training of motor functions - Optimization of musculature status - Evaluation of gross motor functions (specifically: by GMFM-88)	- Physical training: bi-weekly - GMFM-88: annually
Neuropsychologist	- Evaluation of neuropsychological functions (specifically: by BSID-III and VABS-II)	- Annually
Speech therapist	- Optimization of swallowing functions	- Weekly (without feeding tube) - Four times per year (with feeding tube)
Dietician and/or nutrologist	- Optimization of nutritional intake	- Four times per year
Clinical chemist	- Interpretation of TFTs on thyroid hormone analogue therapy	- On indication

Proposed design of a multidisciplinary team for MCT8 deficiency, with suggested roles, areas of attention and frequency per expertise. Abbreviations: EEG, electroencephalogram; PAC, premature atrial complex; TTE, transthoracic echocardiogram; GMFM-88, Gross Motor Function Measure 88; BSID-III, Bailey Scale of Infant Development III; VABS-II, Vineland Adaptive Behavior Scale II; TFT, thyroid function test

Figure S1: Procedures of the International MCT8 Deficiency Registry

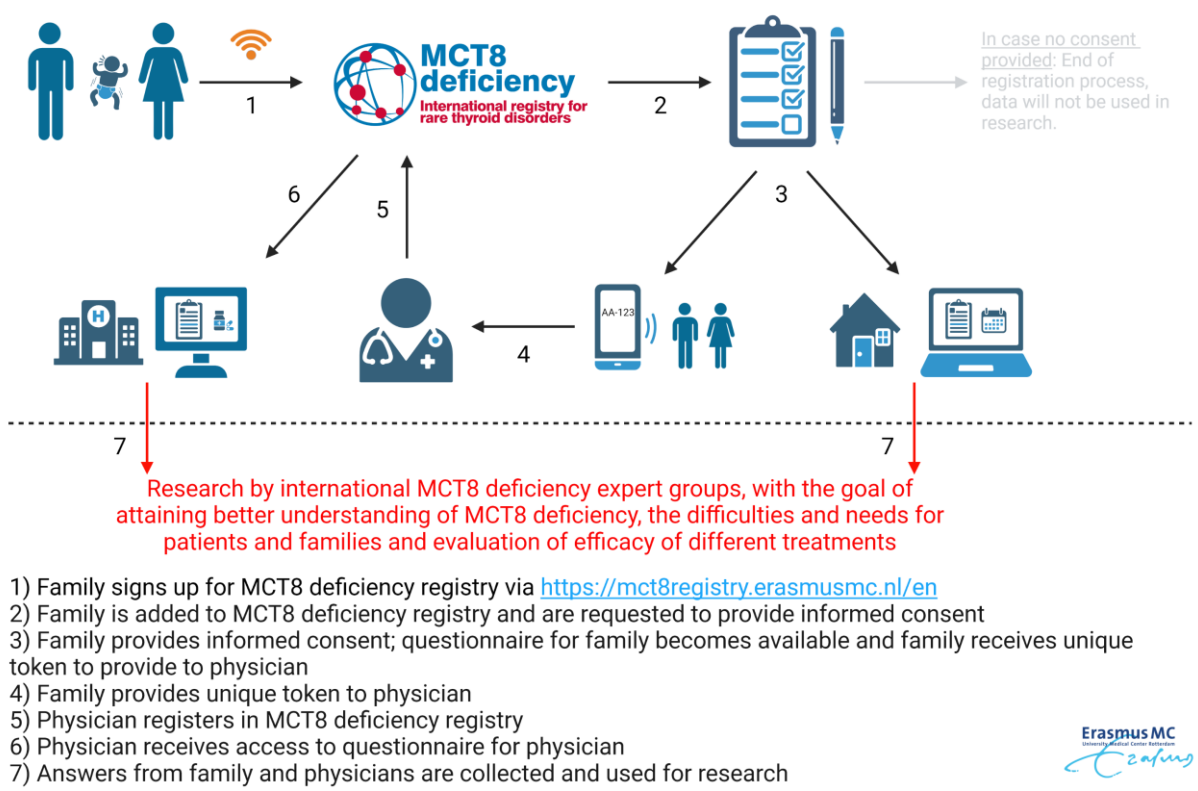
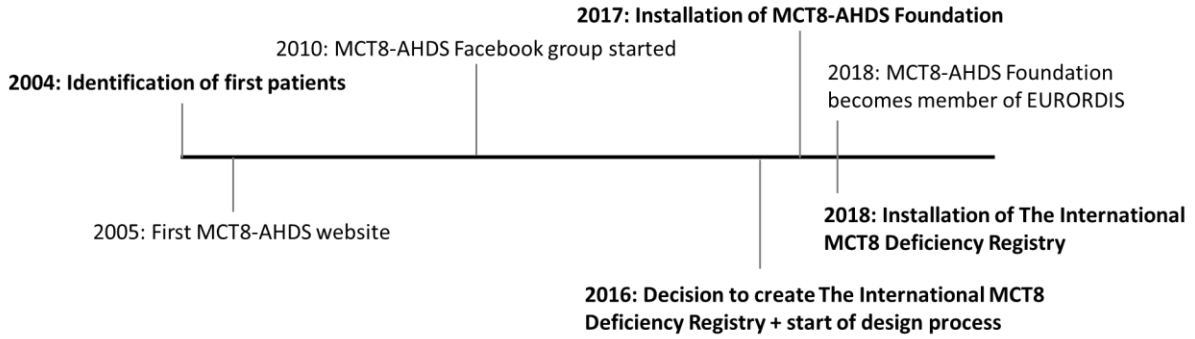


