ISSN: 2643-4571

Holland and Hughes. Int J Rare Dis Disord 2021, 4:036
DOI: 10.23937/2643-4571/1710036
Volume 4 | Issue 2
Open Access

International Journal of
Rare Diseases & Disorders

OPINION PIECE

Reducing Global Health Inequalities in People with Prader-Willi Syndrome: The Role of the International Prader-Willi Syndrome Organization

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Abstract

The International Prader-Willi Syndrome Organization (IPWSO) is a global charity first established in 1991 to support the needs of children and adults with the genetically determined neurodevelopmental disorder, Prader-Willi Syndrome (PWS), together with their families and health and social care professionals working with them. PWS affects all races and both genders equally and is associated with a complex physical and behavioral phenotype that requires interdisciplinary lifelong health support, together with family support and access to specialist social care in adult life. As with other rare disorders people with PWS experience considerable global health inequalities, and in many parts of the world the disorder is not identified, genetic testing is not available, and there is a lack of information, treatments and health expertise available to families. This is at a time when developments in genetics and in the neurosciences are advancing our understanding of and potential treatments for aspects of the syndrome. In this opinion piece we argue that global charities, such as IPWSO, have crucial roles to play in reducing these global health inequalities, which are likely to widen as new treatments become available for only the few living in high resource countries, and also working with other rare disorder organization's to pioneer the use of developing technologies to bring benefit particularly where resources may be severely limited.

Keywords

Prader-Willi Syndrome, International, Rare diseases and disorder

Introduction

Major advances in genetics and in areas such as the neurosciences have substantially improved the possibility of early diagnoses and treatments for people with rare neurodevelopmental disorders. However, in many parts of the world people with these rare disorders may not receive a diagnosis and are unlikely to benefit from such advances due to limited knowledge about rare diseases within the country [1]. Globally, parents of children with Prader-Willi Syndrome (PWS) often tell of the sometimes lengthy and tortuous journey they undertake to receive a diagnosis and to gain the appropriate treatment for their children.

The length and complexity of this journey for the families of children with PWS depends on many factors: The health resources and expertise available in the country, whether living in an urban or rural setting, and the ability to travel and to pay for health care. It also depends on the age at which PWS is first suspected. Whilst the signs and symptoms present at birth indicate the need for investigation, if that moment is lost, the question about the diagnosis may never be asked and the diagnosis will therefore not be made. Parents then struggle to make sense of their child's disability, missing the opportunity for early intervention and, in the case of people with PWS, most likely resulting in a reduced life expectancy.

In this opinion piece we describe the work of the

Citation: Holland A, Hughes M (2021) Reducing Global Health Inequalities in People with Prader-Willi Syndrome: The Role of the International Prader-Willi Syndrome Organization. Int J Rare Dis Disord 4:036. doi.org/10.23937/2643-4571/1710036

Accepted: September 08, 2021; **Published:** September 10, 2021

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International Prader-Willi Syndrome Organization (IPWSO) to illustrate how independent global Organizations can help resolve diagnostic and treatment challenges faced by families, and thereby contribute to better outcomes for people with rare neurodevelopmental disorders, in this case PWS. IPWSO was established in 1991 by parents and professionals in the recognition that in many countries information on PWS was lacking. The membership of IPWSO is comprised of National PWS Associations with 39 countries now being full members with additional informal contacts in over 100 countries. Its Trustee Board is made up of parents and professionals. In 2019 it was registered as a charity with the English and Welsh Charities Commission (registration number 1182873).

Prader-Willi Syndrome

PWS has an estimated birth incidence in high resource countries of approximately 1:20,000 and population prevalence that varies from 1:50,000 to 1:30,000 [2]. It affects both genders and all races equally. PWS arises because of the presence of a 15q11-13 deletion of paternal origin, a maternal chromosome 15 uniparental disomy, or the presence of an imprinting center defect. The consequence of one or other of these abnormalities is the absence of expression of maternally imprinted genes located at the chromosomal locus 15q11-13 [3,4].

