Endocrine (2021) 71:626–633
https://doi.org/10.1007/s12020-021-02622-3

MINI REVIEW

Collaboration for rare diabetes: understanding new treatment options for Wolfram syndrome

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Received: 19 November 2020 / Accepted: 9 January 2021 / Published online: 1 February 2021

Abstract

Background Wolfram Syndrome is a very rare genetic disease causing diabetes mellitus, blindness, deafness, diabetes insipidus, and progressive brainstem degeneration. Neurologic symptoms of affected patients include ataxia, sleep apnea, loss of bladder control, dysphagia, loss of taste, and accompanying psychiatric symptoms as a sign of progressive neurodegeneration. Its genetic cause is mainly biallelic mutations of the Wolframin endoplasmatic reticulum transmembrane glycoprotein gene Wfs1. These result in increased ER stress, which in turn induces apoptosis and leads to the depletion of the corresponding cells and a loss of their physiological functions. Though diabetes mellitus is mostly treated by insulin, there is still no proven cure for the disease in general. It leads to premature death in affected individuals—usually within the 4th decade of live.

Current research and treatment trials Clinical studies are currently being conducted at various locations worldwide to test a therapy for the disease using various approaches.

Potentail of virtual netowrking As rare diseases in general represent a major challenge for individual clinicians and researchers due to the rarity of diagnosis, the lack of evidence and of value of existing research, international cooperation, coordination and networking leading to an alignment of different stakeholders is necessary to support patients and increase knowledge about these diseases, like wolfram syndrome.

Conclusion ENDO-ERN and EURRECA are two EU-funded networks that aim to promote knowledge sharing, education and research on rare endocrine diseases.

Keywords Wolfram syndrome · Rare disease network · Monogenetic diabetes · Clinical research collaboration · ENDO-ERN

Introduction

Wolfram Syndrome (WFS; OMIM #222300) is a rare genetic disease. Affected patients suffer from diabetes mellitus, diabetes insipidus (DI), blindness, impaired hearing, and progressive neurodegeneration, which targets the brainstem and cerebellum. Neurologic symptoms of WFS patients include ataxia, sleep disturbances, loss of bladder

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control, dysphagia, and accompanying psychiatric symptoms as a sign of progressive neurodegeneration. It currently still has a poor prognosis leading to premature death usually within the 4th decade of live due to respiratory failure as a consequence of progressing degeneration of the brain stem area in most cases. Its genetic cause is mainly a biallelic mutation of the *Wfs1* gene, which is located on chromosome 4 and encodes for a protein called wolframin. It is located within the endoplasmatic reticulum (ER), an organelle which plays an important role in the regulation of the intracellular calcium amount and in protein processing and folding. The inheritance pattern is autosomal recessive.

ENDO-ERN is a European Reference Network, which concentrates on rare hormonal diseases. Its main task is the improvement of medical supplies in rare endocrine disorders. It represents a European wide interconnectedness in order to promote knowledge sharing to counteract the uneven distribution of specialized medical knowledge and unequal healthcare provision of people suffering from rare endocrine diseases. It is structured by an equal contribution of pediatric and adult health care providers, who are trained in endocrinology. It is divided in eight subcategories of endocrine umbrella terms, called "Main Thematic Groups" (MTG), like MTG3: genetic disorders of glucose and insulin homeostasis. ENDO-ERN is linked to EuRRECA a Europe-wide registry for rare endocrine diseases.

In this article we provide and discuss new research approaches for the treatment of WFS and reflect the benefit of a collaboration for improving knowledge on treatment approaches, their feasibility in consideration of the rarity of the disease, especially within a well-known European wide, well-structured operative interface like ENDO-ERN and EuRRECA.

Pathogenesis

WFS1, a gene, which is located on chromosome 4p16, is responsible for an important number of patients suffering from WFS. Its product, a transmembrane glycoprotein named wolframin, is located primarily in the ER [1]. This cellular organelle harbors the largest intracellular storage for Ca^{2+} ions, ensures the correct folding, and post-translational modification of proteins. It takes part in several physiological processes, such as post-prandial insulin synthesis within the ER in response to food uptake [2]. In pathological conditions like inflammatory diseases the physiological function of ER can be affected by toxins or cytokines, leading to a condition called ER stress, in which the finely tuned mechanisms of the conventional ER function are affected and an accumulation of misfolded proteins occurs, which causes irreversible damage to the cell leading to apoptosis [3–5]. Known *Wfs1*-mutations impair the ER function, lead to ER stress, and cell apoptosis, especially in pancreatic ß-cells, which then lead to the diagnosis of non-immunologic diabetes, the usual onset of the disease [6–8].

