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Disease characteristics of MCT8 deficiency: an international, retrospective, multicentre cohort study

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Abstract

Background—Disordered thyroid hormone transport, due to mutations in monocarboxylate transporter 8 (MCT8), is characterized by intellectual and motor disability due to cerebral hypothyroidism and chronic peripheral thyrotoxicosis. Phenotypic characteristics and natural history of MCT8 deficiency have not been systematically evaluated.

Methods—In this international, multicentre, study, retrospective data (2003 to 2019) from patients with MCT8 deficiency followed in 47 centres, was analysed. Our primary objectives were to determine neurocognitive outcomes and overall survival. We also assessed clinical parameters, including anthropometric characteristics, biochemical markers and neuroimaging findings.

Results—151 subjects with 73 different MCT8 mutations were included. 21·2% (32/151) of patients died at a median age of 10·5 years (range 1·6-71·0), with main causes of mortality being pulmonary infection (18·8%) and sudden (cardiac) death (18·8%). Survival differed significantly between individuals who attained head control or not (log-rank test: p=0·002; hazard ratio 3·99 95%CI 1·89-8·76). The limited motor and cognitive abilities of patients did not improve with age. T3 concentrations were elevated in 95·1% (96/101) and total T4 concentrations were reduced in 89·5% (94/105) of patients. 71·1% (59/83) patients were underweight (<-2SD). Cardiovascular abnormalities were frequent, with 53·2% (25/47) of patients exhibiting elevated systolic blood pressure, and 75·6% (34/45) of patients having premature atrial contractions and 31·3% (20/60) having resting tachycardia.

Interpretation—Our description of characteristics and natural history of MCT8 deficiency in a large patient cohort reveals poor survival with a high prevalence of treatable underlying risk factors and provides knowledge which informs clinical management and future evaluation of therapies.

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Contributors

SG, FSvG, WEV, IFMC, and MD designed the study, acquired and analysed the results and drafted and approved the manuscript. All other authors contributed to the acquisition, analysis, and interpretation of data, and approved the manuscript.

Declaration of Interest

The Erasmus Medical Centre (Rotterdam, Netherlands), which employs SG, FSvG, IMvB, MD, MMvdK, CAU, MCYdW, and WEV, might receive royalties from Rare Thyroid Therapeutics (the manufacturer of Triac) in the future, dependent on any future commercialisation. None of the authors will benefit personally from any royalties. Rare Thyroid Therapeutics had no influence on the conduct or analysis of this study. All other authors declare no competing interests.

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Introduction

Thyroid hormones are crucial for normal physiological processes, particularly neurodevelopment, and regulation of basal metabolic rate, throughout life (1, 2). Intracellular bioavailability of thyroid hormones is governed by membrane transporter proteins that facilitate their cellular entry (3). Monocarboxylate transporter 8 (MCT8) is a specific thyroid hormone transporter that is crucial for transport of tri-iodothyronine (T3) and thyroxine (T4) in several tissues, including the brain (4–8). Mutations in the gene encoding MCT8 (*SLC16A2* on chromosome Xq13.2) cause MCT8 deficiency, also known as Allan-Herndon-Dudley syndrome (AHDS), a debilitating disorder with an estimated prevalence of 1 in 70 000 male individuals (9–11).

MCT8 deficiency is characterized by profound neurodevelopmental delay and a wide range of severe clinical sequelae secondary to chronic peripheral thyrotoxicosis which cannot be effectively treated with conventional (anti)thyroid drugs (3, 10, 11). In 2019, a clinical trial showed that treatment with triiodothyroacetic acid (Triac) ameliorates key features of peripheral thyrotoxicosis and might improve neurocognitive outcomes if treatment is commenced early in life (12).

Robust, comprehensive data regarding the phenotypic characteristics and natural history of patients with MCT8 deficiency are lacking, as the phenotype has only been recorded in single case reports or small case series with related patients [*e.g.* (13, 14)]. Furthermore, these reports used differing clinical methods precluding consistent assessments, and merely focused on the neurological phenotype, neglecting the peripheral clinical features of the disorder (3, 14). Data on survival and neurodevelopmental outcomes in this disorder are not known. The lack of consistent quantitative knowledge of the natural history and the phenotypic spectrum of MCT8 deficiency hampers early diagnosis and uniform clinical management including the evaluation of a disease-modifying therapy.

Given the paucity of recorded data and with access to a large patient cohort via an international collaborative network for this rare disorder, we have sought to provide comprehensive and uniform phenotypic characterization of MCT8 deficiency using clinical, radiological, and biochemical data.

Methods

Study design and participants

This international study was initiated on 14 October 2014 by founding a consortium of centres where patients with MCT8 deficiency were followed up.

The key inclusion criterion was genetically confirmed MCT8 deficiency. Additionally, data on first-degree and second-degree male relatives with clinical MCT8 deficiency (when genetic testing was not available at that time) were included. There were no exclusion criteria. Our cohort consisted of patients that had been enrolled in the international, multicentre Triac Trial [NCT02060474, (12)], patients who participated in the named patient program for Triac treatment and patients for whom Erasmus MC fulfilled a consultancy

role. A subgroup of participants has been reported before with available individual case descriptions (n=47), or has been reported on aggregated level (n=46, (12)) (figure S2A). For such patients, updated and exhaustive data were collected. For analysis of serum thyroid function tests, only patients whose measurements were performed in the central laboratory of the Erasmus MC were considered to avoid inter-assay variation. For in-depth clinical and biochemical phenotyping only those patients were enrolled that either participated in the Triac Trial (12) or in the named patient program to ensure data had been captured by trained personnel and according to standard operating procedures.