Figure S1: Overview of the different steps in the International MCT8 Deficiency Registry. The requirement of a unique token for caregiving physicians ensures no data can be shared without full informed consent. Figure created with BioRender.com.

440 **Figure S2: Timeline of the design and implementation of the International MCT8 Deficiency**

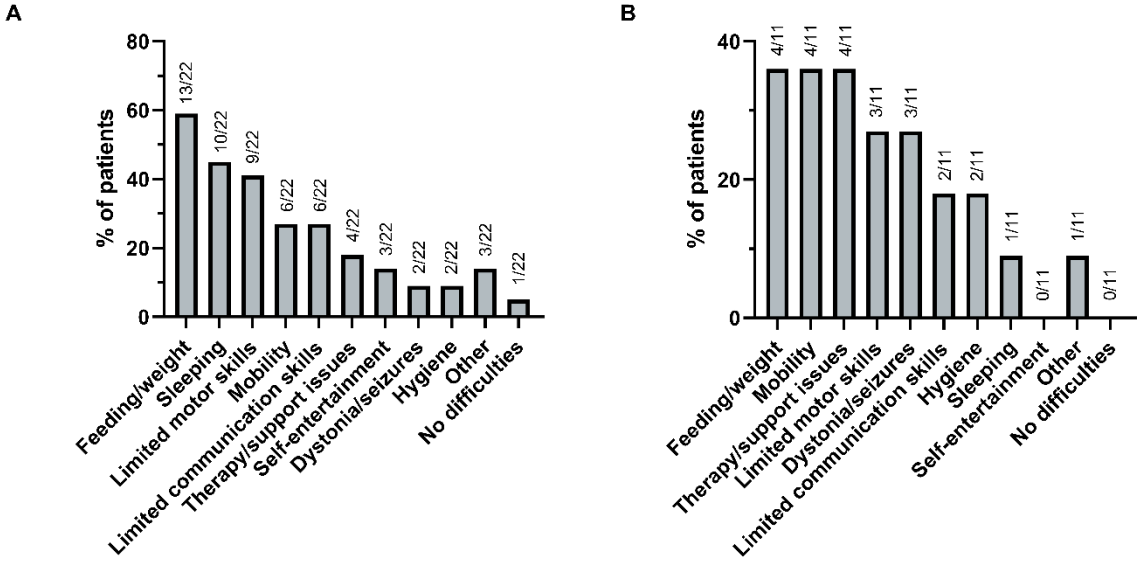
441 **Registry**



442

443 **Figure S2:** Timeline of the design and implementation of the International MCT8 Deficiency Registry
444 and the MCT8-AHDS Foundation. Pivotal moments are shown in bold. Data regarding the MCT8-AHDS
445 Foundation was derived from mct8.info/about-us. Abbreviations: EURORDIS, European Organisation
446 for Rare Diseases.

