RARE NEUROLOGICAL DISEASES: AN OVERREVIEW OF PATHOPHYSIOLOGY, EPIDEMIOLOGY, CLINICAL FEATURES AND PHARMACOECONOMIC CONSIDERATIONS IN THE TREATING

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RETKE NEUROLOŠKE BOLESTI: PREGLED PATOFIZIOLOGIJE, EPIDEMIOLOGIJE, KLINIČKIH KARAKTERISTIKA I FARMAKOEKONOMSKA RAZMATRANJA U LEČENJU

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ABSTRACT

Rare diseases (RD) are serious chronic diseases affecting small number of people compared to the general population. There are between 6000 and 8000 RDs, which affect about 400 million people worldwide. Drugs used for causal treatment of RDs are called orphan drugs. RDs bear great clinical and economic burden for patients, their families, healthcare systems and society overall. There are at least two reasons for the high cost of treatment of RDs. First, there is no causal therapy for majority of RDs, so exacerbations, complications, and hospitalizations in those patients are common. The second reason is high price of available orphan drugs, which are not cost-effective when traditional pharmacoeconomic evaluation is employed. The pharmacoeconomic aspect of the treatment of RDs is especially important in the field of neurology, since at least one fifth of all RDs is composed of neurological conditions. The aim of this paper was to provide a concise overview of the pathophysiological, epidemiological and clinical characteristics of some of the most important and common rare neurological diseases, with special reference to their impact on society and economy.

Keywords: Rare diseases, Dravet syndrome, Tuberous sclerosis complex, Lennox-Gastaut syndrome, Angelman syndrome, Prader-Willi syndrome, Duchenne Muscular Dystrophy, Spinal muscular atrophy, orphan drugs, pharmacoeconomics,

SAŽETAK

Retke bolesti (RB) su ozbiljne hronične bolesti koje pogađaju mali broj ljudi u odnosu na ukupnu populaciju. Postoji između 6000 i 8000 RB, koje pogađaju oko 400 miliona ljudi širom sveta. Lekovi koji se koriste za kauzalno lečenje RB nazivaju se lekovi siročići. RB predstavljaju veliki klinički i ekonomski teret za pacijente, njihove porodice, zdravstvene sisteme i društvo uopšte. Postoji najmanje dva razloga za visoku cenu lečenja RB. Prvo, za većinu RB ne postoji kauzalna terapija, tako da su egzacerbacije, komplikacije i hospitalizacije česte kod ovih pacijenata. Drugi razlog je visoka cena dostupnih lekova siročića, koji nisu isplativi kada se primene tradicionalni principi farmakoekonomske evaluacije. Farmakoekonomska aspekt lečenja RB je naročito značajan u oblasti neurologije, s obzirom da je najmanje jedna petina svih RB sastavljena od neuroloških stanja. Cilj ovog rada bio je da se pruži sažet prikaz patofizioloških, epidemioloških i kliničkih karakteristika nekih od najčešćih retnih neuroloških bolesti, sa posebnim osvrtom na njihov uticaj na društvo i ekonomiju.

Ključne reči: retke bolesti, Dravetin sindrom, Tuberozno skleroza kompleks, Lenoks-Gastoov sindrom, Angelmanov sindrom, Prader Willijev sindrom, Dišenova mišićna distrofija, Spinalna mišićna atrofija, lekovi siročići, farmakoeconomija.

INTRODUCTION

Rare diseases (RD) are serious chronic diseases affecting small number of people compared to the general population (1). Since there is geographical variation of prevalence, not all RDs are considered as such in various regions of the world (2). According to European Union Regulation on Orphan Medicinal Products, a disease is considered as being rare when its prevalence is 5 per 10000 or less (3). On the other hand, in the United States a rare disease is one that affects less than 200,000 people (4). There are between 6000 and 8000 RDs, which affect about 400 million people worldwide (1). In about 80% of cases, RDs have genetic origin, while the other causes of RDs can be classified as immunological, oncological and toxicological (5).