Ethical considerations

This study conforms to the Declaration of Helsinki, Good Clinical Practice guidelines and was evaluated and approved by the appropriate local institutional review boards or ethics committees. However, for the retrospective analysis of existing datasets of patients in routine clinical care, the majority of centres did not require additional specific institutional review board approval. For other centres, studies were either ethically approved or the ethics committee provided a waiver for approval. Informed consent was obtained from the parents or legal representatives of all enrolled patients, unless the relevant institutional review board and/or local regulations had authorized the use of anonymised patient data without additional consent.

Procedures

An overview of study assessments and investigations is provided in Figure s1 and in the Supplementary Methods.

Outcomes

Our primary objective was to analyse the overall survival of patients with MCT8 deficiency and document causes of death. We also compared survival between patients who did or did not attain full head control and between patients who were underweight or not.

Other key objectives were to document neurocognitive function using uniform criteria and assess their relationship to biological age as a measure of disease progression and developmental outcome and to describe the occurrence of extra-neurological features.

Statistical analysis

We summarised continuous variables as mean and standard deviation (SD), or median and range. We established overall survival and compared patients with and without full head control with log-rank analysis. Survival was defined as the age at last date known alive. Correlations between biological age and scores on different neuropsychological assessments were explored using linear regression. For these analyses, we excluded patients with a less severe neurocognitive phenotype, defined as individuals that attained at least two of the following developmental milestones: talking in simple words, achieving head control, sitting independently, and/or walking with assistance. All statistical tests were two-sided, and p values of less than 0·05 were considered statistically significant. Statistical analyses were performed using GraphPad Prism, version 6 (GraphPad, La Jolla, CA, USA).

Role of funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

In 47 centers, 151 patients of 22 different nationalities (8 ethnicities) were enrolled between October 14th 2014 and January 17th 2020 (figure s1). In 106 cases serum thyroid function tests had been measured in the central laboratory, and 86 had been checked according to standardised protocols for in-depth phenotyping at a median age of 4·8 years (interquartile range [IQR] 1·9-9·8, range 0·4-66·8) (figure s1).

The demographics and characteristics of the enrolled patients are summarised in table s1. In the 151 enrolled cases, 73 different underlying MCT8 mutations were identified, of which 38 had not been reported before (figure s2B). A total of 17 mutations were identified in at least two unrelated families. All 35 missense mutations were located in the transmembrane helices (figure s3). The median age at diagnosis was 24·0 months (range: 0·0-744·0) (figure 1A), but the median age at onset of first symptoms was 4·0 months (range: 0·0-13·0) (figure 1A). Consequently, the median time to diagnosis was 18·0 months (IQR 7·8-63·0, range 0·0-738·0). The most frequently reported initial concerns that prompted medical evaluation were gross developmental delay (78·6%), hypotonia (39·8%), feeding problems (8·2%), and poor weight gain (7·1%) (figure 1B).

32 (21·2%) patients had died at a median age of 10·5 years (IQR 5·3-18·8, range 1·6-71·0). The main causes of death were pulmonary infections (18·8%), sudden (cardiac) death (18·8%), and aspiration pneumonia (9·4%) (figure 1C). In 15 (46·9 %) of 32 deceased subjects the cause of death was unclear and postmortem examinations had not been performed. The median overall survival was 35·0 years (95% CI 8·3-61·7; figure 1D). The 10-, 18-, and 60-year survival probabilities were 85% (95% CI 78·0-92·0), 69·8% (58·2-80·3), and 34·8% (10·2-59·3), respectively. Patients attaining full head control had a median survival of 63·0 years (95% CI 40·6-85·4) compared with patients who did not attain head control who had a median survival of 30·3 years (15·5-45·0; HR 3·99, 95% CI 1·89-8·76, p=0·002; figure 1E). Patients having underweight had a median survival of 30·3 years compared with patients not having underweight who had a median survival of 71·0 years (HR 3·83, 95% CI 1·05-13·92, p=0·04; figure 1F).

The prevalence of specific neurological features in patients included in the in-depth phenotyped cohort (N=86, median age 4·8 years, IQR 1·9-9·8, range 0·4-66·8) is reported in table 1 and figure 2, and neurological sequelae are summarized in figure s4 and figure s5. All patients had moderate-to-severe intellectual disability with a severe delay in motor and language development (table s2). Only 6 (7·7%) patients achieved independent sitting and were less severely affected than the other patients (figure 2A and B). The median score on the Gross Motor Function Measure 88 (15) did not exceed 10% of the total score that should be obtained by healthy 4-year old children (figure 2B, table s2). Among 30 subjects that had been evaluated at a median age of 7·4 years (range 0·4-66·8) with the Bayley Scales

of Infant Development III (16), the median developmental age was well-below 12 months on all tested sub-domains (figure 2C and D, figure s6A-C, table s2). When analyzing data from just severely affected patients, none of the scores in any of the developmental domains improved with age, with fine motor skills even showing regression (figure 2E and F, figure s6D-G).

