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REVIEW

Multidisciplinary Care of Patients with Inherited Metabolic Diseases and Epilepsy: Current Perspectives

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Abstract: More than 650 inherited metabolic diseases may present with epilepsy or seizures. These diseases are often multisystem, life-long and induce complex needs of patients and families. Multidisciplinary care involves all stages of disease management: diagnostics, specific or symptomatic, acute and chronic treatments, and integrated care that takes into account not only medical, but also manifold psychosocial, educational, vocational and other needs of patients and their caregivers. Care coordination is indispensable to ensure smooth transitions of care across life and disease stages, including management of emergencies, transition from pediatric to adult services and palliative care. Care pathways are highly diverse and have to find the right balance between highly specialized and locally provided services. While multidisciplinary teams consist of many professionals, a named supervising physician in a highly specialized healthcare setting and a care coordinator are highly important. As the greatest burden of care always falls onto the shoulders of patients and/or families, patient empowerment should be a part of every care pathway and include provision of required information, involvement into common decision-making, patient's and family's education, support for self-management, liaison with peer support groups and emotional/ psychological support. Due to the rarity and complexity of these diseases, sufficient expertise may not be available in a national healthcare system and cross-border services (virtual or physical) in the recently developed European Reference Networks should be ensured through the proper organization of referral systems in each EU and EEA country. Finally, digital technologies are particularly important in the provision of services for patients with rare diseases and can significantly increase the availability of highly specialized services and expertise.

Keywords: integrated care, transition, care pathways, care coordination, patient empowerment, management of emergencies

Introduction

Following a recent update of the definition and classification of inherited metabolic diseases (IMD), more than 1600 IMDs were described (http://www.iembase.org/).[1] Although it is frequently presumed that IMDs are uncommon cause of epilepsy or seizures,[2,3] timely diagnosis of these diseases is particularly important for several reasons: 1) As many as 600 (37%) IMDs out of 1616 currently described (as of 22.10.2021, accessed through http://www.iembase.org/) may involve epilepsy or seizures as the main or one of many symptoms (Box 1). Only a subset of these IMDs may be diagnosed through conventional metabolic testing, therefore, their true prevalence may have been underestimated in previous metabolic testing-based studies.[4,5] Moreover, novel groups of IMDs have recently been defined (eg, congenital disorders of autophagy, disorders of the synaptic vesicle cycle) and many of these novel diseases may present with epilepsy or seizures;[6,7] 2) Specific etiological treatments are being developed for an increasing number of IMDs and it is imperative to diagnose these diseases and institute treatments in time.[8,9] Conventional treatments of epilepsy can be ineffective in

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some IMDs, while specific etiological treatments (eg, in pyridoxine-dependent epilepsy[10] may fundamentally improve patient's prognosis and enable fulfilling life for the patient and his/her family. 3) Even in cases where specific treatments are not available, precise diagnosis of IMD may still be highly beneficial to patients and families as it allows halting diagnostic odyssey and avoidance of further, sometimes invasive testing.[11] In some cases potentially detrimental treatments may be withheld as in the case of epilepsy due to some mitochondrial diseases where valproates may induce fatal hepatic failure.[12] Besides, genetic diagnosis gives prognostic information, enables appropriate targeted long-term follow-up, informed reproductive choices for families, inclusion into clinical trials and engagement into patient organizations.[4,13] In cases of refractory epilepsy, identification of germline mutations in specific genes contraindicates surgery while mutations in other genes do not.[14] A subset of IMDs is highly amenable to ketogenic dietary treatment.[15] Generally, diagnosis of IMD is more likely to change management of a patient compared to other genetic diagnoses: in a recent study of 59 patients with early-onset epilepsy who got the genetic diagnosis through whole exome sequencing (12 of them (20%) were diagnosed with IMD), clinical management following genetic diagnosis was changed in 5 patients with IMD (42% of patients with IMD) and 17 patients without IMD (36% of patients without IMD).[16] Therefore, precise diagnosis of IMD is highly important for further multidisciplinary integrated care of patients.

The vast majority of IMDs that may present with epilepsy or seizures are multisystem, life-long disorders where epilepsy or seizures is just one among many other symptoms. Multidisciplinary care involves all stages of management: diagnostics, acute and chronic treatments, and long-term integrated care for patients with complex needs. Not only medical, but also manifold psychosocial, educational, vocational and other needs of patients and their caregivers must be taken into account.[17,18] In this narrative review we investigate various aspects of multidisciplinary care and discuss about some key challenges, opportunities and suggestions for the organization of high-quality care services that meet expectations of patients and families and conform to current patient-centered and value-based care principles. Further research on the overall organization of multidisciplinary, integrated care and various aspects of service provision may enable optimization of complex care and, eventually, better outcomes for IMD patients with epilepsy or seizures and their caregivers.

Materials and Methods

We performed literature searches using PubMed and Medline electronic databases using the various combinations of the following search terms: "epilepsy" OR "seizures" AND "inherited metabolic diseases" OR "inborn errors of metabolism" OR "multidisciplinary care" OR "care coordination" OR "transition of care" OR "self-management". Further searches were informed by references in the publications and related features in PubMed. Searches were limited to English language and included a period of 2010 to current (October 2021) period.

