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Adaptation of Pediatric Palliative Care Groups to Metabolic Diseases: Beyond the Pathways

Gustavo Marquezani Spolador[1]*; Rita Tiziana Verardo Polastrini[1]; Ivete Zoboli[1]; Ana Cristina Henrique[1]; Elaine Freitas[1,3]; Andréa Gislene do Nascimento[1,4]; Fernanda Monti[2]; Camila Pugliese[2,4]; Fernando Kok[2]; Silvia Maria de Macedo Barbosa[1]; Clarissa Bueno[2]

[1]Children's Pain and Palliative Care Unit, Instituto da Criança e do Adolescente do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Brazil.

[2]Department of Neurometabolic Diseases, Instituto da Criança e do Adolescente do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Brazil.

[3]Department of Social Work and Social Care, Instituto da Criança e do Adolescente do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Brazil.

[4]Department of Nutrition and Dietetics, Instituto da Criança e do Adolescente do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Brazil.

***Corresponding Author(s):** Gustavo Marquezani Spolador
Department of Pain and Pediatric Palliative Care, University of Sao Paulo, Sao Paulo, Brazil.
Email: gustavospolador@gmail.com

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Synopsis: Trajectories of inborn metabolic diseases in palliative care: Beyond the pathways.

Abstract

The Palliative Care (PC) aims to control suffering in the physical, psychological, spiritual and social spheres. The growing number of studies that emphasize the importance of PC in the field of Inborn Metabolic Diseases (IMD) reinforce the substantial frequency of these conditions in the palliative setting. However, the representation of IMD in PC is restricted to a single group of complex chronic conditions, which does not reach the complexity of these diseases. From the four pre-defined groups in pediatric palliative care, the IMD corresponding to the clinical courses were adapted. In group 1, conditions such as organic aciduria and urea cycle defects; in group 2 fatty acid oxidation disorders and MCT/GLUT; group 3 includes lysosomal, peroxisomal and CDGs; in group 4 are amino acids synthesis defects, metabolite repair, cellular processing and trafficking and mitochondrial disorders. These groups are not static, and conditions may behave with characteristics of one of them at some point in life. The proposal enables the health professionals who care for people with metabolic diseases to recognize potential patients who can benefit from palliative care.

Introduction

The interface between Palliative Care (PC) and Inborn Metabolic Diseases (IMD) remains incipient. Despite disease modifying treatment, the great majority of IMD have no cure and the surveillance resides in symptoms management and diet approach.

Keeping in mind the PC basic premise of preventing and controlling physical suffering and the multisystem presentation of many IMD, the establishment of a parallel between these two areas of health is clear. In addition to diagnosis, PC adds to disease-modifying care, when available, in assistance underlying therapy [1].

Concepts of palliative care

The PC is an interdisciplinary approach aimed at adults and children that aims to prevent and relieve the suffering in the biological, social, spiritual and psychic spheres of a disease. The PC are also intended for the patient's family, as the disease affects everyone [1].

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The diseases treated in the palliative setting are mainly complex chronic conditions, requiring progressive and continuous care early in the course of a disease, rather than solely in the end-stages, as is commonly associated [2].

Epidemiology of palliative care

According the World Health Organization (WHO), the epidemiology of Palliative Care (PC) varies considering the population age, knowing that adult group corresponds to 67,1% of all palliative care needs and the most prevalent conditions are the malignant neoplasms (28,2%), HIV disease (22,2%), cerebrovascular diseases (14,1%), dementia (12,2%) and external causes (6,4%) [1].

In the pediatric population, the number is considerably smaller compared to adults, round 7% of the total global palliative care needs and the conditions which need palliative assistance are HIV disease (29,6%), premature birth (17,7%), congenital malformations (16,2%), external causes (16%) and inflammatory diseases of the Central Nervous System (5,6%) [1].

However, it is important to consider the country in which palliative care is provided, as pathologies can change in frequency. Also based on WHO, in adults, the upper-middle income countries need more PC (38%), followed by lower-middle income (29%) and high income (24%). In pediatrics, the lower-middle income countries are the ones most in need of PC (49%), followed by low-income countries (32,4%) and upper-middle income (16%) of which Brazil is part [1].