RDs bear great clinical and economic burden for patients, their families, healthcare systems and society overall (6), because these conditions usually require complex multidisciplinary treatments. Despite significant progress in recent years, even 95% of RDs still do not have specific, causal therapy (7). Drugs used for causal treatment of RDs are called orphan drugs (8). Although pharmaceutical companies receive various incentives for the development of orphan drugs, such as financial support, tax credits, and extended market exclusivity, they keep high prices of orphan drugs, excusing themselves with a necessity to recoup the costs of their development (9). With an annual rate of 6%, the global orphan drugs market has grown dramatically in recent years, from \$ 54.5 million in 2005 to \$ 81.8 million in 2011 (9). Although traditional approach for the assessment of cost-effectiveness cannot be applied in the case of orphan drugs, due to the principle of equality or non-discrimination (10), there is a lot of controversy and mistrust regarding the high prices of orphan drugs (9). This concern is particularly pronounced in neurology, since at least one fifth of all RDs is composed of neurological conditions (11); for their treatment more than 200 orphan drugs have been approved so far (12).

The aim of this paper was to provide a concise overview of the pathophysiological, epidemiological and clinical characteristics of some of the most important and common rare neurological diseases, with special reference to their impact on society and economy.

DRAVET SYNDROME

Dravet syndrome (DS), previously known as severe myoclonic epilepsy of infancy (SMEI), is rare genetic form of epileptic encephalopathy which usually manifests during the first year of life (13,14). Pathophysiologically, DS belongs to the group of channelopathies, because in more than 80% of cases it occurs as a result of mutations of gene encoding sodium voltage-gated channel alpha subunit 1 (SCN1A gene), although approximately 20% of SCN1A mutation carriers do not have a developed DS (15). Rarely, atypical clinical forms of DS may be associated with other genetic mutations, such as SCN2A, SCN8A, GABRA1, GABRG2, PCDH19, STXBP1, and SCN1B (16). DS usually begins in

the first year of life with prolonged, generalized clonic or hemiclonic seizures, while the other types of seizures, such as myoclonic, focal and atypical absence seizures, occur between the first and fourth year of life (17). Patients with DS also acquire speech impairment, ataxia, hypotonia, sleep disturbances, the developmental id delayed and there is higher risk of premature mortality (18,19). DS is considered as a rare condition with an estimated prevalence 1-9/100000 (20) and incidence between 1 in 15000 and 1 in 40000 live births (21,15).

There is currently no causal therapy for DS. Modern treatment of DS includes the use of symptomatic, anticonvulsant therapy with the aim of reducing the frequency of seizures and improving the quality of life of patients (22). First line anticonvulsant drugs include clobazam and valproate, while sodium channel blockers, such as phenytoin, carbamazepine and levetiracetam, are contraindicated in DS. However, seizures in DS are highly resistant to standard pharmacotherapy, even in the case of anticonvulsant combinations (23). Therefore, in recent years, Food and Drug Administration (FDA) has approved the use of cannabidiol, stiripentol and fenfluramine for the treatment of seizures associated with DS in patients 2 years old, and older, mostly as an add-on therapy to first-line anti-convulsants clobazam and valproate (24-26).

If compared to other drug-resistant epilepsies, DS is associated with lower quality of life and higher direct healthcare costs (27). Burden-of-illness study conducted in Germany showed that total annual direct health care costs, including allowance for care, per patient were above €24,000 (28). In USA, direct healthcare costs associated with DS are estimated to be higher than \$27,000 per year per patient, while indirect costs consisting of additional time spent by DS caregivers were above \$80,000 (20). Cost-utility studies showed that, from the perspective of the Canadian healthcare payer, stiripentol was not cost effective when used for the treatment of DS (29), while adjunctive cannabinoid oil was cost-effective when compared with clobazam and valproate alone for children with DS (30).