According to the human protein atlas *WFS1* has a low tissue specification and is detected in numerous tissues (https://www.proteinatlas.org/ENSG00000109501-WFS1/tissue). However its amount is elevated in brain tissues as the allocortex, amygdala, hippocampus, brain stem area, and olfactory bulb [9, 10], in pancreatic islets of Langerhans [11], other endocrine tissues like the parathyroid gland, cells in seminiferous ducts of testis, placenta derived trophoblastic, renal tubular cells, and in the heart [12].

Common clinical presentations

WFS is also known as DIDMOAD, the acronym of DI, **D**iabetes **M**ellitus, **O**ptical **A**trophy, and **D**eafness which represent the cardinal symptoms. These are infrequently accompanied by growth retardation, urologenital disorders like testicular atrophy, neurogenic bladder disorders, hydronephrosis, hypothyroidism, sleep disturbances, neurologic symptoms [13]. DM could be revealed as the most common clinical complication of WFS (98.21%), followed by optical atrophy (OA) in 82.41%, deafness caused by progressive sensorineural hearing loss in 48.21%, DI in 37.76%, and neurological complications in 17.09% respectively in a study regarding 412 individuals with WFS [14]. WFS is a disease without any cure, which leads to premature death in the 4th decade in affected people [15].

The clinical course is usually characterized by a precise chronological order of the different symptoms, starting with non-immunologic insulin dependent diabetes mellitus at the age of 6 [16]. Although not all pathologic pathways can be described exactly, its onset seem to reflect the degeneration of pancreatic ß cells by ER stress, which lead to an early insulin dependence. However, in contrast to patients with type 1 diabetes (T1D), ketoacidosis is a rare complication in WFS patients and remission period is usually elongated when compared to T1D. In addition diabetes in WFS is characterized by a reduced insulin need, lower HbA1C, and a decreased frequency of microvascular complications, when compared to T1D [15, 17].

Optical atrophy, a condition which becomes symptomatic through defect peripheral vision followed by a loss of color vision, appears at the mean age of 11 years [15, 16, 18].

Diabetes insipidus (DI), which affects about 75% of WFS patients, usually occurs at the age of 14 years. DI is a well-known clinical component in WFS patients, which is usually well controlled, following the normal guidelines of DI management [13].