Children born with this rare disorder are extremely hypotonic at birth and fail to thrive, often requiring neonatal intensive care. With age a later phenotype emerges, with evidence of developmental delay and mild intellectual disabilities, the manifestations of growth and sex hormone deficiencies of hypothalamic origin [5], and the emergence in early childhood of hyperphagia consequent upon an impaired satiety response to energy intake [6]. If access to food is not controlled, life-threatening obesity develops and life expectancy is markedly reduced, largely due to the consequences of the hyperphagia and obesity-related co-morbidities [2,7,8]. A neuropsychiatric phenotype characterized by a marked propensity to repetitive and ritualistic behaviors, severe skin-picking, and temper outbursts has a significant impact on quality of life for individuals and their families [9]. Serious mental illness may develop in late childhood particularly in those with a specific genetic type of PWS [10]. Scoliosis, kyphosis and kyphoscoliosis are common with rates reported as high as 85% in people with PWS and mainly becoming apparent in early childhood or in the teenage years and requiring monitoring and in severe cases major surgery [11]. Early diagnosis is important as severe obesity can be prevented through informed dietary management. Growth hormone replacement to normalize growth and improve lean body mass can also be started. Needs go beyond just those of health and include: The need for knowledge and expertise within the educational sector, access to specialist social care provision in adult life where access to food is controlled, and links with the police and others in the criminal justice system if someone with PWS is in trouble with the law due to food stealing or because of an outburst.

A global perspective on rare diseases

At an international level the World Health Organization has included rare diseases in its campaign for universal health coverage and has proposed the establishment of centers of excellence for rare diseases globally. There are influential national, regional and international lobbying groups examples of which are listed in Table 1. These organizations aim to influence high-level policy development relevant to rare diseases and disorders. For example, Rare Diseases International, in partnership with EURORDIS and the NGO Committee for Rare Diseases, has launched a global campaign calling for a UN Resolution on addressing the Challenges of Persons Living with a Rare Disease and their families (Table 1).

In addition, the International Rare Diseases Research

Table 1: Regional and international rare disease organizations.

Organisations	Web addreess
Asian Pacific Alliance of Rare Disease Organisations (APARDO)	https://www.apardo.org/
Eurordis	http://www.eurordis.org/
Rare Diseases International (RDI)	https://www.rarediseasesinternational.org/
Global Genes	https://globalgenes.org/
International Rare Diseases Research Consortium	https://www.irdirc.org/
National Organisation for Rare Disorders (NORD)	https://rarediseases.org/
Iberioamerican Alliance for Rare Diseases (ALIBER)	https://aliber.org/web/en/
UN NGO Committee on Rare Diseases	https://www.ngocommitteerarediseases.org/
International Collaboration on Rare Diseases and Orphan Drugs (ICORD)	http://www.icord.es/
WHO Collaborative Global Network for Rare Diseases (CGN4RD)	https://www.rarediseasesinternational.org/rdi- signs-memorandum-of-understanding-with- the-world-health-organization/

Consortium (https://www.irdirc.org/) provides a framework for co-ordinating and facilitating research, including tissue collection and bringing together data from different countries. At national level countries are expected to have a rare diseases plan, and there are regions of the world and individual countries that have centers of expertise for specific rare disorders. This is the context within which a syndrome-specific organization such as IPWSO sits, and where it may be able to exert some influence at regional and global levels [12].

Recently the Economist Intelligence Unit [13] published a global analysis on the diagnoses and treatments of people with rare neurological diseases. Of the total estimated number of over 7000 rare diseases, approximately 7% are estimated to be rare neurological diseases, and among this group are those with rare and very rare neurodevelopmental syndromes, usually of genetic origin, such as PWS. In the Economist's paper families were reported as describing struggling to engage with what are often multiple services over a short period of time, poor communication between services, uncertainty as to their rights, and difficulty finding the time to attend to the numerous issues. For some rare disorders, PWS included, 25% of patients reported waiting between 5 and 30 years for a diagnosis. Lack of access to financial support, disability benefits, and rehabilitation services and treatments were among many other concerns raised. Although growth hormone treatment for children with PWS has been offered in many countries since the 1990s, in other countries it continues to be unavailable or unaffordable. In Africa specifically, the challenge for governments is to balance the needs of those with rare disorders against a background of endemic major communicable diseases [14].

These global inequalities in the diagnosis and treatment of rare diseases are present at a time when major advances have been made in the diagnoses of rare diseases of genetic origin and the ability to investigate disease mechanisms, which has led to the potential for disease-specific treatments [15]. In many countries early diagnosis and access to reliable information and treatments are now a reality. However, in other places, such as in many countries in Africa, strategies such as the African rare diseases initiative is looking to innovative solutions for the provision of genetic testing and genetic expertise, and also making the case for expanding the role of patient advocacy groups [14]. The International Rare Diseases Research Consortium has set a goal for all patients coming to the attention of services with a suspected rare disease to be diagnosed within one year [14]. However, whilst advances in diagnostic testing and in our understanding of PWS are certainly welcome, if the circumstances are such that a lack of neonatal intensive care facilities result in infants dying shortly after birth, or if PWS is not suspected in the first place or, in some cases, cultural factors inhibit families coming forward, families will see no benefit. Similarly, if access to reliable and timely diagnostic testing and the expertise to interpret the results are not available, or if information on the disorder is absent or misleading and/or available treatments are too costly, then affected individuals and their families will be left with uncertainty about their future options. In Table 2 we summarize the barriers and potential solutions to improving this diagnostic and treatment journey for families. The problems identified are those told to us by families from countries encompassing the full economic spectrum.