TUBEROUS SCLEROSIS COMPLEX

Tuberous sclerosis complex (TSC) is a rare, autosomal dominant genetic disorder characterized by the occurrence of multiple benign tumors in different organs (31,32). This rare disease is a result of mutations in either TSC1 gene located on chromosome 9 encoding protein called hamartin, or TSC2 gene located on chromosome 16 and producing the protein tuberlin (33). Mutations of these genes result in decreased synthesis of hamartin and tuberlin, causing excessive activation of mTOR (mechanistic target of rapamycin) pathway. Overactivation of mTOR leads to abnormal cell differentiation and development, resulting with the occurrence of non-cancerous (benign) tumors in various organs (32,33). Clinical manifestations of TSC have great phenotypic variability (34), but in most patients the central nervous system is

predominantly affected (32). In more than 90% of TSC patients there are structural CNS lesions in the form of cortical tubers, subependymal nodules (SEN) or subependymal giant-cell astrocytoma (SEGA) (32). Epilepsy is the most common and clinically challenging manifestation of TSC, affecting approximately 85% of TSC patients. Seizures commonly include epileptic spasms and focal seizures, although almost any seizure type can occur in individuals with TSC (35,36). Patients with TSC are also at high risk of developing a range of behavioral, psychiatric, intellectual, neuropsychologic, and psychosocial difficulties, called as tuberous sclerosis-associated neuropsychiatric disorders (TAND) (37). The most common non-neurological manifestations of TSC are various skin abnormalities, renal angiomyolipomas and lung lesions (32). Annual incidence rate of TSC is estimated at approximately 1 per 18,000 live births (38), while prevalence ranges from 1 to 5 per 10,000 (39,40).

Several drugs are available for symptomatic treatment of TSC; in the first place, vigabatrin was approved by FDA as the first-line treatment of infantile spasms in TSC (41). In addition to inhibition of gamma aminobutyric acid (GABA) transaminase, vigabatrin also acts as an inhibitor of mTOR, which explains its effectiveness in treatment of seizures associated with TSC (42). However, the rate of vigabatrin-resistant seizures is high in patients with TSC (32), and in 2018 FDA approved everolimus for adjunctive treatment of adult and pediatric patients aged 2 years and older with TSC-associated partial-onset seizures (43). Everolimus inhibits mTOR and could be considered as a targeted treatment (44). It is also approved for the treatment of renal angiomyolipoma not requiring immediate surgery, and subependymal SEGA in patients with TSC (45,46). The last approved drug for treatment of seizures associated with TSC was cannabidiol (in July 2020), in patients one year of age and older (47). In addition to the pharmacological treatment, there are other treatment options for seizures associated with TSC, that include surgery, a ketogenic diet, and vagus nerve stimulation (32).

Similar to patients with DS, TSC patients have increased burden-of-illness compared with the general population and patients with many other chronic diseases (48,49). Mean annual total direct costs in Germany were estimated at €25,808, wherein the greatest costs come from the use of mTOR inhibitors, whose annual use requires €17,432 (50). On the other hand, total annual indirect costs are estimated at €1,2696, but €7100 are consequence of inability to work (50). Patients with TSC experience moderate-to-high levels of pain or discomfort, anxiety and depression (51), whereby the quality of life is especially reduced in individuals with pharmaco-resistant epilepsy associated with TSC (52).

LENNOX-GASTAUT SYNDROME

Lennox-Gastaut syndrome (LGS) is rare, but severe form of childhood-onset epileptic encephalopathy characterized by multiple types of seizures and cognitive impairment (53). In approximately 75% of cases, LGS has an identifiable