Terms and Definitions

IMD was defined as any primary genetic condition in which alteration of a biochemical pathway is intrinsic to specific biochemical, clinical and/or pathophysiological features.[1]

Multidisciplinary care was defined as a care when professionals from a range of disciplines work together to deliver comprehensive care that addresses as many of the patient's needs as possible.[19]

Care coordination involves deliberately organizing patient care activities and sharing information among all of the participants concerned with a patient's care to achieve safer and more effective care.[20]

Care pathways were defined as a complex intervention for the mutual decision-making and organization of care processes for a well-defined group of patients during a well-defined period. Defining characteristics of care pathways include: a) an explicit statement of the goals and key elements of care based on evidence, best practice, and patients' expectations and their characteristics; b) the facilitation of the communication among the team members and with patients and families; c) the coordination of the care process by coordinating the roles and sequencing the activities of the multidisciplinary care team, the patients and their relatives; d) the documentation, monitoring, and evaluation of variances and outcomes, and e) the identification of the appropriate resources.[21]

Patient empowerment was defined as patient engagement through which individuals and communities are able to express their needs, are involved in decision-making, take action to meet those needs.[22]

Self-management was defined as the interaction of health behaviors and related processes that patients and families engage in to care for a chronic condition.[23]

Transitional care was defined as the purposeful, planned movement of adolescents and young adults with chronic physical and medical conditions from child-centered to adult-oriented health care systems.[24]

Palliative care was defined as the active total care of body, mind and spirit, (as well as) giving support to the family. It begins at diagnosis, and continues regardless of whether or not a patient receives treatment directed at the disease.[25]

Ultra-rare disease was defined as a disease with a prevalence of <1 per 50,000 persons.[26]

Seizures were defined as a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.[27]

Epilepsy was defined as a disease of the brain defined by any of the following conditions: (1) At least two unprovoked (or reflex) seizures occurring >24 h apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; (3) diagnosis of an epilepsy syndrome.[28]

Epilepsy syndromes were defined as syndromes that have a typical age of seizure onset, specific seizure types and EEG characteristics and often other features which when taken together allow the specific epilepsy syndrome diagnosis.[29]

Discussion

Inherited Metabolic Diseases Presenting with Epilepsy or Seizures

More than 1600 IMDs are currently on the list of IMD classification http://www.icimd.org/; http://www.iembase.org/,[1] 600 of them (37% of all described IMDs) may present with epilepsy or seizures (Box 1). All these IMDs are rare or ultra-rare diseases, and various stages of their management require highly-specialized services and expert knowledge that goes beyond those available at primary or secondary healthcare level. IMDs presenting with epilepsy or seizures are highly heterogeneous: although involvement of central nervous system (CNS) leads to the most disabling and life-threatening symptoms, any other body system or tissue may also be affected with frequently multisystem presentation.[30,31]

CNS involvement in these diseases results in a wide spectrum of symptoms including global developmental delay, autism, behavioral problems and intellectual disability,[9] other more common neurological presentations include neuro-degenerative and movement disorders.[32,33] Epilepsy may be a dominating symptom (eg, pyridoxine-dependent epilepsy[10] and other developmental and epileptic encephalopathies (DEE) due to IMD),[34] or a more variable symptom in a subset of all patients with a given disorder (eg, succinic semialdehyde dehydrogenase deficiency).[35] In other cases, symptomatic seizures occur only during acute metabolic decompensation or develop as a consequence of brain damage during metabolic crises (eg, organic acidurias).[36] Seizures can be amenable to conventional anti-seizure drugs (ASD), although a substantial number of IMDs are associated with severe and treatment-resistant forms of epilepsy, including DEE[34] or status epilepticus.[37,38] Presentations of IMDs may be highly diverse, but metabolic etiologies should be considered in unexplained neonatal or infantile seizures, refractory seizures, seizures related to catabolic stress (eg, due to fasting, intercurrent illness or surgeries), multisystem presentation, family history or parental consanguinity.[39] The first symptoms of IMDs usually develop in children, however, adolescent or adult-onset presentations are being increasingly identified. Treatments of many IMDs have been optimized leading to an increasing number of patients who survive well into adulthood and, on the other hand, with the improvement of genetic diagnostics IMDs adult persons for whom diagnostics was previously not available, can now be studied.[40–42] Currently, almost 50% of approximately 33,000 patients in the European Reference Network for IMDs MetabERN are adults.[43]

Conventional methods for the diagnosis of epilepsy (as seizure semiology, electrophysiological or neuroradiological investigations) may sometimes provide diagnostic clues to IMDs, however, most frequently findings are non-specific.[13] Importantly, IMDs may present with any seizure and epilepsy type and any epilepsy syndrome, while some epilepsy-related brain lesions as neuronal migration defects may be due to IMD.[44] Precise diagnosis of IMD may be achieved only through metabolic and/or molecular genetic testing that is usually available in specialized laboratories only.[4,45]

Many IMDs are amenable to specific etiological treatments,[9,46] and many new potential personalized therapies are currently at various stages of clinical research and will be presumably translated into clinical practice in coming years.[8]

Box 1 Genes Associated with Inherited Metabolic Diseases Involving Epilepsy or Seizures as a Symptom