In adult PC, a Brazilian study carried out in primary care identified the main patients eligible for this assistance as dementia (27%), cerebrovascular diseases (26%), muscular diseases (12%), other neurological diseases (11%) and congestive heart failure (10%) [2].

A recent study shows the prevalence of health condition at a Pediatric Palliative Care (PPC) clinic from a quaternary hospital in Brazil. It highlighted as more frequent pathologies epidermolysis bullosa (36.9%), neurological non-Inborn Metabolic Diseases (19.0%), IMD (14.3%), dysmorphological and chromosomal disorders (8.5%) and skeletal disorders (6.9%) [3].

Epidemiology of inborn metabolic diseases

The general prevalence of IMD varies from 1:800 to 1:2500 live births. Variation in the prevalence of these conditions is closely related to the population in which epidemiological studies are carried out. Therefore, in countries with a high degree of consanguinity there is an increase in rates of metabolic disorders [4,5].

Table 1 summarizes the results of 3 studies in different populations. Waters (2018) assessed the global prevalence of IMD over the years 1980 to 2017 using a meta-analysis. Moammar (2010) presented epidemiological data from a province in Saudi Arabia between 1983 and 2008. Applegarth (2000) estimated the diagnosis of hereditary metabolic diseases in a predominantly Caucasian population in Canada [6-8].

Table 1: Assessment of the prevalence of IMD in different populations [6-8].

IMD	Class	Prevalence (For 100.000 Live Births)		
		Waters (2018)	Moammar (2010)	Applegarth (2000)
All IMD	All	50,88	149	40
Aminoaciopathies	All	14,69	23	15,1
	Phenylketonuria	6,55	7	7,5
	MSUD	1,22	7	-
	Homocystinuria	0,41	2	-
	NKH	-	1	-
	Tyrosinemia type I	-	3	-
Organic acidurias	All	8,71	29	3,7
	Propionic	1,07	4	-
	Methylmalonic	1,68	6	-
	Isovaleric	0,51	4	-
	Biotinidase deficiency	1,64	2	-
Fatty acid oxidation disorders	All	6,51	11	-
	MCAD	5,78	1	-
	SCAD	-	2	-
	LCHAD	-	1	-
		-		
	CPT II	-	2	-
Urea cycle disorders	All	2,91	7	1,9
	Citrullinemia	-	4	-
Carbohydrates metabolism disorders	All	6,19	10	
	Galactosemia	-	10	2,8
Glycogen storage diseases	All	-	10	2,3
Lysosomal disorders	All	13,25	44	7,6
Peroxisomal disorders	All	4,13	3	3,5
Mitochondrial diseases	All	8,16	8	3,2

Inborn metabolic diseases in palliative care

The interrelationship between metabolic diseases a PC is little explored in the literature. Few studies mention palliative care as the foundation of many IMDs, since most do not have disease-modifying treatments.

The first study that highlights PC in the context of IMD dates back to 2018. Carried out in a specialized PPC unit over 44 months, an incidence of 15% of patients with IMD was observed, of which the most frequent pathologies were lysosomal storage diseases (48.2%), mitochondrial diseases (34.5%) and aminoacidopathies (7%) [9].

Also, according to Hoell *et al.*, the average referral time for patients with metabolic diseases to the PC service was 2.6 years with extensive symptomatological burden, mainly neurological, respiratory and gastrointestinal, with no statistical difference between groups with metabolic crises and those without crises. Furthermore, it points out that even for PC professionals, the trajectory of these conditions can be unpredictable, which makes decision-making processes difficult [9].

In 2021, the interaction between PC and IMD became more evident with a Turkish publication that evaluated the prevalence of metabolic diseases that were hospitalized and received evaluation by the PC team over 1 year. In this service, the IMD rate was 19.2%, with complex molecule disorders being the most prevalent (50%), followed by energy disorders (27.7%) and intoxication (22.3%) [10].

For 20 years, a PPC clinic observed the frequency of IMD, which was 14%, with patients in group 3 (complex molecules) being the most frequent (64.7%), especially sphingolipidosis. The median age of PPC referral was lower in patients with IMD compared to those without IMD. However, no difference was identified between the IMD pathophysiological groups in the time between diagnosis and PPC referral [11].