Pregnancy and delivery were unremarkable in the majority of cases, with most children having good Apgar scores, normal birth weight at term and head circumference (table 1). At first presentation, most patients had global hypotonia with a pronounced head-lag on vertical suspension and upper trunk slipping through. Typically, by the end of the first year, dystonic posturing of the limbs and neck were noted. Exaggerated deep tendon reflexes were present in 80·3% (57/71) of cases, and 90·5% (67/74) of patients developed hypertonia in wrists, knees or heels with age attributed to dystonia and spasticity. Primitive reflexes remained present in 91·1% (51/56) cases, with a positive tonic neck reflex (81·0%) and glabellar sign (80·0%) being most prevalent, irrespective of patient age. Electro-encephalogram (EEG)-confirmed seizures were observed in 15 (23·1%) of 65 patients, and mostly involved generalized, absence-like episodes without a clear motor component.

MRI scans of the brain were available in 13 patients, performed at a median age of 8·0 months (range: 5·0-187·0), with 8 patients having at least one follow-up scan available (table 1, figure s4, table s3). The most consistent finding was a global delay in myelination, evidenced by diffuse residual hyperintense white matter in specific brain regions on T2-weighted images. Myelination improved with age, but had not fully normalized in the oldest patient (15 years) with available data. Most cases showed diffuse cortical and subcortical atrophy with dilatation of the ventricles, widening of the subarachnoid spaces demonstrated by prominence of the supra- and infra-tentorial sulci. In 6 (85·7%) of 7 patients magnetic resonance spectroscopy (MRS) showed an increased choline peak and a decreased N-acetyl aspartate (NAA) peak, which is compatible with aberrant myelination and general atrophy. These neuroradiological findings were supported by postmortem findings in the brain of a deceased 8-year old patient, showing global reduction of brain volume and diffuse reduction in myelination (see supplementary results).

Serum thyroid function tests were available in 106 treatment-naïve patients at a median age of 5·3 years (IQR 2·1-11·0, range 0·4-66·8). Serum TSH concentrations were within the normal range in 93 (88·6 %) of 105 patients (figure 3A). Serum free and total T4 concentrations were below the age-specific lower limit in 94 (88·7 %) of 106 and 94 (89·5%) of 105 patients, respectively (figure 3B and figure s7A and s7B). Mean serum T3 concentrations exceeded the age-specific upper limit in 96 (95·1%) of 101 patients (figure 3C), which resulted in a pronounced increase in the T3/T4 ratio (figure s7C). Reverse T3 (rT3) concentrations were decreased in 76 (90·5%) of 84 patients (figure s7D), with a concomitant increase in the T3/rT3 ratio (figure s7E). In 3 out of 7 subjects TRH-stimulation tests showed an inadequate TSH response. In 7 (87·5%) out of 8 subjects in whom T4-based neonatal screening results were available, total T4 concentrations were below the 20th percentile (figure 3D). Serum total T4 concentrations were significantly less reduced in patients with less severe versus those with a severe neurocognitive phenotype (figure s7F). Serum T3 concentrations were not significantly different between these groups (figure s7G).

Consequently, the T3/T4 ratio, a marker of thyroid hormone metabolism in peripheral tissues, was significantly lower in patients with a less severe phenotype (figure s7G).

In-depth phenotyping of peripheral clinical features was undertaken in 86 patients (median age 4·8 years, IQR 1·9-9·8, range 0·4-66·8) and the main findings are summarised in table 2 and table s4. Body weight for age showed progressive deterioration over time, with 59 (71·1%) of 83 patients being severely underweight (<-2SD) (figure 3E, table 2). 27 (35·5%) of 76 patients were tube fed, although impaired swallowing function was reported in 55 (71·4%) of 77 patients. Body height for age also deteriorated with age (figure 3F). Delayed sexual maturation was present in 5 (26·3%) patients (figure s8A-D). Among patients over 8 years of age, bone mineral density (BMD) was below the 5th percentile, but bone turnover markers were generally within the low-normal range (figure s9A-D).

The mean resting heart rate measured by electrocardiography was 110 (±20) beats per minute, with 20 (31·3%) of 64 patients exceeding the 90th percentile of heart rate (figure 3G) (17). Systolic blood pressure exceeded the 90th percentile in 25 (53·2%) of 47 patients whereas the diastolic blood pressure exceeded the 90th percentile in 17 (36·2%) of 47 patients (figure 3H) (18, 19). Detailed cardiovascular assessment was available in 50 patients. At the time of evaluation, 47 (94%) of 50 patients reportedly had no cardiovascular abnormalities and were not receiving any treatment. 3 (6·0%) of 50 patients had second-degree atrioventricular block (Mobitz I: 1; Mobitz II: 2) and 6 (12·0%) of 50 patients had (incomplete) right bundle branch block. In addition, corrected QT interval (QTc) was above the 98th percentile in three out of 39 (7·7%) patients (table 2, figure s10A). Even though most patients were completely immobile, 24h ambulatory cardiac monitoring showed a high resting heart rate (103±13 beats per minute) with frequent episodes of tachycardia and premature atrial or ventricular contractions (figure 3I, table s4). One childhood patient had an episode of atrial fibrillation and another had non-sustained ventricular tachycardia (table 2). Cardiac echocardiography studies performed in 26 patients revealed dilated aortic root (>+2SD for age, range 2·0-3·4 SD) in 7 (26·9%) patients, and relatively small left ventricular wall dimensions (figure s10B).

Serum concentrations of sex hormone binding globulin were elevated in 69 (88·5%) of 78 patients (figure 3J), whereas total cholesterol concentrations were in the low normal range (figure s11A). Serum alanine aminotransferase, aspartate aminotransferase, and gamma-glutamyl transferase concentrations were mildly elevated in a substantial proportion of patients (table 2, figure s11B-D), whereas ammonia concentrations were mostly normal (figure s11E). Of note, two patients reportedly had an episode of hepatic dysfunction following a (viral) infection.