Disorders of amino acid metabolism: *AASS, ACAD8, ACADSB, ACY1, ADK, ALDH18A1, ALDH4A1, AMT, ARG1, ASL, ASNS, ASPA, ASS1, AUH, BCKDHA, BCKDHB, BCKDK, CBS, CPS1, DBT, ECHS1, ETHE1, GAD1, GCDH, GLDC, GLS, GLUD1, GLUL, GPT2, HIBCH, IVD, MCCC1, MCCC2, MLYCD, MMUT, MTR, NAGS, NAT8L, OTC, PAH, PCCA, PCCB, PHGDH, PRODH, PSAT1, PSPH, PYCR2, SLC1A1, SLC1A2, SLC1A3, SLC1A4, SLC25A13, SLC25A15, SLC6A1, SLC6A19, SQOR, SUOX.*
Disorders of peptide and amine metabolism: *GSS, ODC1, SMS, XPNPEP3.*
Disorders of carbohydrate metabolism: *ALDOB, EPM2A, FBP1, GCK, GK, GLYCTK, GYS1, GYS2, HK1, NHLRC1, PC, PCK1, PFKM, PGK1, PRKAG2, RPIA, SLC17A5, SLC2A1, SLC45A1.*
Disorders of fatty acid and ketone body metabolism: *ACADM, ACADS, ACAT1, CPT1A, CPT2, ETFA, ETFB, ETFDH, HADH, HADHA, HADHB, HMGCL, HMGCS2, SLC16A1, SLC25A20.*
Disorders of energy substrate metabolism: *ACO2, DLAT, DLD, FH, GAMT, GATM, IDH2, IDH3A, MDH2, MPC1, PDHA1, PDHB, PDHX, PDP1, SLC13A5, SLC6A8, SUCLA2, SUCLG1.*
MT-DNA related disorders: *MT-ATP6, MT-ATP8, MT-CO1, MT-CYB, MT-ND1, MT-ND3, MT-ND4, MT-ND5, MT-ND6, MT-TC, MT-TF, MT-TH, MT-TI, MT-TK, MT-TL1, MT-TN, MT-TP, MT-TQ, MT-TR, MT-TS1, MT-TS2, MT-TV, MT-TW.*
Nuclear-encoded disorders of oxidative phosphorylation: *APOPT1, ATP5F1A, ATP5F1D, ATP5MD, BCS1L, COX10, COX14, COX15, COX20, COX4I1, COX6B1, COX8A, CYC1, FASTKD2, FOXRED1, HCCS, LRPPRC, LYRM7, NDUFA1, NDUFA10, NDUFA11, NDUFA12, NDUFA2, NDUFA4, NDUFA9, NDUFAF1, NDUFAF2, NDUFAF3, NDUFAF4, NDUFAF5, NDUFAF6, NDUFB11, NDUFB3, NDUFB9, NDUFS1, NDUFS2, NDUFS3, NDUFS4, NDUFS6, NDUFS7, NDUFS8, NDUFV1, NDUFV2, NUBPL, PET100, SCO1, SCO2, SDHA, SDHAF1, SDHD, SURF1, TACO1, TIMMDC1, TMEM70, UQCC2.*
Disorders of mitochondrial cofactor biosynthesis: *BOLA3, COQ2, COQ4, COQ5, COQ6, COQ8A, COQ8B, COQ9, IBA57, ISCA1, LIAS, LIPT2, NFS1, PDSS2.*
Disorders of mitochondrial DNA maintenance and replication: *DGUOK, MPV17, POLG, POLG2, RRM2B, SAMHD1, TK2, TWNK.*
Disorders of mitochondrial gene expression: *AARS2, CARS2, DARS2, EARS2, FARS2, GFM1, GFM2, GTPBP3, GUF1, HSD17B10, IARS2, KARS1, LARS2, MRM2, MRPL12, MRPS22, MRPS34, MTFMT, MTO1, NARS2, PARS2, PNPT1, QRSL1, RARS2, RMND1, TRIT1, TRNT1, TSFM, TUFM, VARS2, WARS2.*
Other disorders of mitochondrial function: *AFG3L2, AIFM1, ATAD3A, CLPB, CLPP, DNAJC19, FBXL4, GOT2, HSPD1, HTRA2, LONP1, MDH1, MICU1, MIPEP, PMPCB, PPA2, PTRH2, RTN4IP1, SLC25A1, SLC25A10, SLC25A12, SLC25A22, TIMM50, TXN2.*
Disorders of metabolite repair and proofreading: *ACSF3, D2HGDH, L2HGDH.*
Disorders of lipid metabolism: *ABCD1, ACOX1, ALDH3A2, AMACR, BSCL2, CERS1, CERS2, CHKB, CYP27A1, DDHD2, DEGS1, DHCR24, DHCR7, EBP, ELOVL4, FA2H, FAR1, FDFT1, FIG4, HSD17B4, HSD3B7, INPP5K, LBR, LSS, MBOAT7, MFSD2A, MVK, NSDHL, OCRL, PCYT2, PEX5, PEX7, PI4K2A, PIK3CA, PIK3R2, PLA2G6, PLCB1, PTEN, SGPL1, SYNJ1.*
Disorders of lipoprotein metabolism: *VLDLR.*
Disorders of nucleobase, nucleotide and nucleic acid metabolism: *AARS1, ADA2, ADARB1, ADAT3, ADSL, AIMP1, AIMP2, AMPD2, ATIC, CAD, CARS1, CLP1, DALRD3, DPYD, DPYS, EMG1, EPRS1, FARSB, FTSJ1, IARS1, IFIH1, ITPA, KARS1, LAGE3, LARS1, NARS1, NSUN2, NT5C3A, OSGEP, POLR3A, PRPS1, PUS3, QARS1, RARS1, RNASEH2A, RNASEH2B, RNASEH2C, RNASET2, RPL10, SARS1, SNORD118, TP53RK, TPRKB, TREX1, TRMT1, TRMT10A, TSEN15, TSEN2, TSEN34, TSEN54, UBTF, UPB1, VARS1, WDR4, YARS1.*
Disorders of tetrapyrrole metabolism: *ALAD, CPOX, HMBS, PPOX, UGT1A1.*
Congenital disorders of glycosylation: *ALG1, ALG11, ALG12, ALG13, ALG14, ALG2, ALG3, ALG6, ALG9, ATP6AP1, ATP6AP2, ATP6V0A2, ATP6V1A, B3GALNT2, B3GLCT, B4GAT1, CCDC115, DHDDS, DOLK, DPAGT1, DPM1, DPM2, DPM3, EXT2, EXTL3, FCSK, FKRP, FKTN, FUT8, GMPPA, GMPPB, GNE, GPAA1, HS6ST2, LARGE1, MAN1B1, MGAT2, MOGS, MPDU1, NANS, NDST1, NGLY1, NUS1, OSTC, PGAP1, PGAP2, PGAP3, PGM1, PIGB, PIGG, PIGH, PIGK, PIGL, PIGM, PIGN, PIGO, PIGP, PIGQ, PIGS, PIGT, PIGU, PIGV, PIGW, PIGY, PMM2, POMGNT1, POMK, POMT1, POMT2, RFT1, SLC35A1, SLC35A2, SLC35A3, SLC35C1, SRD5A3, SSR4, ST3GAL3, ST3GAL5, STT3A, STT3B, TMEM165, UGDH, UGP2.*