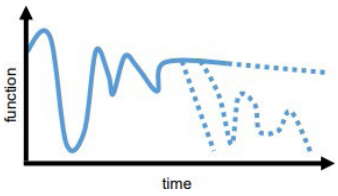
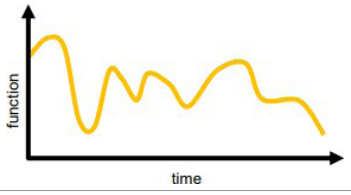
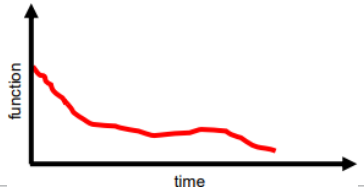
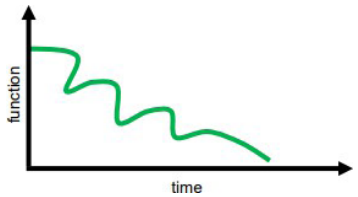
Regarding symptoms, respiratory were the most frequent, being the main responsible for the hospitalizations. Other frequent symptoms were neurological, including convulsions, hypotonia, movement disorders and spasticity. Gastrointestinal symptoms were also present with many patients (66%) who were fed through nasogastric catheter and percutaneous gastrostomy tube due to swallowing dysfunction and vomiting [10].

Discussion

With the aim of facilitating the understanding and dimension of complex chronic conditions eligible for pediatric palliative care, four indication groups were created, which are presented in table 2 [12].

Recognized as representatives of one of the groups in the field of pediatric palliative care, inborn errors have always been allocated to group 3 of chronic complex conditions. However, recognizing their broad pathophysiological characterization, as well as the course of the diseases, maintaining IMDs only in this group limits the recognition of other pathologies whose course is different from that described and which could benefit from early palliative care.

Table 2: Proposal for adaptation of pediatric palliative care groups for inborn metabolic diseases.

Group	Description	Classic examples	IMD Examples	Trajectories
1	Life-threatening conditions for which curative treatment may be feasible but can fail	Cancer, organ failures of heart, liver, kidney, transplant and children on long- term ventilation	Organic acidurias, Urea cycle disorders	
2	Conditions when premature death is inevitable; these may involve long periods of intensive disease- directed treatment aimed at prolonging life	Cystic fibrosis, Duchenne muscular dystrophy, SMA	Fatty Acid Oxidation Disorders (FAOD), MCT/ GLUT	
3	Progressive conditions without curative treatment options, where treatment is exclusively palliative and may commonly extend over many years	Inborn metabolic diseases	Lysosomal storage disorders (LSD), peroxisomal disorders (PD), Congenital disorders of glycosylation (CDG)	
4	Irreversible but non-progressive conditions causing severe disability leading to susceptibility to health complications and likelihood of premature death	Cerebral palsy, congenital infections, spina bifida	Metabolite repair defects, AA and FA synthesis defects, mitochondrial disorders, cellular processing and trafficking	

Group 1: Feasible curative treatment

In the context of pediatric palliative care, group 1 corresponds to conditions that have the possibility of curative treatment, which may fail (Figure 1). As general representatives of this group, we have congenital heart disease and cancer [12].

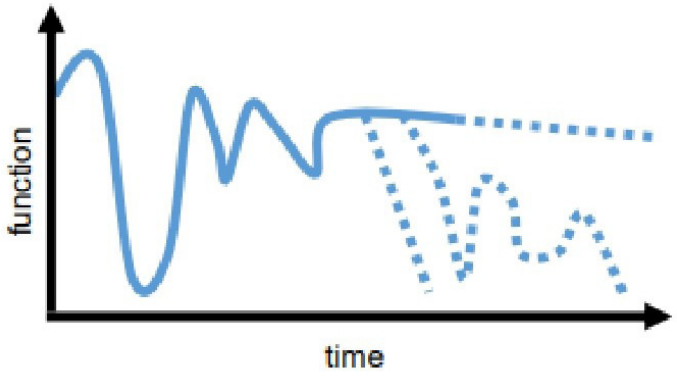


Figure 1: Trajectory of group 1 metabolic diseases eligible to palliative care.