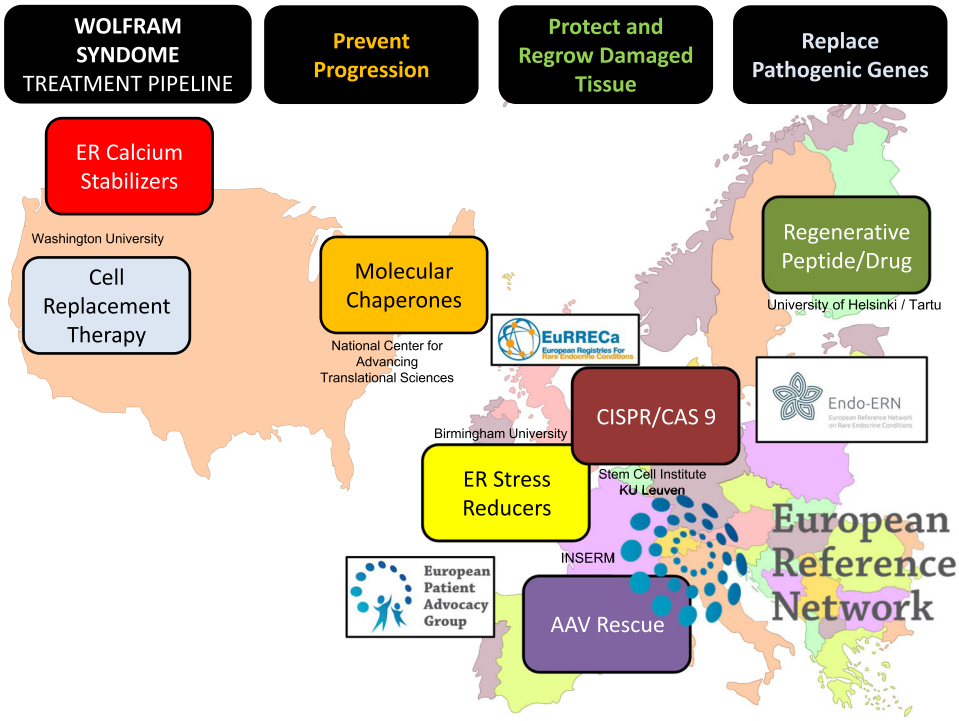

Fig. 1 Connecting the European Network for Rare Endocrine Conditions with major stakeholders in rare genetic disorders of glucose and insulin homeostasis exemplified by the various approaches in the treatment pipeline for Wolfram Syndrome

Deafness is a condition following sensorineural hearing defect in patients with WFS. The symptom occurs in the late adolescence and progresses slow. However in the third decade about 62% of WFS patients suffer from a manifest hearing impairment [19, 20].

WFS is accompanied by several neurologic symptoms with various onset and frequency. Cerebellar ataxia is the most common neurologic condition in WFS patients [16]. Other appearing neurologic symptoms include nystagmus, dysarthria, dysphagia, mental retardation, or even epilepsy [21].

Current research and treatment trials for Wolfram syndrome

The various research approaches concerning the treatment of WFS can be divided into those that are intended to prevent the progression of the disease, treatment methods that aim to protect or revive damaged tissue, especially pancreatic β-cells and retinal cells, or therapies that attempt to replace damaged or mutated genes (Fig. 1).

Therapeutic approaches that aim to prevent or slow down the disease progression, are currently focused on stabilizing the intracellular calcium concentration, supporting protein folding, and regulating the redox system to achieve ER homeostasis. Dantrolene sodium, which is mainly known from the treatment of malignant hyperthermia and therapy-difficult muscle spasms, is discussed to bear potential of calcium stabilization in the ER by influencing of ER calcium transporters. Mouse model research could reveal a suppression of the apoptosis rate and restoration of dysfunctional ß-cells for WFS by using dantrolene sodium [22]. A phase 1b/2a trial is currently conducted in order to investigate the effectiveness and safety of dantrolene sodium therapy in pediatric and adult WFS patients (Clinical Trial Number: NCT02829268) in St. Louis, MO, USA. New ER stabilizers, which are intended to ensure greater effectiveness and bioavailability, are currently tested in preclinical studies. Molecular chaperons like 4-phenylbutyric acid and tauroursodeoxycholic acid, which support correct protein folding in the ER and reduce ER stress, are tested for their potential in slowing down the degenerative process in neurologic and pancreatic ß-cells [23].

Valproic-acid (VPA), known as an antiepileptic drug, is also known act to reduce ER stress-induced apoptosis in mice and it has a neuroprotective effect in WFS patients [24]. Currently a phase 2 study with VPA in pediatric and adult patients is conducted in Birmingham, UK (ClinicalTrials.gov: NCT03717909). Its effect is expected to promote *WFS1* expression. This prevents increased ER stress and apoptosis particularly in nervous tissue [25, 26]. A recent clinical study in the ultra-rare autosomal-dominant WFS type showed promising effects on valproate-acid when combined with 4-phenylbutyric acid [27].

Another promising approach aims at the prevention of elevated ER stress by glucagon-like peptide 1 (GLP-1), which decreases the apoptosis rate in the cell model in WFS [28]. Recent studies from Estonia and Japan show a decrease in the severity of diabetes and a neuroprotective effect for WFS in rodents [28–30]. Single-center phase 1

clinical studies with GLP-1 are currently conducted in Brussels, Belgium and St. Louis, MO, USA

The complex genetic background of WFS suggests a potential role for treatment with the gene editor CRISPR-Cas9. Since beta cells have already been destroyed, the treatment must be carried out on stem cells which are later differentiated and transplanted. A recent study reported gene therapy to cure WFS in affected people. The underlying gene defect of *WFS1* was corrected by using CRISPR-Cas9 within human stem cells, which were differentiated into ß-cells and transplanted into ß-cell depleted mice, leading to a restart of insulin production and blood sugar regulation [31]. However, further studies are needed to confirm the validity of these findings.