(*Continued*)

Box 1 (Continued).

Disorders of organelle biogenesis, dynamics and interactions: *AP1S2, AP3B2, AP3D1, AP4B1, AP4E1, AP4M1, AP4S1, ARCN1, ARFGEF2, BCAP31, COG2, COG4, COG5, COG6, COG7, COG8, COL4A3BP, DNM1L, GOSR2, LYST, MFF, MICOS13, MYO5A, PEX1, PEX10, PEX12, PEX13, PEX14, PEX16, PEX19, PEX2, PEX26, PEX3, PEX5, PEX6, PISD, PNPLA8, RAB18, RAB27A, RAB3GAP1, RUBCN, SCYL2, SERAC1, SLC25A46, SPATA5, STAT2, STX11, STXBP2, TANGO2, TRAK1, TRAPPC11, TRAPPC12, TRAPPC2L, TRAPPC4, TRAPPC6B, TRAPPC9, VPS11, VPS13A, VPS13B, VPS4A, YIF1B.*
Disorders of complex molecule degradation: *AGA, ARSA, ASAH1, ASAH1, ATP13A2, CLN3, CLN5, CLN6, CLN8, CTSA, CTSD, CTSF, DNAJC5, EPG5, FUCA1, GALC, GBA, GLA, GLB1, GM2A, GNS, GRN, HEXA, HEXB, HGSNAT, IDS, KCTD7, MANBA, MFSD8, NAGA, NAGLU, NEU1, NPC1, NPC2, PPT1, PSAP, SCARB2, SGSH, SMPD4, SNX14, SPG11, SUMF1, TECPR2, TPP1, WDR45.*
Disorders of vitamin and cofactor metabolism: *ALDH7A1, ALPL, BTD, DHFR, FOLR1, GCH1, GPHN, HCFC1, HLCS, LMBRD1, MMAA, MMACHC, MMADHC, MADHC, MOCS1, MOCS2, MTHFD1, MTHFR, MTHFS, MTRR, NADK2, NAXD, NAXE, NNT, PANK2, PLPBP, PNPO, PTS, QDPR, SLC19A2, SLC19A3, SLC25A19, SLC25A42, SLC46A1, SLC5A6, SPR, TPK1.*
Disorders of trace elements and metals: *ATP7A, ATP7B, CCS, FTL, SEPSECS, SLC33A1, SLC39A8.*
Neurotransmitter disorders: *ABAT, ALDH5A1, ATAD1, CLTC, DBH, DNAJC6, DNM1, DYNC1H1, GABBR2, GABRA1, GABRB1, GABRB2, GABRB3, GABRG2, GLRA1, GLRB, GRIA2, GRIA3, GRIA4, GRIN1, GRIN2A, GRIN2B, GRIN2D, GRM1, GRM1, IL1RAPL1, KIF1A, KIF5A, KIF5C, PRRT2, SLC18A2, SLC6A5, SNAP25, SNAP29, STX1B, STXBP1, SV2A, SYN1, TBC1D24, TH, VAMP2.*
Endocrine metabolic disorders: *ABCC8, AKT2, HNF1B, KCNJ11, MC2R.*

Note: the classification of IMDs presented according to Ferreira et al[1] http://www.icimd.org/; http://www.iembase.org/.

Specific treatments include nutritional or vitamin/ cofactor supplementation therapies, relatively inexpensive and frequently highly effective treatment modalities.[47] Enzyme replacement and small molecule therapies, stem cell and solid organ transplantations, and cell or gene therapies may also provide opportunities of highly effective specific treatments. It is imperative for clinicians to have a sufficient index of suspicion for these diseases in order to identify and diagnose them in time, as early diagnosis and treatments may prevent major neurological sequelae and enable favorable outcomes.[13]

Care Experiences of Patients and Their Families

Although, to the best of our knowledge, there are no studies that specifically investigate care experiences of patients with IMDs that involve epilepsy or seizures and their families, studies of related patient groups (eg, patients with IMDs, early refractory epilepsy or epilepsy associated with intellectual disability) suggest, that both the overall organization of multidisciplinary, integrated care and various aspects of this care (eg, transition of care or care coordination) are insufficient.[18,48,49] Fragmented health and social care systems do not meet expectations and needs of patients and families, there is a lack of support in navigating complex care pathways and insufficient communication among professionals and sectors, especially at transition of care points. Due to the scarcity of knowledge and awareness about these rare diseases, patients and families may be insufficiently provided with the necessary information about the disease, its presumed course, prognosis, possible comorbidities, as well as available services and supports, including psychological support and peer support groups. Patient education, empowerment and inclusion into common decision-making is also lacking.[18,50] In some cases developed informational materials do not meet patients' and caregivers' needs in terms of content and form (eg, preferences of web-based information versus written).[51] Importantly, patients' and families' needs change along the clinical path of the disease, therefore, they have to be assessed repeatedly and addressed accordingly.[18] Caregivers of children with IMDs relate that these deficiencies are especially burdensome outside the highly-specialized settings, when encountering professionals unfamiliar with the child's disease.[52] A distinctive feature of rare diseases with metabolic and epileptic emergencies is their unpredictability and often associated uncertainty, that evokes even higher anxiety, depression and other psychological and emotional issues of caregivers. These facts associated with difficulties in decision-making demand a close communication with professionals which is sometimes felt by patients as very difficult.[17,49,50] Finally, care organization and quality of services is highly unequal across and sometimes within countries.[36,53]