cause (54). The most common causes that contribute to development of LGS are congenital infections, infections of the CNS such as encephalitis or meningitis, brain injuries and developmental brain malformations (55). Children with previous history of West syndrome and TSC could also develop severe forms of LGS (56). No underlying cause can be identified in 25% of patients with idiopathic or cryptogenic form of LGS characterized by a later onset of seizures (55). Although the cause of LGS is known in most patients, the exact pathophysiological mechanism leading to the occurrence of seizures in patients with LGS is unknown. The most common types of seizures in patients with LGS are tonic and atonic (57). About two thirds of patients with LGS have at least one episode of nonconvulsive status epilepticus during lifetime (57,58). In addition to epilepsy, majority of children with LGS develop intellectual disability, behavioral and psychiatric problems (58). LGS accounts for 1-2% of all epilepsy types (59), and 2-5% of childhood epilepsy (59,60). The estimated incidence of LGS is 0.1-0.28 per 100,000 (54). The lifetime prevalence at the age of ten is about 26 per 100,000 (54).

Several antiepileptic drugs have been approved for the treatment of LGS including valproate, clobazam, felbamate, lamotrigine, rufinamide and topiramate (55). Valproate is considered to be the first-line therapy, due to its multiple mechanism of action and high efficacy both in generalized and focal seizures, while lamotrigine and topiramate are effective alternatives (61). However, seizures in LGS patients are highly resistant even to combinations of anticonvulsants, so adequate seizure control with resolution of cognitive and psychosocial dysfunction is rarely achieved (61). In order to overcome high rate of resistance of seizures to conventional antiepileptic drugs, oral solution of cannabidiol has recently been approved for the treatment of LGS. Cannabidiol is approved as add-on therapy of seizures associated with LGS in conjunction with clobazam, for patients 2 years old, and older (62). Besides, encouraging preliminary results of a phase III, randomized, controlled study showing satisfactory efficacy and safety of fenfluramine in the treatment of LGS, have recently been presented, suggesting that fenfluramine may soon be approved for use in this indication (63,64).

Patients with LGS use healthcare services more often, and make higher costs than patients without epilepsy (65). Total annual healthcare costs in LGS patients before cannabidiol use was estimated at \$65,000 (65). Patients with LGS on additional cannabidiol therapy have \$35,000 higher healthcare costs. Preliminary analysis did not prove cost-effectiveness of cannabidiol as add-on therapy in patients with LGS (66).

ANGELMAN SYNDROME

Angelman syndrome (AS) is genetic neurodevelopmental disease characterized by severe physical and learning disabilities (67). It occurs as a result of various genetic mutations and deletions of the maternally expressed and paternally imprinted ubiquitin protein ligase E3A (UBE3A) gene encoding

enzyme called ubiquitin protein ligase E3A. These genetic variations lead to loss of the function of the enzyme and the accumulation of ubiquitin-selected proteins in the brain causing tissue damage (67,68). Patients with AS suffer from severe intellectual disability, speech impairment, motor dysfunction, seizures, and autism. These children have happy and smiling facial expression with a protruding tongue. Microcephaly is common and is not noticed immediately after birth, but before the third year of life in almost all patients (69). The loss of function of UBE3A gene subsequently leads to reduced activation of extra synaptic GABA A receptors and attenuation of tonic inhibition, producing seizures in almost 80% of AS patients (70). Besides seizures, movement disorders and gastrointestinal problems are also common (67,69). AS is rare condition that occurs in one in 15,000 live births or 500,000 people worldwide (71).

There is no approved causal therapy for AS, so current treatment is based on supportive therapy (67). Epilepsy treatment involves use of conventional antiepileptic drugs. Although valproate and clonazepam are the most-commonly prescribed antiepileptic drugs in AS, lamotrigine, levetiracetam and clobazam are more effective for the treatment of seizures associated with AS. Non-pharmacological treatments, such as ketogenic diet and vagal nerve stimulation, can also be used in patients with AS (72). Gaboxadol (OV101), an experimental, highly selective orthosteric agonist that activates δ -subunit-containing extra synaptic GABA A receptors, did not show statistically significant efficacy in changing score on the clinical global impression-improvement-Angelman syndrome scale (73). Antacids, proton-pump inhibitors or H2 blockers can be used for the treatment of gastrointestinal reflux in children with AS syndrome, while in the case of constipation, a diet rich in fiber and laxatives are advised. Melatonin showed high efficacy for the treatment of sleep disorders in patients with AS. For motor delay treatment physiotherapy, orthotics, and occupational therapy are required, while speech and language therapy is used for improvement of speech and communication (74).