447 **Figure S3: Difficulties in daily life after stratification for age**

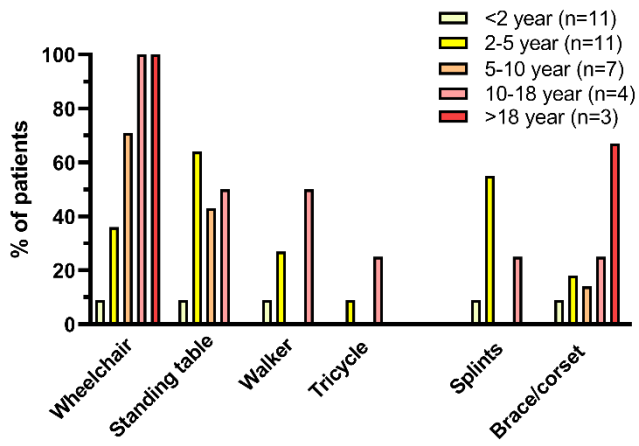


448

449 **Figure S3:** Difficulties in daily life care in patients <5 years (A) and ≥5 years of age (B). Numbers

450 underlying the percentages are shown above the bars.

451 **Figure S4: Use of mobility aids upon aging**



452

453 **Figure S4:** Parent-reported use of mobility aids, after stratification for age at registration.

Figure S5: Presenting symptoms

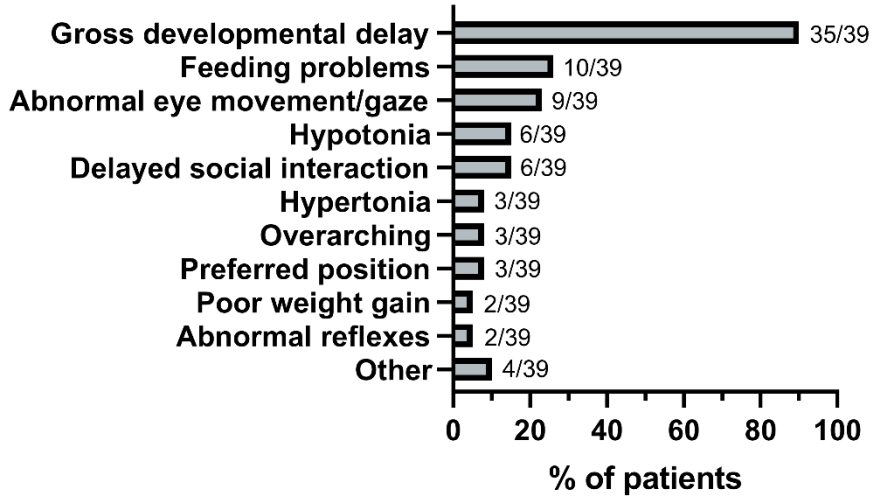


Figure S5: First signs and symptoms observed by parents. Numbers underlying the percentages are shown next to the bars.

Figure S6: Difference in diagnostic delay between patients born before 2017 *versus* patients born in or after 2017, after exclusion of patients born before 2004.