Establishing a parallel with major errors in metabolism, some organic aciduria such as methylmalonic aciduria, in which there is the possibility of end-stage renal failure and consequently kidney transplantation, the palliative intention must prevail from the moment of diagnosis and intensify during this period.

Another important treatment in the field of intoxication disorders is liver transplantation, which constitutes an important metabolic stabilization strategy used mainly in propionic acidemia, methylmalonic acidemia and urea cycle defects [13].

Regarding this point, the transplant process involves considerable emotional burden on the patient and family, which *per se* already constitutes the field of action of palliative medicine [14].

Group 2: Long disease-directed treatment

Exploring the second group of life-limiting and life-threatening conditions in PPC, the general representatives are cystic fibrosis and Duchenne muscular dystrophy, for which prolonged intensive disease control treatment is necessary, despite new therapies and targeted drugs (Figure 2) [12].

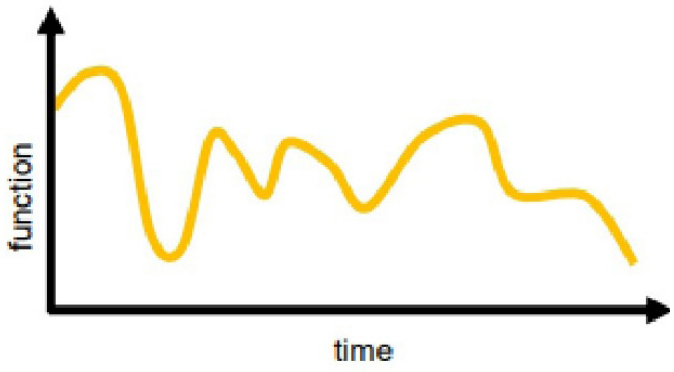


Figure 2: Trajectory of group 2 metabolic diseases eligible to palliative care.

Transposing the aforementioned concept to IMD, Fatty Acid Oxidation Defects (FAOD) such as Long-Chain 3-hydroxyl-CoA Dehydrogenase (LCHAD) deficiency involve prolonged treatment throughout life, progressing with episodes of rhabdomyolysis, retinal degeneration and peripheral neuropathy. In Medium-Chain Acyl-CoA Dehydrogenase (MCAD) deficiency, although 50% of patients remain asymptomatic, encephalopathy can occur without hypoglycemia [15].

Recent study showed the impact of FAOD on the daily life of parents and caregivers. Through a questionnaire with the care challenges of these patients, it found high disease burden of caregiver during infancy and fear of the impact of their children in career. Another important data was the moment of diagnosis. Fear, concern and sadness were the emotions more prevalent during this moment [16].

In defects of membrane energy carriers (MCT and GLUT), prolonged treatment is also a reality [17]. In MCT8 deficiency, for example, hypotonia, intellectual impairment and movement disorders and contractures can occur and there is no specific treatment. In GLUT1 deficiency, epileptic encephalopathy, movement disorders and developmental delay may improve with the ketogenic diet [18].

In this regard, parents of patients with MCT8 deficiency revealed a burden in the daily management of their children. Difficulties related to eating, limited motor milestones and sleep were the most prevalent. While during the diagnostic trajectory, late diagnosis and evaluation by many specialists were the main difficulties faced by these families [19].

Group 3: No curative treatment

Classically allocated to this group, in which there is no curative treatment to date, not all IMD present the course mentioned in figure 3.

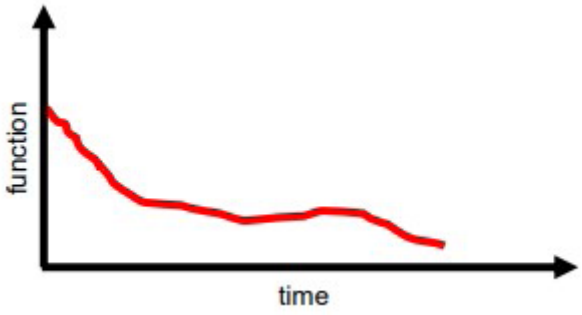


Figure 3: Trajectory of group 3 metabolic diseases eligible to palliative care.