Healthcare burden is high for AS patients and their families, because this condition requires high rates of healthcare resource utilization and supportive therapy utilization (75). About 86-96% of patients with AS requires physical, occupational and/or speech therapy (75). Hospitalizations are common in patients with AS and significantly contribute to the total cost of treatment. *Domínguez-Berjón et al.* (76) showed that 86% of AS patients had at least one hospitalization. The most common reasons for hospitalization in patients with AS are seizures, lower respiratory infections and surgery. In study of *Khan et al.* (75) 57% of individuals with AS had at least one surgery before requirement in study.

PRADER-WILLI SYNDROME

Prader-Willi syndrome (PWS) is rare genetic neuroendocrine disorder characterized by lethargy, hypotonia, hormone deficiency, feeding difficulties and developmental delay (77). It is caused by inexpression of genes inherited from the

paternal chromosome 15q11-q13 region. The most common cause of PWS is paternal 15q11-q13 deletion which occurs in approximately 70% of patients with this syndrome. Maternal uniparental disomy 15 or both 15s from the mother is the second most common cause of PWS, affecting 25% of patients with the syndrome. Finally, in small number of patients (1-3%) PWS is associated with the defects in the imprinting center which controls the expression of imprinted genes in this chromosome region (78). Clinical manifestations of PWS vary with age, and mostly are non-specific (79). Neonates with PWS are often hypotonic. The infantile hypotonia in PWS usually results with feeding difficulties and failure to thrive, requiring assisted feedings with nasal gavage or gastrostomy tube (79). Craniofacial anomalies, such as dolichocephaly, almond-shaped eyes, a thin upper lip, a narrow minimal frontal diameter, are also common (78). PWS is particularly characterized by endocrine and metabolic disorders, which arise due to hypothalamic dysfunction, and include growth hormone deficiency, central adrenal insufficiency, hypogonadism, hypothyroidism, hyperphagia, obesity and diabetes mellitus (80). Developmental delay, seizures, behavioral problems and autism spectrum disorders are also common in children with PWS (78). The estimated prevalence of PWS is 1 in 10,000 to 20,000 individuals with approximately 400,000 affected individuals worldwide (81,82).

Management of PWS requires multidisciplinary approach and the participation of geneticists, endocrinologists, nutritionists, pulmonologists, as well as physical, occupational, and speech therapists (83). Higher fat/lower carbohydrate diet focused on restriction of calories is advised (84). Growth hormone is recommended in patients with PWS as early as at the time of diagnosis (85). Human chorionic gonadotropic hormone is used in PWS patients with lower testicle position (85). Testosterone is approved for PWS patients older than 15 years for treatment delayed puberty, while transdermal patches of estrogen is used in females with PWS for hypogonadism (85). Antidepressants, antipsychotics and antiepileptic drugs are used for treatment of psychiatric conditions in PWS patients (83). Efficacy of tesomet, fixed-dose combination therapy of tesofensine (a triple monoamine reuptake inhibitor) and metoprolol in treatment of PWS and hypothalamic obesity, will be examined in Phase 2b study (86).

PWS is a significant health-related problem from a social perspective and has a significant impact on quality of life both for PWS patients and their caregivers (87,88). *López-Bastida et al.* (87) estimated that average annual costs per patient with PWS in Europe ranged from €3937 to €67,484, with direct healthcare costs somewhere between €311 and €18,760, and direct non-healthcare costs between €1269 and €44,035; labor productivity is decreased, adding to total costs from €0 to €2255. In France, indirect costs resulting from loss of productivity were estimated at €32,542 for adult patients with PWS (88).