43 (84·3%) of 51 patients had low muscle mass. Creatinine concentrations in serum were within the low-normal range for age (figure 3K). Serum creatine kinase concentrations were mostly low-normal (figure 3L), with some exceptions in patients with recent seizures or severe dystonic episodes. Serum lactate concentrations were slightly increased in 3 (27·3%) of 11 patients (Figure s11F).

Gastroesophageal reflux disease was present in 79·2% (38/48) of patients and this often required pharmacological intervention. Spontaneous gastrointestinal bleeding was reported in 2 patients and was the cause of death in one of them. Constipation was present in 62·3% (37/63) of patients. 29 (69·1%) of 42 patients had recurrent (pulmonary) infections (table 2).

Discussion

To our knowledge, this international, multicentre, retrospective study is unique, representing quantitative evaluation of the natural history of MCT8 deficiency in the largest cohort of patients with this disorder. We have documented key clinical features together with biochemical and radiological correlates as well as outcomes in this rare but potentially treatable condition. Our findings will facilitate accurate diagnosis, guide management, and inform conduct of future therapeutic intervention trials.

A principal finding is that overall survival of patients with MCT8 deficiency is greatly diminished, with an overall median life expectancy of 30 years. Stratification of analyses revealed that patients who attain full head control are more likely to survive longer than those who do not. Accordingly, attaining full head control, as a marker of improved neurodevelopment, could be a relevant endpoint for future therapeutic trials in MCT8 deficiency.

The most common cause of death was pneumonia, caused either by aspiration or by infections. Aspiration, due to impaired swallowing function, is frequently observed in patients with MCT8 deficiency, and this could be mitigated by tube feeding. However, a substantial number of patients that exhibited swallowing problems were not tube fed and thus remained at risk for aspiration. With underweight being strongly linked to survival, tube feeding can prevent adverse clinical sequelae and potentially improve survival (20). The second major cause of mortality was sudden death. Although its aetiology remains unclear, available data points to a cardiac cause, with the high prevalence of premature atrial and ventricular contractions, which are uncommon in healthy individuals especially in childhood (21–25). We also observed non-sustained ventricular tachycardia and QTc prolongation in some patients, with both considered risk factors for sudden cardiac death. Moreover, a substantial proportion of patients exhibited systolic hypertension and/or tachycardia and had several structural and electrophysiological cardiac changes that have been linked to these traits. As the vast majority (94·0%) of patients reportedly had no history of cardiac problems, these cardiovascular abnormalities likely remain clinically undiagnosed in this population. This observation calls for inclusion of cardiovascular assessment in the management of this disorder. With loss of body weight and many cardiovascular abnormalities being attributable to chronic thyrotoxicosis, reduction in circulating T3 concentrations in patients could represent effective treatment for these aspects of the disorder. Indeed, in a recent clinical trial, treatment with the thyroid hormone analogue Triac efficiently reduced serum T3 concentrations and improved key clinical features such as loss of body weight and reversal of abnormal cardiovascular parameters in MCT8 deficiency (12).

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The current study also identified several other clinical features that require treatment or close followup, of which gastro-esophageal reflux disease, scoliosis, hip luxation, and constipation have the highest prevalence. The presence of mildly elevated aminotransferases and the occurrence of transient hepatic failure in at least three reported cases following a viral infection [this report and (11)], suggest that drugs with hepatotoxic side effects (e.g. anti-epileptic drugs as frequently used in this population) should be used with extra caution.

Our comprehensive documentation of neurological sequelae in patients with MCT8 deficiency revealed that the combination of global hypotonia, hypertonia due to dystonia and spasticity and persistence of primitive reflexes was present in up to 90% of patients. Delayed myelination on MRI was consistent with other studies (14, 26, 27). Taken together, these clinical and neuroimaging characteristics may facilitate early diagnosis of MCT8 deficiency and in discriminating this entity from other neurodevelopmental disorders.

Our study highlights major delay in diagnosis of this disorder, with a minority of cases being identified in the first year of life. This is mainly attributable to the non-specific initial clinical features with lack of awareness of the specific characteristics of this disorder among clinicians. Having documented that circulating T3 concentrations are elevated in patients below one year of age, the combination of clinical and radiological features with measurement of serum T3 concentrations may constitute a key clue for early diagnosis. The low T4 concentrations measured in patients with MCT8 deficiency in the neonatal screening indicates the potential to diagnose MCT8 deficiency in newborns, perhaps with a modification of the current neonatal screening strategy. The importance of early diagnosis is supported by preclinical studies in which Triac completely prevented abnormal neurological development in animal models of MCT8 deficiency when administrated at birth (28). A future phase 2 clinical trial will investigate the effects of Triac on neurodevelopment, with treatment being commenced at a very young age (NCT02396459).

This study has limitations inherent to its retrospective design. However, MCT8 deficiency is a rare disorder with surviving patients being located throughout the world such that retrospective analysis of available clinical data was the most suitable way to increase our understanding of this disorder. In general, such study design is prone to collection of an incomplete dataset, subjective evaluation of patients with variable followup. However, in this study, data in the majority of cases had been collected uniformly during baseline assessment of patients wither participating in the Triac Trial or in named patient treatment programs, providing an unique opportunity for systematic cross-sectional evaluation of key clinical outcomes. Although selection bias cannot be excluded, our study included a substantial proportion of currently diagnosed patients.