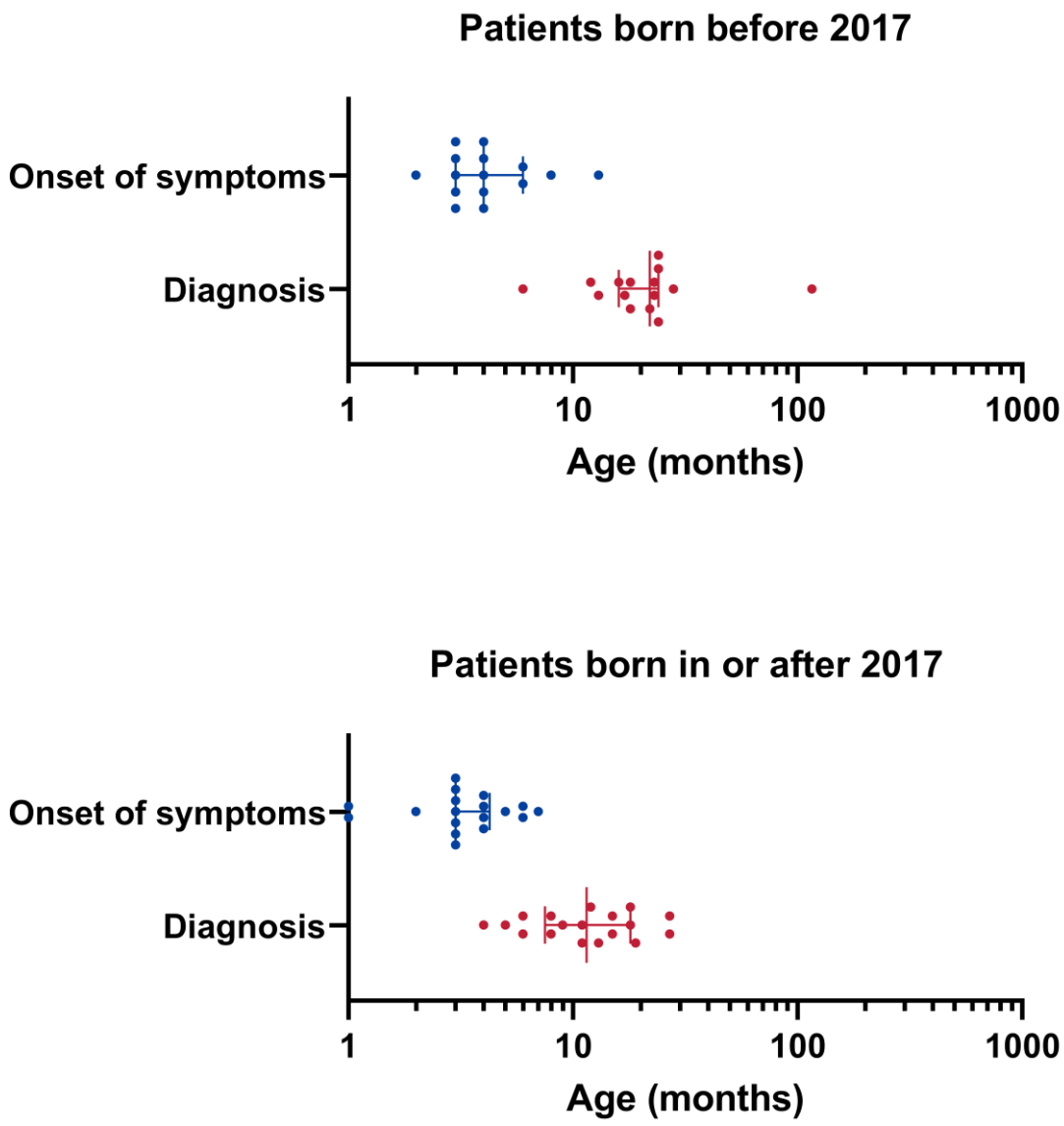
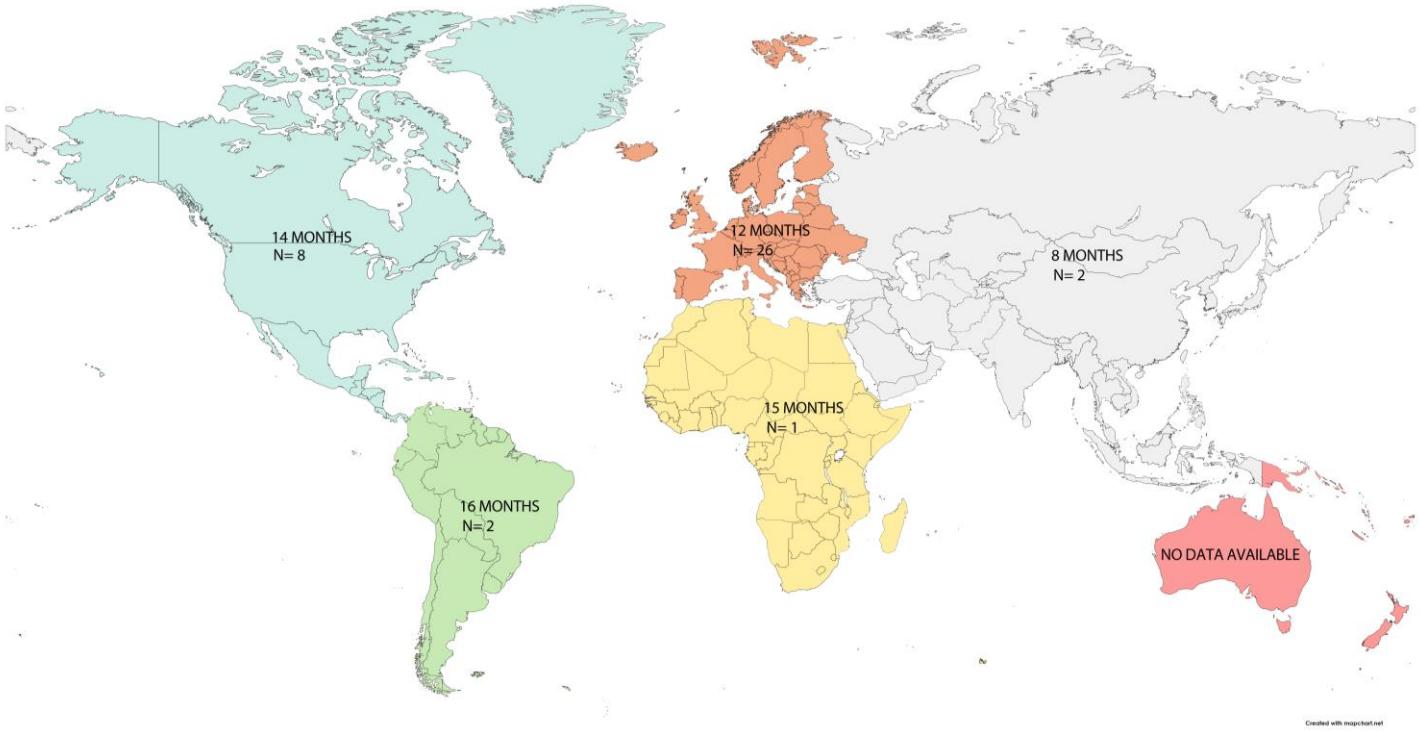


Figure S6: Parent-reported age of onset of symptoms and age of diagnosis in patients born before 2017 (upper panel) *versus* patients born in or after 2017 (lower panel), after exclusion of patients born before October 2004.

464 **Figure S7: Diagnostic delay per continent**



465 **Figure S7:** Median diagnostic delay after stratification for continent of residence at registration. Figure

466 created with mapchart.net.

References

1. Friesema EC, Grueters A, Biebermann H, Krude H, von Moers A, Reeser M, et al. Association between mutations in a thyroid hormone transporter and severe X-linked psychomotor retardation. Lancet. 2004;364(9443):1435-7.

2. Dumitrescu AM, Liao XH, Best TB, Brockmann K, Refetoff S. A novel syndrome combining thyroid and neurological abnormalities is associated with mutations in a monocarboxylate transporter gene. Am J Hum Genet. 2004;74(1):168-75.