DUCHENNE MUSCULAR DYSTROPHY

Duchenne Muscular Dystrophy (DMD) is rare autosomal-recessive, progressive neuromuscular disease characterized by weakness and atrophy of the muscles (89). It is caused by mutations of DMD gene located on X chromosome encoding protein dystrophin. These mutations lead to a decrease in dystrophin production, resulting with loss of integrity of myofiber membrane and muscle necrosis. Destroyed muscle tissue become replaced by fibrous connective tissue and fat, leading to degeneration of skeletal and cardiac muscle (90). DMD occurs almost exclusively in boys, affecting approximately 1:3500 to 1:6000 live male births and 1:500,000,000 female births (91). DMD usually becomes apparent early during childhood, with muscle weakness and wasting, starting from proximal limb muscles. As the disease progresses, distal muscles of legs, forearms, neck and trunk become affected. Patients with DMD have reduced bone density and an increased risk of osteoporosis and fractures. By the time of adolescence, these patients develop complications such as neuromuscular scoliosis, restrictive lung disease, obstructive sleep apnea, cardiomyopathy and gastrointestinal dysmotility (92,93). Stationary cognitive dysfunction, attention deficit and autistic spectrum disorder are also common in boys with DMD (94).

Management of patients with DMD is complex and involves participation of physical, psychosocial and drug therapy. Moderate exercise including swimming, cycling, and low-resistance strength training is advised in DMD patients (95). Corticosteroids are gold-standard of management, and are recommended to all patients with DMD (96,97). Two corticosteroids used in DMD patients most frequently are prednisone/prednisolone and deflazacort (96). In children with DMD 10 years of age and older, initiation of angiotensin converting enzyme inhibitor or an angiotensin receptor blocker is recommended (98). Psychosocial therapy is recommended for the treatment of psychiatric and problems with behavior, while pharmacotherapy should be used with caution due to possible adverse effects (96). In addition to symptomatic therapy, the FDA in the past few years approved 3 antisense oligonucleotides: eteplirsen, golodirsen and viltolarsen, for the treatment specific types of DMD (96). Eteplirsen is approved for the treatment of DMD in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping, while golodirsen and viltolarsen are approved in DMD patients with confirmed mutation of the DMD gene that is amenable to exon 53 skipping (96).

DMD is associated with a significant economic burden with many different costs (99,100). *Cavazza et al.* showed that average cost of DMD patients is approximately ten times higher compared to the overall population (99). The average annual cost per person in 2012 ranged from €7657 in Hungary to €58,704 in France. Direct non-medical costs accounted for the largest share of total costs, ranged from 64% in Germany to 89% in Hungary and United Kingdom (99). *Landfeldt et al.* showed that mean annual direct medical cost per patient with DMD was \$11,240, \$7,300, \$15,940, and

\$28,590, for German, Italian, UK, and US patients, respectively (100).

SPINAL MUSCULAR ATROPHY

Spinal muscular atrophy (SMA) is a group of severe neuromuscular disorders characterized by degeneration of alpha motor neurons in the spinal cord, resulting in progressive muscle atrophy, weakness and paralysis (101,102). The most common form of SMA is due to homozygous disruption of survival motor neuron (SMN1) gene localized at chromosome 5q, while non-SMN1-related SMA is present in less than 5% of infantile SMA and it is characterized by anterior horn cell degeneration (103). SMA is divided to 4 types based on the age of onset and maximum motor function achieved. SMA type 1 includes very weak infants with reduced fetal movements in utero, inability to sit independently and short survival time (102,104). Type 2 of SMA includes non-ambulant patients able to sit but unable to walk independently, while SMA type 3 refers to ambulant patients with childhood onset of disease (102). Finally, SMA type 4 is the adult-onset form of disease including patients with proximal muscular weakness and hypotonia who are able to walk in adulthood (101). The estimated incidence of SMA is 1:11,000 live births (105), while prevalence of SMA ranges from 1-9 per 100,000 (106).