In summary, this study provides a comprehensive and structured in-depth characterisation of the phenotype of MCT8 deficiency. The current study first reports poor survival in this disorder, with 30% of patients dying in childhood. Having identified pulmonary infection and sudden death (our data suggests cardiac arrhythmia as underlying basis) as the major causes of mortality, timely intervention with Triac therapy may ameliorate the poor prognosis in this disease. Furthermore, our finding that survival is particularly poor in patients with impaired neurological development (head control), provides a basis

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for therapeutic intervention targeted at this subgroup. Our findings underscore the need for a multidisciplinary approach in the management and follow-up of patients with MCT8 deficiency. In addition, our observations represent an unique, quantitative dataset of the natural history of this disorder which may serve as a historical control for future interventional studies in this rare disorder, for which a biological control group is often deemed not feasible. Accordingly, we suggest that this study enhances our understanding of the clinical sequelae and longterm outcome of MCT8 deficiency and also facilitates the diagnosis and management of this disorder.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data sharing

Because of the rarity of MCT8 deficiency, individual participant data beyond that reported here will not be shared, to safeguard patient privacy.

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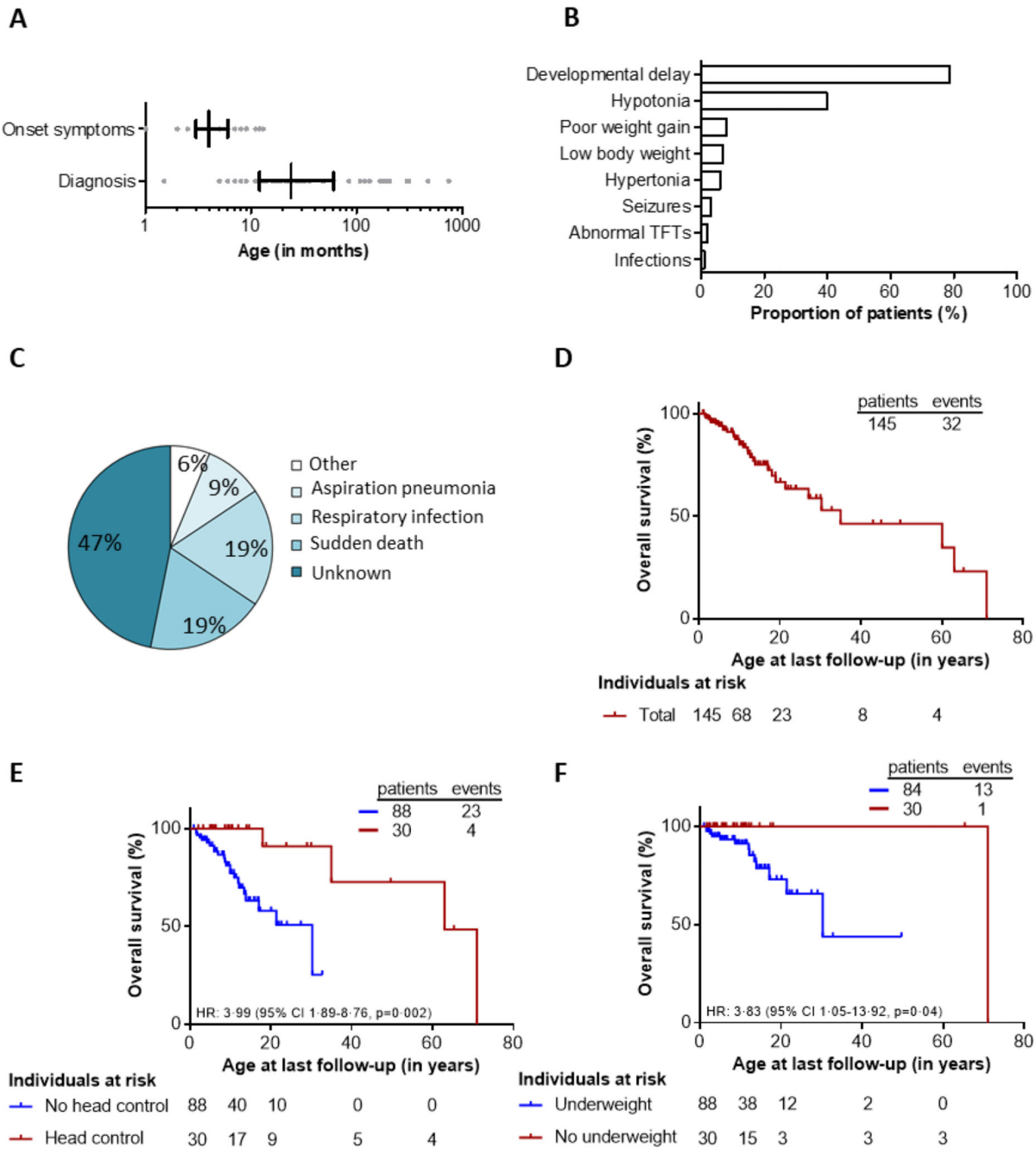

Figure 1.

Panel **A** graphically presents the mean ± SEM (black lines) age at onset of symptoms and panel **B** the age at time of diagnosis. Grey dots represent measurements in individual patients. Panel **C** shows the causes of death in patient with MCT8 deficiency. HR: hazard ratio. Panel **D** shows the overall survival based on age at last follow-up (Kaplan-Meier estimates). Panel **E** shows the Kaplan-Meier estimates of MCT8-specific survival in patients who attained head control (red line) *versus* those who did not (blue line) and panel **F** those in patients with (blue line) *versus* without (red line) underweight.