The Goals of Multidisciplinary Care

Due to their multisystem, frequently life-long nature, IMDs that involve epilepsy or seizures usually induce complex long-term needs of patients and their families. The goals of integrated, multidisciplinary care are to place patients and their families at the center of care services planning in order to fully respond to their needs, to address holistically not only health-related but also other (psychological, social, educational, vocational) issues, and to ensure high-quality, accessible and effective services.[54] Summarized goals of integrated, multidisciplinary care for patients with IMDs that involve epilepsy or seizures are presented in Box 2.

Care pathways for these diseases are highly complex and diverse (Figure 1) due to several reasons: 1) Heterogeneity of IMDs that may present with epilepsy or seizures; 2) Diversity in health systems' organization and available expertise; 3) Patient and family-related factors (eg, rural vs urban living place or willingness to engage into self-management). Healthcare pathway of any rare disease consists of highly-specialized and less specialized services that may variably involve diagnostics, specific and symptomatic treatments, surveillance, rehabilitation, palliative care, cross-border care, patient empowerment, social and community services. Highly-specialized care services for rare diseases are usually provided in the Centers of Excellence (CoE) with sufficient expertise and infrastructural resources (as equipment and multidisciplinary teams of experts). These services are usually expensive, centralized and provided far away from patient's home, therefore, it is highly important to find the right balance between highly-specialized and local services: in all cases where services may be safely provided locally or require continuous provision (eg, psychological and social support), they have to be provided closer to patient's home, while ensuring appropriate specialized support when needed, empowerment of local care providers, patients and their families, and effective communication among all care providers.[53]

Comprehensive patient care includes not only healthcare services at different levels of the health system, but also other services to meet the complex needs of patients and their families, including psychological, social, educational and vocational issues, all of which pose significant challenges for care coordination.[55] While general practitioners usually lack time, knowledge and resources to ensure multipronged care coordination for patients with rare diseases, (specialist) nurse coordinators or case managers at the CoE and/ or at the primary care level are uniquely positioned to provide appropriate care coordination and management of transitions of care.[56] Trusting patient-provider relationship between nurses and patients/ families supports active communication and allows identification of priorities and barriers for integrated care and self-management, enables holistic, proactive management, continuity of care and improved patient outcomes.[56,57]

Patients with IMDs involving epilepsy or seizures are highly active healthcare users with complex trajectories across care systems and multiple transitions of care across life and disease stages (eg, transition from pediatric to adult services or transition to palliative care). Patients and families face particular challenges at these transition points.[43,58] Hence, these transitions have to be anticipated, planned, proactively prepared and discussed with the family and care providers.

IMDs involving epilepsy or seizures frequently present with epilepsy or metabolic decompensation-related emergencies, where timely treatments may determine patient's outcomes.[36,37] Management of these emergencies evoke particular challenges for families and needs particular consideration from the side of professionals: patients and their families must

Box 2 The Goals of Multidisciplinary Care in IMD Patients with Epilepsy or Seizures

- Address the needs of patients with complex care needs and their families in a holistic, comprehensive, family-centered way.
- Find the right balance between highly-specialized and locally provided services in the individual patient care plans.
- Ensure proper care coordination and communication between families and caregivers through the involvement of (specialist) nurse coordinators or case managers.
- Ensure proper management of care transitions by giving special consideration to all life stage-related (eg, transition from pediatric to adult services, pregnancy and perinatal care) and disease stage-related (eg, transition to palliative services) transitions.
- Ensure proper management of emergencies (including those related to metabolic decompensation and/or epilepsy-related emergencies).
- Provide multipronged empowerment of patients and families, including provision of required information, involvement into common decision-making, education, support for self-management, liaison with peer support groups and emotional/ psychological support.
- Exploit international collaboration (in particular ERNs) and digital technologies for accessible, cost-effective and high-quality care.