Patients with severe forms of SMA often require pulmonary support in the form of noninvasive ventilation. In addition, gastrointestinal surgery, such as laparoscopic gastromy and Nissen fundoplication, is often performed in those patients. Also, the treatment of patients with SMA requires active participation of both orthopedists and physical medicine specialists (107). However, in the recent years there have been tremendous improvements in multidisciplinary clinical care of SMA patients, since new treatment options have been approved (108). Nusinersen is antisense oligonucleotide that promotes functional SMN2 production and thereby increases the amount of functional SMN protein produced. It showed favorable long-term benefit-risk profile both in SMA patients with infantile-onset and later-onset (109). In 2019 FDA approved onasemnogene abeparvovec as the first gene therapy approved to treat children less than two years of age with SMA (110). It is an adeno-associated viral vector-based therapy delivering a functional copy of the SMN1 gene to the motor neurons through a single intravenous infusion (111). Finally, in 2020 FDA approved risdiplam, orally administered, survival motor neuron 2 (SMN2)-directed RNA splicing modifier, for the treatment of SMA in adults and children 2 months of age and older (112).

SMA is another rare neurological disease with tremendous burdens for patients, their families, caregivers and society. Before the advent of novel drugs, the estimated annual outpatient cost for infantile SMA was approximately \$55,538, while annualized inpatient cost was \$100,000 per infantile SMA patient (113). Nusinersen costs \$118,000 per vial and the annual cost of treatment with it ranges from \$354,000 to \$708,000 for the first year of the treatment (114).

It was not cost-effective in Sweden in 2017, but it still gained reimbursement for pediatric patients with SMA type I-III (115). Priced \$2.125 million for a single dose, onasemnogene abeparvovec is the most expensive drug on the market (116). However, since it is one-time therapy, onasemnogene abeparvovec has cost-effectiveness advantage over the chronic, lifetime treatment of SMA (117).

In Table 1 prevalence and mean annual cost of treatment for some other rare neurological diseases are shown.

CONCLUSION

RD impose high economic and social burden for patients, caregivers and society overall. This particularly applies to rare neurological diseases that are mostly chronic and require long-term pharmacotherapy. There are at least two reasons for the high cost of treatment of RDs. First, there is no causal therapy for majority of RDs, so exacerbations, complications, and hospitalizations in those patients are common. The second reason is high price of orphan drugs, which are not cost-effective when traditional pharmacoeconomic evaluation is employed. However, humanitarian and egalitarian principles of healthcare require supporting research of specific drugs for treatment of RDs. Causal therapy of RD could be cost-effective in long-term, through improvement of the general condition of patients, reduction of the number of hospitalizations and decrease of the burden on caregivers and society.

Table 1. List of selected rare neurological diseases with estimated mean annual cost of treatment per patient

Disease	Estimated prevalence(/100,000)*	Estimated mean annual cost of treatment per patient	Country	Reference
Becker muscular dystrophy	1.53	€39,060	Germany	Schreiber-Katz et al. 2014 (118)
Guillain-Barré syndrome	3.5	\$318,966	United States	Frenzen 2008 (119)
Chronic inflammatory demyelinating polyradiculoneuropathy	3.7	£22,085	England	Mahdi-Rogers et al. 2014 (120)
Multifocal motor neuropathy	1.5	£22,812	England	Mahdi-Rogers et al. 2014 (120)
Amyotrophic lateral sclerosis	3.85	\$30,934	United States	Larkindale et al. 2014 (121)
Myotonic dystrophy	6.7	\$18,236	United States	Larkindale et al. 2014 (121)
Fragile x syndrome	32.5	€4951	Hungary	Chevreul et al. 2016 (122)
		€21,586	Italy	
		€31,008	Spain	
		€35,737	France	
		€58,862	Sweden	
Huntington disease	2.7	£21 605	United Kingdom	Divino et al. (2013)
Rett syndrome	10	\$21,158	Australia	Hendrie et al. 2014 (124)

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