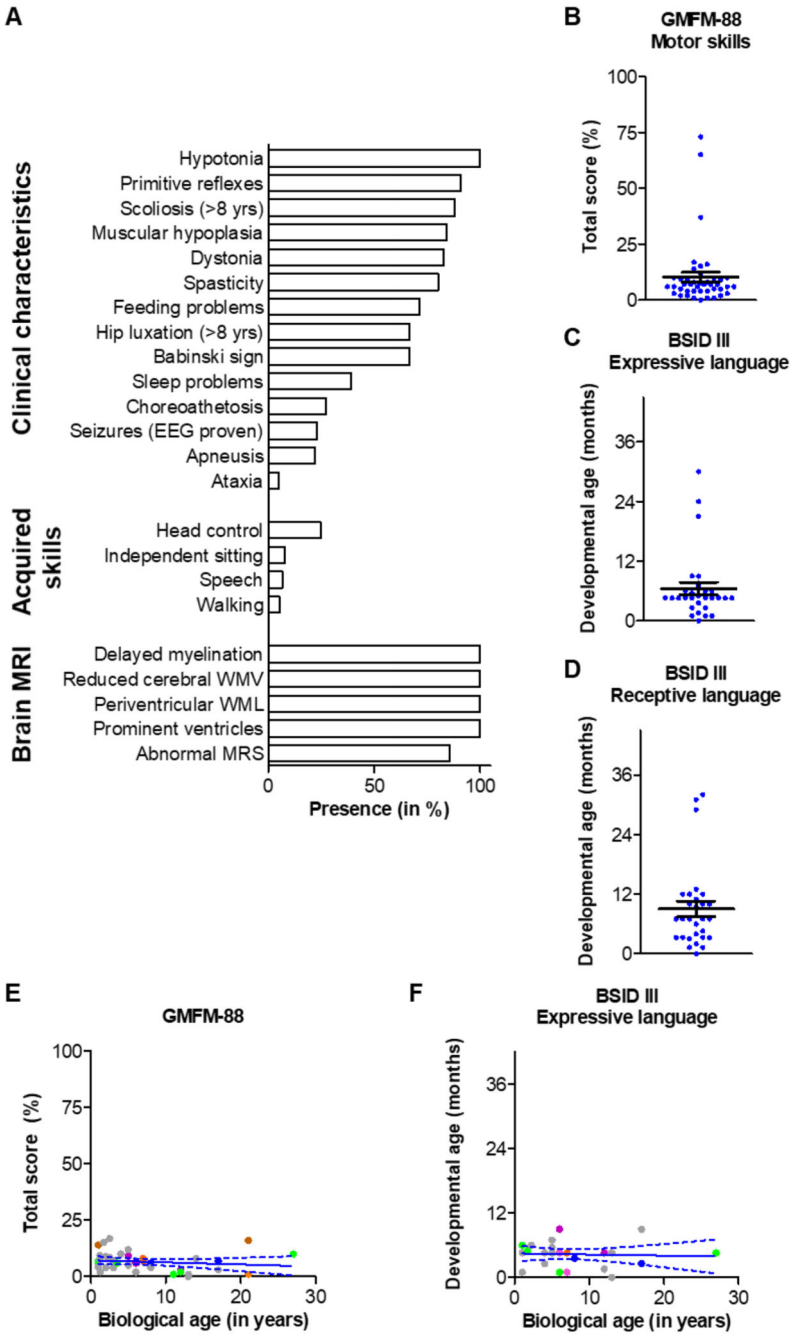

Figure 2.

Panel **A** shows the prevalence of clinical, radiological and developmental key features in MCT8 deficiency. Bars indicate the proportion of patients presenting the indicated feature at first presentation. Panel **B** represents the gross motor function development in patients with MCT8 deficiency measured by the Gross Motor Function Measure (GMFM) 88 (15). A 100% score indicates the level of development that is achieved by a healthy 4-year old child. Panel **C** shows the development of expressive language and panel **D** the development of receptive language, measured by the respective sub-domains of the Bayley Scales of Infant

Development (BSID) III (16). Scores are expressed as developmental age in months. Blue dots indicate measurements in individual patients and black lines indicate the mean ± SEM score. Panel **E** shows the relation between GMFM 88 score and panel **F** the developmental age on the sub-domain expressive language of the BSID III *versus* the chronological age using linear regression (the 95% CI is displayed as blue dotted lines). Only severely affected patients were considered in panel **E** and **F**. Linear regression was used to plot the trend and the 95% confidence intervals (blue lines). Patients harboring the same genetic mutation are displayed in the same color: p.F230del (green), c.651-652+20del (blue), G564R (purple), p.A565fs566X (pink), and R271H (orange). Unique mutations are colored in grey.