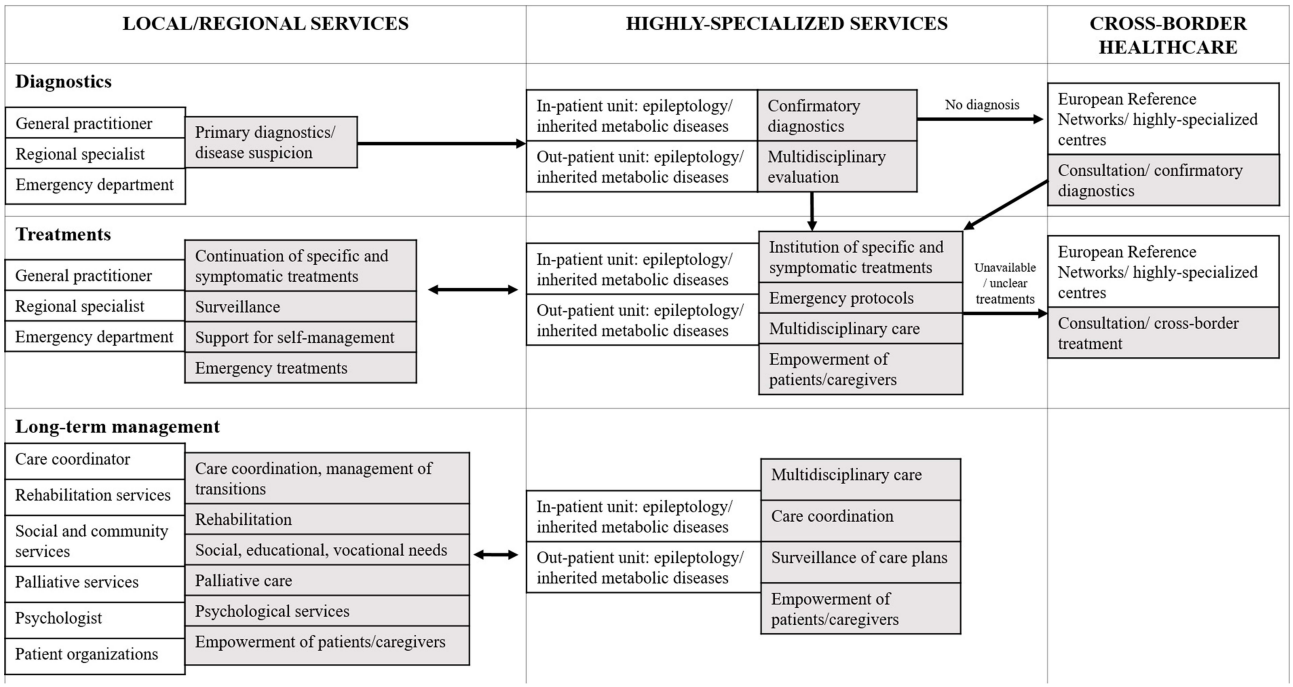

Figure 1 Care pathways for IMD patients with epilepsy or seizures.

be able to recognize the first signs of an imminent or occurring emergency, have predefined plans for immediate action (eg, oral emergency regimens for nutritional therapies, emergency seizure protocols) and knowledge on how to monitor the patient's condition, when and where to go for emergency care. These plans must also include 24h/7 days contacts for emergency specialist assistance. In some cases, the patient first goes to the nearest hospital; in such cases, it is necessary to ensure proper communication between healthcare providers and transfer of samples or patients to highly-specialized institutions when required.[36,50] Widespread availability of evidence-based emergency protocols is highly important; through international collaboration involving MetabERN, generic emergency protocols for patients with fasting intolerance in eight languages and an on-line tool for generating protocols for individual patients were developed (https://www.emergencyprotocol.net/).[59]

The greatest burden of care for IMDs that involve epilepsy or seizures always falls on the shoulders of patients and/or families, therefore, each care pathway must include empowerment that must be family-centered.[60] A lack of consideration of family's needs, including not only direct caregivers but also other family members (eg, siblings) harms their ability to provide effective care and may have detrimental effects on patient's outcomes and wellbeing of the whole family.[61] Depending on disease, organization of care in a given country and patient/ family-related factors, empowerment includes provision of required information, involvement into common decision-making, patient's and family's education, support for self-management, liaison with peer support groups and emotional/ psychological support.[18,48,52,62] Self-management is critical for individuals with epilepsy and their caregivers in order to maintain optimal physical, cognitive, and emotional health, especially in cases of refractory epilepsy or handling such challenging treatments as ketogenic diets.[63] Although high benefits of these interventions were demonstrated,[64–66] their implementation is still insufficient and requires considering many factors at the person, program, and systems levels.[67]

International collaboration is indispensable in addressing various aspects of highly-specialized care for rare diseases, therefore, 24 European Rare Diseases Networks (ERNs) for rare and complex diseases were launched in 2017.[68] These ERNs provide virtual and physical cross-border services not available in patient's country of origin, moreover, they develop highly required resources for multidisciplinary, integrated care including clinical practice guidelines, educational programmes, recommendations and tools for integrated multidisciplinary care.[43,53] Patients with IMDs that involve epilepsy or seizures may require services of several ERNs: MetabERN was developed for patients with IMDs, EpiCARE

is for rare epilepsies, ERN-RND is for rare neurological disorders, and TransplantChild may be required in cases where there is a need for liver, stem cell or other transplantations. The accessibility of ERNs must be ensured through the proper organization of care pathways and referral systems towards ERNs.[53]

Digital technologies have paved the ways for innovative eHealth services, including teleconsultations for patients and professionals, electronic tools for patient monitoring, self-management and education, and more. Although these services are particularly important for patients with rare diseases and can significantly increase the availability of highly-specialized services and expertise, they are often not properly organized, regulated and reimbursed. The pandemic significantly increased the deployment and use of these services across all healthcare areas, including epilepsy care.[69] These achievements are expected to be sustained and exploited for the benefit of patients and their families in the post-pandemic period. Besides, recent explosive spread of digital communication technologies enables liaison among rare disease patients and families dispersed across countries and continents and formation of peer support groups that may provide highly required emotional and practical support and advices, empowerment, advocacy and decrease the feelings of abandonment and isolation.[60] Therefore, impact of digital technologies on service provision and outcomes should be evaluated and exploitation of these technologies along the entire care pathway where required should be encouraged.

Life and Disease Stage-Related Issues

Neonatal Screening

Many IMDs involving epilepsy or seizures are included into neonatal screening programs when they have specific treatments that can improve significantly the prognosis. According to global standards, patients diagnosed through neonatal screening are usually provided with the full range of services that have a big impact on prognosis and quality of life, from screening to diagnosis, institution of treatment, monitoring, and long-term, multidisciplinary management.[70] However, some newborns may develop acute symptoms before the results of neonatal screening are obtained, lists of screened IMDs differ among countries, and only a subset of all IMDs presenting with epilepsy or seizures are suitable for neonatal screening.[71,72] It is therefore essential for neonatologists to know what diseases are being screened for in their country and where to get the information on IMD screening, diagnostics and expert advice on emergency treatment.