The work of the International Prader-Willi Syndrome Organization (IPWSO)

IPWSO has two overarching roles. First, supporting people with PWS, families, and health and social care professionals, particularly in countries where there is no National PWS Association. Secondly, supporting our members and representing their needs and those of people with PWS and their families at regional and international levels in the rare diseases community and

Table 2: A diagnostic and treatment journey.

Diagnostic and treatment journey	What is required	Barriers	Solutions	What IPWSO can offer
Recognising and acknowledging there is a problem.	Health professional skilled in assessment. Access to information to guide differential diagnosis.	Cultural attitudes inhibiting acceptance of possible disability. Access to knowledge and expertise.	Improved understanding of disability and the causes. Trained community-based health professionals. Remote access to information and genetic expertise	Access to help line for parents and professionals when PWS suspected (when no national PWSA).

Receiving a diagnosis.	Awareness of genetic tests. Access to and availability of genetic tests. Availability of genetic expertise to interpret findings (remote).	No or limited access to health expertise. Genetic test for PWS and other rare disorders not available. No or limited access to genetic laboratory and expertise.	Nurse screening. On-line database of rare disorders. Accessible genetic diagnostic program for rare disorders. Access to genetic center (remote).	Information on PWS on-line and as printed material (translated into other languages). Free access to genetic testing. Access to help line (when no National PWSA).
Access to information.	Parents to gain knowledge of PWS and of support and treatment requirements. Professionals to have access to knowledge and best practice guidance.	Information not available in the necessary language. No access to the internet. Limited literacy.	Access to translated material (on-line or printed). Information accessible on different devices (e.g. mobile phones). Local network of parents and others with knowledge (such as a National PWS Association).	Provision of material. Local workshops for families and professionals (face-to-face or remote). IPWSO ECHO programs for parents, health professionals and care providers. International conferences for parents, professionals and care providers every three years (travel scholarships available).
Access to treatments and services.	Health expertise available to advise on and initiate treatments. Access to treatments and services. Treatments and services are affordable. Treatments and services adapted to family and environmental circumstances.	Limited access to health professionals. Health professionals reluctant to treat, PWS has considered outside their expertise. Treatments and services not approved by authorities or not available. Lack of other expertise and services (e.g. physiotherapy, dietician, social care). No universal health coverage.	National rare diseases plan committing to making expertise, treatments and services available for rare disorders. Centre of expertise in the country to support health professionals in other areas of the country (remote and face-to-face mentoring).	Provision of best practice guidance. Support to campaigns seeking approval of treatments and services approved elsewhere in the world. ECHO programme (see above).

beyond. We focus below specifically on three aspects of our work and consider future developments relevant to rare diseases in general, not just PWS.

Making a diagnosis: Ideally, the diagnosis of PWS should be made shortly after birth, but if it is not, other characteristics, such as hyperphagia, extreme obesity, short stature and sexual immaturity, may alert someone to the possibility of PWS at a later stage. Our experience is that social media is increasingly used by families to obtain information and to make a presumptive diagnosis, subsequently seeking confirmation through genetic testing. Given concerns about the accuracy of

information on the internet, it is a priority for IPWSO to maintain a strong social media presence and a website with accurate and scientifically sound information that can be trusted. Where PWS may be suspected clinically, IPWSO offers free diagnostic testing if it is not available locally or if it is unaffordable. This is always done through the local doctor responsible for the person's care, with the expert genetic analysis being undertaken at the Baschirotto Institute for Rare Diseases (BIRD) in Italy. During the 18 years that IPWSO has provided free diagnostic testing it has developed strong relationships with clinicians around the world who send samples for testing as needed. It is encouraging that some of the clinicians who have used this service in the early years no longer do so as genetic testing is now provided in their own countries. However, IPWSO receives few or no requests for diagnostic testing from certain countries where we know genetic testing is not available, suggesting that many people with PWS in those countries continue to go undiagnosed. When requests are received they often relate to older children and adolescents, highlighting the lack of awareness of how PWS presents in infancy.