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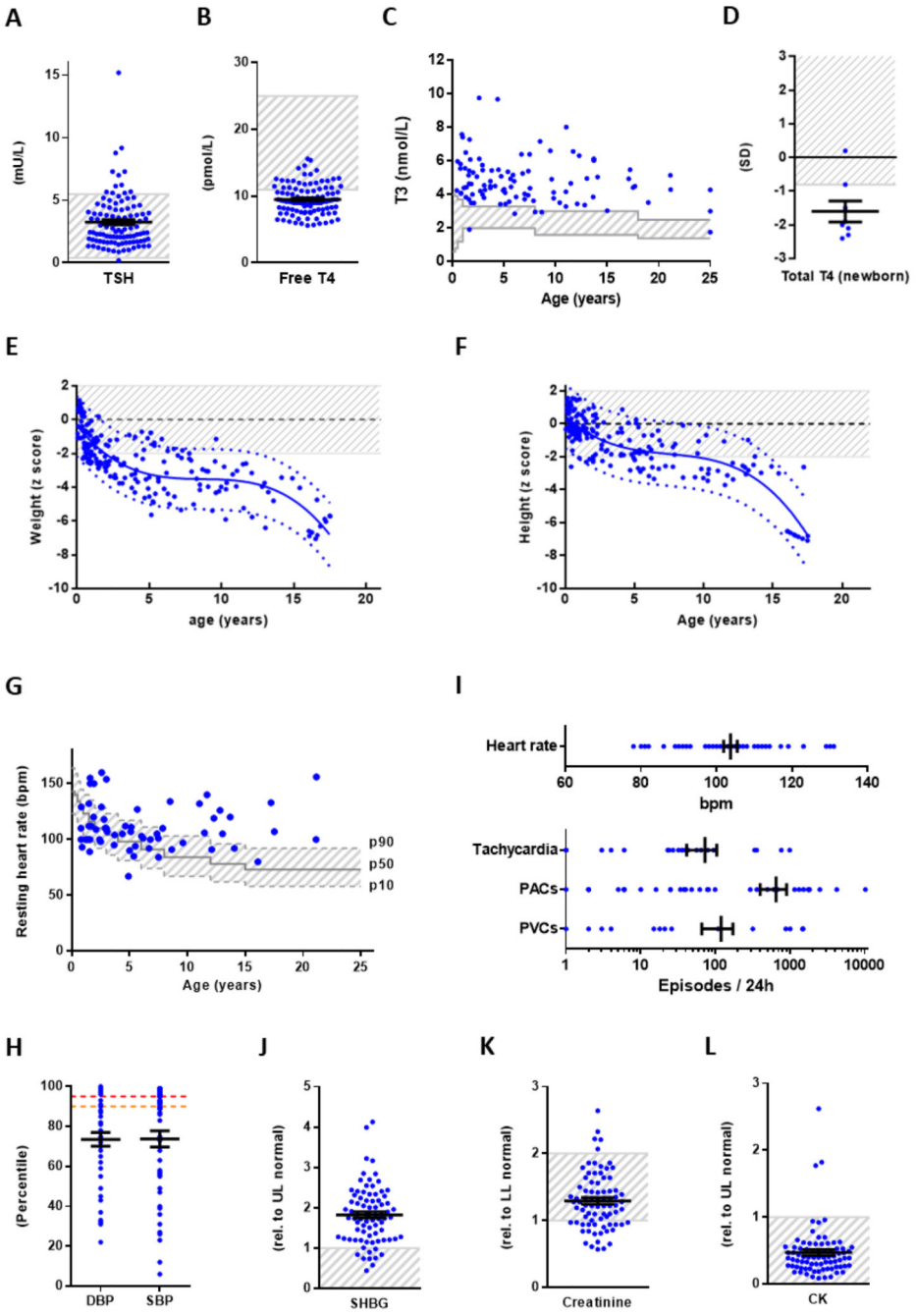

Figure 3.

Mean ± SEM (black lines) serum concentrations of thyroid stimulating hormone (TSH) (panel **A**) and free T4 (panel **B**). Panel **C** presents the serum total T3 concentrations *versus* age. Panel **D** shows the available results on total T4 measurements during neonatal screening expressed in SDs. Blue dots represent measurements in individual patients and grey areas the normal range. Panel **E** shows the natural course of bodyweight change in patients with MCT8 deficiency. Blue dots represent available historical bodyweight measurements in untreated patients. Non-linear (third order) polynomial regression was

used to plot the trend with its 95% error band. Similarly, panel **F** shows the natural course of body height. Panel **G** shows the resting heart rate by age. Normal range in healthy children is derived from (17). Panel **H** shows the mean ± SEM diastolic and systolic blood pressure. The orange line represents the threshold for classification as elevated blood pressure and the red line the threshold of hypertension, as defined by the guidelines from the American Academy of Pediatrics (18) and the American College of Cardiology and American Heart Association (19). Panel **I** shows the mean ± SEM (black lines) occurrence of indicated features during 24h cardiac monitoring in 45 individuals. Serum concentration of sex hormone binding globulin (SHBG) (panel **J**), creatinine (panel **K**), and creatine kinase (panel **L**) are expressed relative to the age-specific lower (panel **K**) or upper (panel **J** and **L**) limit of the normal range. Abbreviations: TSH, thyroid stimulating hormone; T4, thyroxine; T3, triiodothyronine; PACs, premature atrial contractions; PVCs premature ventricular contractions; CK, creatine kinase; SHBG, sex hormone binding globulin; LL, lower limit; UL, upper limit. The absolute mean values of all parameters are summarized in table s4.