The role of a health care network in rare disease

The European Union (EU) defines rare diseases as chronic or life-threatening with a prevalence of <1 in 2000 (European Commission Regulation # 141/2000). Despite this, rare diseases in total are not that rare. Following the data of the European-wide patient-organized alliance for rare diseases EURORDIS an amount of 6000 different rare diseases and an affection of 30 million EU citizens is estimated (https://www.eurordis.org/). EURORDIS itself aims to align different patient-driven healthcare networks in order to speak with a united voice for the belongings of patients suffering from rare diseases. To meet these properly several initiatives usually known as nationwide rare disease caring plans have been established recently all over Europe. Despite this, rare diseases remain a challenging task for health care professionals and health care systems. Most of the rare diseases are of complex genetic origin. Studies still suggest an average duration of 6 years until diagnosis and incorrect treatment remains common [32, 33]. Delivery of care and evaluation of clinical outcome in persons with common diseases is often standardized and regularly evaluated (and subsequently improved where needed). Evaluation of care and outcome in persons with rare diseases requests a different approach [34]. Development of networks has already demonstrate its impact on gaining knowledge on best practice in some of the rare diseases [35]. Alignment of experts opinions through international medical networking is an essential step to provide further evidence on best practice in caring for rare diseases [36]. To evaluate the role of new therapies requires the planning and realization of clinical trials for children, especially in a rare disease setting, which is usually demanding due to ethical, socio-economical and medical reasons. When the stage of regulatory trials is reached, a pan-european initiative like Connect for Children, which aims in connecting pediatric clinical trials, is necessary to promote their efficacy (https://conect4children.org/) [37].

The potential of a virtual network via ENDO-ERN for the treatment of Wolfram syndrome

European reference networks (ERNs) are associations of highly specialized centers in Europe funded by the EU, which support the cross-border best possible diagnosis and therapy of patients suffering from rare diseases. They serve to implement and harmonize care standards and to facilitate translational and clinical research [38]. ENDO ERN offers a virtual platform for exchanging ideas, enabling conversation, providing teaching tools, and encouraging research for rare diseases between different centers [39]. It facilitates case-related discussions, teaching issues, and planning of consistent, high-quality research approach [40]. A great potential for failure in international research projects is differing administrative requirements, ethical concerns, and various data documentation [41]. EuRRECA, a European-spread registry for rare diseases aiming to support an international data exchange between clinicians and researchers, born in 2018, is closely linked to ENDO-ERN [42]. Together they provide an interface with excellent prerequisites for the implementation of clinical research projects, due to their comprehensible, Europe-wide, and innovative structure [36, 43]. Potentially linking rare diabetes research to worldwide pediatric diabetes registries like SWEET [44] or networks for T1D research like INNODIA [45] may also generate synergies. Even in such a large registry like SWEET lists currently only 45 people with WFS from 18 centers worldwide (Table 1). Of these, 19 people are treated in 11 European centers of which 5 belong to Endo-ERN. This indicates the need for international

Table 1 Compared to 73,208 pediatric patients with either type 1 or type 2 diabetes a total of 2789 patients in the worldwide SWEET-database have been classified as non-type 1 and non-type 2 diabetes sorted by frequency (updated from (44))

SWEET pediatric diabetes registry	Number of patients
1. Congenital diabetes mellitus (manifested within the first 6 months of life)	513
2. CFRD	474
3. MODY2	384
4. MODY3	119
5. MODY1	69
6. Down Syndrome	64
7. Gluccorticoid induced	55
8. Post transplantation (excludes patients with CF)	55
9. *Wolfram Syndrom*	**45**
Other rare diabetes forms	~1.200

Patients with Wolfram syndrome are in the eighth most common position (shown in "bold")

Table 2 Examples of networks that could be approached for facilitating clinical research into treatments for Wolfram Syndrome