IMDs with Epilepsy or Seizures in Infancy

In some infantile-onset epilepsy syndromes, a considerable subset of patients is diagnosed with IMDs: eg, IMDs have been found in 3% to 22% of infants with West syndrome.[34] Precise genetic diagnosis in these patients may not only enable specific etiological treatments, but also provide prognostic information and guidance for antiseizure treatment. Impact on psychomotor development and cognitive function may vary between some milder developmental encephalopathies to severe epileptic encephalopathies. Clinicians must tailor care towards individual needs and realistic expectations for each affected person; those with developmental encephalopathies are unlikely to gain from aggressive antiseizure medication whilst those with epileptic encephalopathies will gain.[73]

Pediatric to Adult Transition

Transition to adult care represents a vulnerable time in the life of a patient and his/her family.[17,48,49,61] Transition as a purposeful and planned process should address manifold medical, psychosocial, educational, and vocational needs of adolescent and young adult patients as they move from a pediatric to an adult model of care. At the very least, it involves coordination of care between care providers to ensure that the adult providers have sufficient medical and other related information about the patient and his/her family and competence to provide optimal disease management. As much as it is possible, patients should acquire knowledge and skills in the domains of self-care, healthcare decision-making, and self-advocacy in such a way that will prepare them to increase their agency surrounding their healthcare needs.[74] In children with IMDs that involve epilepsy or seizures the primary care provider is usually either pediatric neurologist or metabolic pediatrician. While in transition from pediatric to adult neurologist the largest problem may be excessive anxiety of patients and/or families that is completely resolved with the proper organization of transition,[75] transition among the specialists of metabolic medicine is frequently complicated due to the lack of specialists for adult IMDs.[76] According to the survey of the ERN for IMDs MetabERN, in most European countries transition of pediatric patients and

services for adults with IMDs are insufficiently organized.[43] Expertise in adult metabolic medicine is lacking worldwide, because education on IMDs in adolescents and adults is inadequate and the specialty is mostly not formally recognized.[71] Due to the inherent phenotypic variability of adult IMDs dependent not only from genotype, but also due to the effect of environmental factors, ontogenetic changes and aging and lack of knowledge on many aspects of IMDs associated with prolonged survival and novel treatments (eg, late adverse effects of interventions and definition of new natural histories), the field of adult IMDs is still developing.[77,78]

Pregnancy and Perinatal Care

An increasing number of females with IMDs that may present with epilepsy or seizures enter reproductive age. Pregnancy and perinatal care-related issues in this group of women are dual and involve: 1) IMD-related issues, eg disease effects on fertility, teratogenic effects of a disease (as phenylketonuria) or medicines, challenges of nutritional treatments and metabolic control, worsening of an underlying maternal IMD due to pregnancy, special recommendations for breastfeeding and IMD effects on labour (as skeletal dysplasia in mucopolysaccharidoses).[79] Some IMDs of intermediary metabolism may present for the first time or exacerbate during the perinatal period (eg, urea cycle defects).[40] 2) epilepsy and ASD treatment-related issues, including teratogenic effects of some ASD, seizure control during the pregnancy and in the perinatal period and other associated issues.[80] Therefore, obstetricians – gynecologists have to be involved into multidisciplinary teams for the management of females with IMDs.

Palliative Care

Patients with life-limiting or life-threatening conditions require timely and family-centered palliative care, especially in a pediatric setting.[81] In medical terms, palliative care aims to achieve pain and symptom management, enhanced dignity and quality of life for the patients. Though comfort is often the most common goal identified, symptom identification and treatment remains challenging in nonverbal children with neurological impairments.[58] Besides, in IMDs symptom burden is usually high with neurologic, respiratory and gastrointestinal symptoms being the most frequent and most of those being difficult to treat or even intractable.[82] Another issue in IMDs, pertinent to any rare disease, is a lack of knowledge and inherent uncertainty about prognosis and medical interventions that may complicate decision-making process.[83] Noteworthy, a high number of children with metabolic diseases die in intensive care units. In these cases, an integrated model of care that combines pediatric intensive care and primary pediatric palliative care depending on the disease trajectory might be a fundamental component of the best available standard of care.[81]

Not only medical, but also ever changing social, psychological, emotional and spiritual needs of the family beyond what the primary care team can provide should be addressed.[84,85] Therefore, palliative care should be planned in advance, ideally from the moment of diagnosis, and is best delivered in a team committed to family centered care and open and reflective practice throughout the journey of a child's illness and death, including bereavement period. Quality of relationship and inclusion of a patient and his/her family into a common decision-making are the core elements of palliative care.[84,85] Families and professionals should also acknowledge the unique experiences and needs of siblings, include siblings in medical conversations and care plans when appropriate, and connect siblings to resources for informational and emotional support.[61]

In some cases, diagnosis of an IMD is only achieved post-mortem. Without a clear diagnosis the families find themselves in a very precarious situation, not least regarding end-of-life decisions. For both caregivers and health care professionals, it may be difficult to even consider palliative care because the course of the disease is not predictable Additionally, the lack of a diagnosis raises uncertainty about family planning and the risk of recurrence in future children. In spite of these uncertainties, patients and families have the same rights to receive optimized and symptom-adapted palliative care.[83]

Core and Extended Multidisciplinary Team

Due to the complexity and rarity of IMDs, general practitioners (GPs) are usually unable to provide all the necessary information, services, and support, therefore, it is highly important for patients and families to have a named physician supervising them in a highly-specialized setting and a multidisciplinary team that encompass both local/regional and