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Table 1
In depth phenotyping of neurodevelopmental features

	N=86
Age at assessment (years)	4·8 (0·44-66·8)
Perinatal features	
Pregnancy duration (weeks)	40·0 (32·0-42·3)
Apgar scores >8 after 5 min (n=16)	15 (93·8)
Term birth weight (grams)	3584 (±517)
Microcephaly (<3th centile) at birth (n=11)	2 (18·2)
Neurological examination	
Hypotonia (n=72)	72 (100%)
Primitive reflexes (>1 present) (n=56)	51 (91·1%)
Tonic neck reflex (n=21)	17 (81·0%)
Glabellar sign (n=55)	44 (80·0%)
Startle response (n=25)	17 (68·0%)
Scoliosis (>8 years) (n=17)	15 (88·2%)
Muscle hypoplasia (n=51)	43 (84·3%)
Dystonia (n=69)	57 (82·6%)
Spasticity (n=71)	57 (80·3%)
Urinary / faecal incontinence (>4 years) (n=41)	33 (80·5%)
Feeding problems (n=77)	55 (71·4%)
Hip dislocation (>8 years, n=15)	10 (66·7%)
Plantar extension response (Babinski sign, n=57)	38 (66·7%)
Delayed evoked potentials (<6 months, n=6) *	3 (50·0%)
Sleep problems (n=51)	20 (39·2%)
Tube feeding (n=76)	27 (35·5%)
Strabismus (n=54)	19 (35·2%)
Microcephaly (<3th centile) (n=59)	19 (32·2%)
Nystagmus (n=49)	13 (26·5%)
Extrapyramidal signs (other) (n=28)	7 (25·0%)
Seizures (EEG proven) (n=65)	15 (23·1%)
Apneusis (n=32)	7 (21·9%)
Abnormal hearing (n=44)	1 (2·3%)
Delayed evoked potentials (>1 year, n=3)	0 (0·0%)
Development	
Head control (n=77)	19 (24·7%)
Speech (at least 1 word) (n=76)	5 (6·6%)
Independent sitting (n=78)	6 (7·7%)
Independent walking (n=77)	4 (5·2%)
MRI/MRS characteristics *	
Normal global anatomy (n=13)	13 (100%)
Delayed myelination (n=13)	13 (100%)

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	N=86
Reduced cerebral white matter volume (n=13)	13 (100%)
Periventricular white matter lessions (n=10)	10 (100%)
Prominent supratentorial ventricular system (n=13)	13 (100%)
Prominent peripheral liquor spaces (n=13)	13 (100%)
Low NAA peak (n=7)	6 (85·7%)
High choline peak (n=7)	6 (85·7%)

Data are median (range), n (%), or mean (±SD). Systematic deep phenotyping of neurological phenotype in 86 eligible patients. Median age at last available MRI scan: 18·0 months, range 5·0-187·0); MRS was available in 7 cases. Details are provided in table s2.

*In particular the brainstem-evoked response audiometry was abnormal in children < 1 year of age and showed prolongation of the I-V interval.

Table 2
In depth phenotyping of peripheral features

Characteristic	N=106
Serum thyroid function tests	
Age at measurement (years)	5·3 (0·4-66·8)
Elevated T3 concentrations (n=101)	96 (95·1%)
Reduced free T4 concentrations (n=106)	94 (88·7%)
Deep phenotyping	**N=86**
Age at assessment (years)	4·8 (0·44-66·8)
Biochemical measurements *	
Elevated sex hormone binding globulin (n=78)	69 (88·5%)
Elevated alanine aminotransferase (n=65)	30 (46·2%)
Reduced creatinine (n=79)	22 (27·8%)
Elevated lactate (n=11)	3 (27·3%)
Reduced total cholesterol (n=65)	12 (18·5%)
Elevated aspartate aminotransferase (n=56)	11 (19·6%)
Elevated creatine kinase (n=79)	3 (3·8%)
Clinical features	
Low bone mineral density (>8 years, n=5)	5 (100%)
Hypotrophic musculature (n=51)	43 (84·3%)
Gastro-esophageal reflux disease (n=48)	38 (79·2%)
Premature atrial complexes (n=45)	34 (75·6%)
Recurrent (pulmonary) infections (n=42)	29 (69·0%)
Underweight (<-2 SD, n=83)	59 (71·1%)
Constipation (n=63)	37 (58·7%)
Elevated systolic blood pressure ‖ (n=47)	25 (53·2%)
Increased perspiration (n=60)	29 (48·3%)
Short stature (<-2 SD, n=67)	27 (40·3%)
Premature ventricular complexes (n=45)	19 (42·2%)
Tachycardia in rest † (n=64)	20 (31·3%)
Aortic root dilatation (n=26)	7 (26·9%)
Elevated diastolic blood pressure ‖ (n=47)	17 (36·2%)
Delayed sexual maturation (>8 years, n=19)	5 (26·3%)
Cardiac conduction abnormalities ‡ (n=50)	9 (18·0%)
Cryptorchidism (n=49)	9 (18·4%)
Prolonged QTc interval (39)	3 (7·7%)
Supraventricular tachycardia (n=48)	2 (4·2%)
(Non-sustained) ventricular tachycardia (n=48)	2 (4·2%)
Atrial fibrillation (n=48)	1 (2·1%)

Data are median (range), or n (%). Systematic deep phenotyping of the peripheral phenotype. Please note that most parameters have not been captured in all patients. All absolute and relative values are provided in table s4.

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[*] Reduced and elevated indicated concentrations below or above the normal range (2.5-97.5 centile in the healthy population).

[†] Tachycardia was defined as a resting heart rate above the 90th percentile for the corresponding age, with cut-offs described by Fleming and colleagues (17).

[‡] Three out of 50 patients (5·5%) had a second degree atrioventricular block (Mobitz I:1; Mobitz II:2) and 6 out of 50 patients (12·0%) had an (incomplete) right bundle branch block and 1 patient (2·0%) had a left posterior hemiblock.

[‖] Elevated systolic and diastolic blood pressure were defined using the guidelines from the American Academy of Pediatrics (18) and the American College of Cardiology and American Heart Association (19).