The pathologies exposed here deserve the assistance of specialized palliative care from the moment of diagnosis, whether pre or post-natal. Admittedly, the group with the highest number of disease-modifying therapies, whether enzyme replacement therapy, bone marrow transplantation and more recently gene therapy, presents an intense burden resulting from the disease as well as the treatment [17].

The overload of symptoms for patients and caregivers involves the physical, mental, financial and social spheres. With an average of 8.6 to 16.6 hours of care for patients with lysosomal diseases, the impact on the family's quality of life is a reality [20].

Since caregiver burden is also associated with disease severity and patient burden [21], PC must be offered in parallel to the modifying treatment, reinforcing that this approach is not restricted to the end of life, but throughout life [12].

Group 4: Severe disabilities

The last group includes conditions causing severe disability leading to susceptibility to health complications and likelihood of premature death, whose main representative is cerebral palsy (Figure 4) [12].

In addition to the diagnosis of cerebral palsy, some conditions that mimic these findings are metabolic, including argi-

nase deficiency, multiple carboxylase deficiency and monoamine neurotransmitter disorders [22].

Mitochondrial disorders, cellular processing and trafficking conditions involve numerous chronic symptoms, combined with acute events, which are life-threatening [23].

From the perspective of mitochondrial diseases, 69% of patients present symptoms up to 10 years of age and are generally multisystemic [24]. In addition to the symptomatic patient, the burden on the caregiver, especially the mother, is high and poor health-related quality of life is frequent, particularly related to role limitations, vitality, and mental health, with greater levels of depression and anxiety [25].

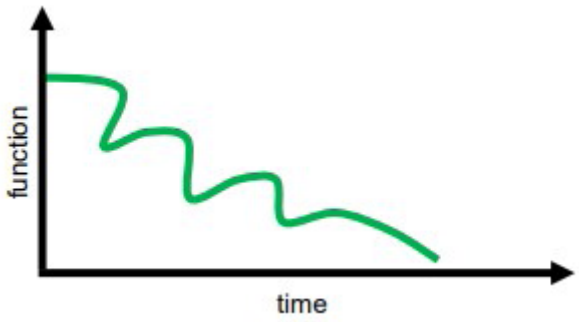


Figure 4: Trajectory of group 4 metabolic diseases eligible to palliative care.

It is important to keep in mind that the groups are not statics. Some conditions may be allocated first to the group 3 and after a procedure, for example, bone marrow transplantation; they change to the group 1 for a while.

The interface between PC and IMD is urgent, as these are conditions that present a wide range of symptoms and require a holistic approach beyond the underlying disease.

Evidently, not all IMDs will be included in the groups corresponding to their pathophysiology, as they present extensive phenotypic heterogeneity. However, this does not preclude this adaptation as a guide for health professionals who care for patients with IMD but are not familiar with palliative care.

Conclusion

These adaptation aims to provide an identification of metabolic diseases in palliative care field. Furthermore, the proposal enables the health professionals who care for people with metabolic diseases to recognize potential patients who can benefit from palliative care.

Author declarations

Ethics approval and consent to participate

The study protocol underwent rigorous scrutiny and was subsequently approved by the Ethics Committee of the Universidade de São Paulo (USP), bearing the approval number CAAE 69446222.1.0000.00681 in accordance with the 466/12 Resolution of National Health Council.

Consent for publication

Human Ethics and Consent to Participate declarations not applicable.

Availability of data and material

No clinical data were used in this article.

Competing interests

The authors Gustavo Marquezani Spolador, Rita Tiziana Verardo Polastrini, Ivete Zoboli, Ana Cristina Henrique, Elaine Freitas, Andréa Gislene do Nascimento, Fernanda Monti, Camila Pugliese, Fernando Kok, Silvia Maria de Macedo Barbosa, Clarissa Bueno declare no conflict of interest.

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Authors' contributions

GMS: Conceptualization, Formal analysis, Investigation, Resources, Writing - Original Draft; **RTVP**: Formal analysis, Investigation, Resources; **IZ**: Visualization, Supervision; **ACH**: Visualization. **EF**: Visualization; **AGN**: Visualization; **FM:** Visualization; **CP**: Visualization; **FK**: Supervision, Project administration; **SMMB**: Supervision**. CB**: Supervision, Project administration.

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