Table 1 Multidisciplinary Teams for Care of IMD Patients with Epilepsy or Seizures

Supervision	Core Multidisciplinary Team	Extended Multidisciplinary Team
Named highly-specialized physician: • Metabolic pediatrician or specialist of adult IMDs; • Pediatric or adult neurologist/ epileptologist; • Geneticist or other specialist.	• General practitioner; • Care coordinator(s); • Laboratory specialists; • Geneticist; • Dietician; • Specialized nurse; • Intensive care specialist; • Rehabilitation specialist; • Psychologist; • Social worker; • Neuroradiologist; • Neurophysiologist; • Neurosurgeon; • Etc. according to the needs.	• Neonatologist; • Obstetrician-gynecologist; • Palliative care specialist; • Pharmacist; • Etc. according to the needs.

highly-specialized settings (Table 1).[45] The specialty of this physician depends on the nature of the disease: where epilepsy or seizures is just the one of many other symptoms or occur only during acute metabolic decompensation, a supervising physician is usually a metabolic pediatrician or a specialist of adult IMDs. In some countries, specialty of metabolic pediatrician is not formalized, while in most countries specialists of adult IMDs are not available or lacking; in these cases functions of supervising highly-specialized physician may be assumed by geneticists or physicians of other specialties.[76] When the predominant symptom of IMD is epilepsy, the supervising highly-specialized physician is usually a pediatric or adult neurologist or epileptologist. These specialists - A metabolic pediatrician or other specialist in metabolic diseases, a pediatric or adult neurologist (epileptologist) - usually lead a whole multidisciplinary team that is ideally based in a dedicated CoE. The multidisciplinary team consists of core members providing the main services to patients and families: in the IMD department, these may include laboratory specialists from biochemical genetic and molecular genetics laboratory, geneticists, dietician, specialized nurse or other care coordinator, neonatologist and intensive care specialist, rehabilitation specialists, psychologists, social workers and play specialist/therapist. In the epilepsy department, the multidisciplinary core team usually consists of laboratory specialists, neuroradiologist, neurophysiologist, neurosurgeon. If necessary, the core team is complemented by other extended team specialists, eg obstetrician-gynecologist, physicians of other specialties, pharmacist, etc. The CoE for rare diseases usually carry out not only provision of highly-specialized healthcare services but also education and research and these additional functions also determine the composition of the multidisciplinary team. There is a need for staff to manage rare disease registries and biobanks, to administer research projects, to conduct clinical trials, to provide education and training and to collaborate with various research and educational institutions.

All multidisciplinary team members follow the same clinical practice guidelines (CPGs) or other evidence-based resources, develop and implement individual patient care plans, therefore, it is highly important to ensure proper communication and collaboration among the entire team. In addition, appropriate team's communication with GPs, other care providers across various levels of health and social care systems and appropriate involvement of patients and families are essential, hence, the role of a specialist nurse coordinator or other care coordinator is indispensable.

Multidisciplinary care should also involve primary care and community level: many long-term mental health, physical therapy and rehabilitation, social services for patients and families, services to address educational and vocational issues are inevitably provided at a primary or community level.[86]

Organization of Services Along the Care Pathway

Due to the heterogeneity, multisystem nature and complexity of IMDs, the need for highly-specialized services and expertise, and complex care pathways that cross various health system levels, sectoral and sometimes even national

borders, the organization of services for patients with IMDs involving epilepsy or seizures and their families is a challenging task. Although these patients are highly active users of care services and their expectations and needs often remain unmet, very little data for evidence-based governance and principles of care organization are available.[53,78] While diagnostic and treatment services are frequently provided simultaneously, precise genetic diagnosis usually establish a crucial landmark for the management of these patients.

Diagnostics

Diagnosis of IMDs requires sufficient knowledge and experience and is almost invariably obtained through the highly-specialized laboratory testing. GPs and local healthcare providers typically have neither the expertise nor the resources to diagnose IMD. Unfortunately, the primary healthcare level, which is often the first medical contact point for any patient, often lacks sufficient awareness and index of suspicion for rare diseases and health system literacy on where to refer the patient for specialized services.[87–89] IMDs are implicated with an additional diagnostic urgency due to the fact that many of them have specific etiological treatments. In order to ensure timely diagnosis and treatment and to reduce diagnostic odyssey, it is necessary to properly organize care pathways and referrals systems towards CoE and ERNs in health systems and to increase IMD awareness and education among care providers.[53]

Treatments and Long-Term Surveillance

Once a precise diagnosis has been established, individual patient's care plan must be developed that is not only evidence-based but also meets the individual needs of the patient and his or her family. Unfortunately, CPGs for rare diseases are very scarce,[90] while the awareness of and implementation of existing guidelines is clearly deficient and highly unequal across countries.[91] Fortunately, ERNs are currently intensively working on the development of novel CPGs for rare diseases and implementation of existing ones.

Depending on the nature of the disease and other factors (such as health system organization, available expertise and resources at primary and local level, patient and family empowerment, etc.), the individual care plans should include initial and follow-up examinations (laboratory and instrumental testing, consultations of specialists), disease monitoring, management of emergencies, family support, genetic counseling and testing, and expected transition points across illness and life stages.

Conclusion

Due to the heterogeneity, multisystem nature and complexity of IMDs, the need for highly-specialized services and expertise, and complex care pathways that cross various health system levels, sectoral and sometimes even national borders, the organization of services for patients with IMDs involving epilepsy or seizures and their families is a challenging task. Multidisciplinary care should place patients and their families at the center of care services planning and to respond to their complex needs, including not only health-related but also other (psychological, social, educational, vocational) issues.

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