Initiative	Potential collaboration for Wolfram	Website
ERN	European Reference Networks (ERN) are virtual networks involving Reference Centres across Europe. They aim to tackle complex or rare medical diseases or conditions that require highly specialized treatment and a concentration of knowledge and resources.	https://ec.europa.eu/health/ern_en
ENDO-ERN	The ERN on rare endocrine conditions (Endo-ERN) aims to improve access to high-quality healthcare for patients with hormonal disorders including those with a genetic basis such as Wolfram syndrome.	https://endo-ern.eu/
EURRECA	EuRRECa (European Registries for Rare Endocrine Conditions) includes an e-reporting programme (e-REC) and a core registry that collects a common dataset and clinician and patient reported outcomes. The project will also develop a list of affiliate detailed disease registries that are approved for data sharing.	https://eurreca.net/
SWEET	The SWEET worldwide clinical pediatric diabetes registry can also contribute to combine forces in tackling diagnostic challenges, and in improving care for the rare forms of diabetes such as Wolfram Syndome	https://www.sweet-project.org/
EURODIS	EURORDIS-Rare Diseases Europe is a unique, non-profit alliance of 949 rare disease patient organizations from 73 countries that work together to improve the lives of the 30 million people living with a rare disease in Europe.	https://www.eurordis.org/
CONNECT4CHILDREN	c4c is a large collaborative European network that aims to facilitate the development of new drugs for the pediatric population.	https://conect4children.org/
INNODIA	INNODIA is a global partnership with one common goal: "To fight type 1 diabetes". As Wolfram has certain features of type 1 diabetes the INNODIA clinical trial network could be approached for potential clinical studies	https://www.innodia.eu

collaboration to move the different treatment trials for WFS forward (Fig. 1).

Following the guidelines of the International Rare Disease Research Consortium (IRDiRC) a realization of short-time diagnosis and effective patient treatment in rare diseases must be achieved until 2027 [46]. Previous research identified international collaboration, communication and monitoring as an essential step to walk this path successful [47]. Future clinical trials in WFS should take the burden of monocentric research in rare diseases in account and encompass international collaboration in order to optimize the validity and timeline of the research (Table 2).

Conclusion

A person who suffers from a disease is not responsible for the fact that it is rare. Yet s/he is the person with the disadvantage and the suffering. Not only from the disease itself, but especially due to the variability in knowledge and insufficient harmonization of cross border healthcare for persons with rare conditions. Medical scientific research is an established method to obtain knowledge about a disease, its cause, diagnosis entity, prognosis, but also treatment options. In the field of rare diseases, applying evidence based medicine evidence with regard to available diagnostic and therapeutic options is more complex due to the very limited numbers of affected people. The only possibility to move forward is to increase the number of subjects. This is especially applicable for rare diseases such as WFS. ENDO-ERN, a Europe-wide endocrinology network, offers an excellent base for further collaboration and clinical studies in the field of rare diseases. The network is supported by funding from the EU.

For the future, it is desirable that the mature network software available from e.g., EuRRECA, ENDO-ERN and other international registries and networks will be used to share the experience of knowledge exchange, especially in rare diseases.

For many rare diseases, the relationships and the course of the disease can only be understood and better treatment options be researched when clinicians work together across borders: What few cannot achieve, can be obtained together

Infobox: Wolfram syndrome

- is a very rare disease usually characterized by young onset diabetes mellitus, OA, deafness, DI, and symptoms of proceeding neurodegeneration.

- should be considered in any case of primarily insulin-dependent non-immunologic diabetes mellitus beginning during childhood.
- must kept in mind by caring physicians if the course of diabetes in an adolescent/young adult is further complicated by neurological symptoms, visual/hearing disturbances or DI.
- Can be proven by molecular genetic analysis of the *WFS1* gene or (even more rarely) the *CISD2* (*WFS2*) gene if suspected.

Acknowledgements The authors would also like to thank the European Society of Endocrinology, the International Society for Pediatric and Adolescent Diabetes and the European Society for Pediatric Endocrinology for their generous support.

Funding This paper is based on work performed with the support of non-profit organizations and public bodies for funding of scientific research conducted within the European Union: Innovative Medicines Initiative Joint Undertaking under grant agreement 115797 (INNODIA), which include financial contributions from European Union's Seventh Framework Programme (FP7/2007-2013) and Horizon 2020 research and innovation programme, EFPIA, JDRF, the Leona M. and Harry B. Helmsley Charitable Trust, the C4C initiative receiving funding from from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 777389 supported by the European Union's Horizon 2020 research and innovation programme and EFPIA, and the project '777215/ EuRRECa' which has funding from the European Union's Health Programme (2014–2020). SWEET is a registered non-profit charity in Hannover, Germany. It is financed through membership fees of the participating centers (based on income of country of residence according to the World Bank) and corporate members (for the current list see www.sweet-project.org).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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