Best practice in treatment and support: A key objective of IPWSO is to support the development of expertise, not only in the diagnosis of PWS, but in the subsequent treatment and care of those diagnosed. One of the major challenges for IPWSO is the extreme differences globally in health systems and their ability to respond to the needs of people with rare disorders. We acknowledge these limitations but at the same time encourage those working in countries with limited resources to aspire to best practice. IPWSO can help families and clinicians to make the case in their country, for example, for access to growth hormone treatment. On the IPWSO website there is access to material in different languages that covers all major aspects of diagnosis, treatment and support from childhood through adult life. In an effort to educate professionals who may be unaware of the Syndrome or uncertain how to recognize it, IPWSO hosts information booths at medical conferences around the world and actively seeks out opportunities to share information in areas of the world and in languages in which few resources exist. IPWSO has a helpline and our Clinical and Scientific Advisory Board provides advice to clinicians when asked to do so. When requested, IPWSO has also helped organize and fund local and regional workshops to bring together experts in the care and treatment of people with PWS and local families and professionals. Every three years IPWSO hosts an international event with conferences for clinicians and researchers, families, people with PWS, and care providers. At the last conference in Cuba in 2019, 480 people from 43 countries attended. These included delegates from low and middle-income countries who were awarded IPWSO travel grants to attend. As described below this work of disseminating information is now supplemented by our virtual ECHO® programmes. These were started before the COVID-19 pandemic and have been central to our work since the pandemic.

Project ECHO®: In 2019 IPWSO started Project ECHO® in partnership with the ECHO® Institute at the University of New Mexico, USA. These programmes use zoom technology to develop communities of good practice and, through the general principle of 'All teach all learn', foster networks of expertise globally. The four IPWSO ECHO® programmes include: Leadership, Health, Latin America (in Spanish), and Professional care providers. Each programme targets a different audience: The Leadership programme is primarily for parents who are taking a leadership role in their countries either through a National Association or in developing such an association. As with all ECHO® programmes the general format is a presentation and discussion on a specific topic, followed by what is referred to as a 'challenge', where a member of the ECHO® group presents a problem they are facing for general discussion. In the Health ECHO®, which is primarily for health professionals, this 'challenge' may be an anonymised case discussion. The Latin American ECHO® is mainly aimed at health professionals. These online meetings take place once every two weeks or once a month. So far 638 people from 48 countries have registered for one of the four ECHO®s and overwhelmingly positive feedback has been received after each session.

This is only the second ECHO® programme established for a rare disorder (the first was for Ehlers Danlos syndrome) and our experience is that it has significant benefits in reducing the feelings of isolation felt by parents and professionals and provides a valued forum for support and discussion.

The Future

Since IPWSO was first founded it has been the sharing of experiences of people with PWS, parents, and professionals from around the world, together with our developing understanding of PWS through research, which has informed the work of IPWSO. In addition to supporting individuals with PWS and their families it has also been important to work with families in different countries to support their efforts to establish National PWS Associations and to identify local professional expertise. In IPWSO's thirtieth year we are now consulting on how IPWSO's future role might develop. What can and should charities such as IPWSO do? Orphan drug regulations have increased the possibility of new treatments, and new techniques in drug discovery open the door to the identification of new agents to be tested. It is also clear that developments in science and technology are likely to change how people with rare diseases are diagnosed and supported. The challenge is to deliver globally what we already know to be good practice and to also ensure that advances in treatment

are available regardless of where you live or your ability to pay. In this respect IPWSO is engaged with Rare Diseases International in support of the WHO campaign for universal health coverage. However, it is also clear that the way services are delivered in high resource countries may not necessarily be the best way for other countries, particular with the cost of staff and the existence of skill shortages. There may also be cultural differences in how and by whom support is offered to adults with PWS with a greater expectation that care will be provided by families rather than organizations paid to provide support. We reflect on future developments by considering technological developments in genetics and information and knowledge transfer.

Acquiring knowledge about PWS

The availability of information and the opportunity to gain knowledge has been transformed by the internet and social media. Access to information no longer depends solely on having access to health professionals. However, information by itself is insufficient. The ECHO® programmes discussed earlier is about the 'democratization of knowledge'. Knowledge can transform the lives of people with PWS when it is readily available to parents, health professionals, those providing care and also, for example, teachers in school. For rare disorders in particular there is a strong case for an international organization, such as IPWSO, to be a reliable source and distributor of knowledge and IPWSO must constantly be aware of how technology is used globally, and adapt its communication methods accordingly. We have redesigned the IPWSO website with material available in different languages, and sections that address the needs of parents and professionals. We use social media to inform those who need to know of any additions.

New approaches to genetic diagnoses

Advances in rapid genome sequencing and the development of portable and relatively cheap gene sequencing equipment (for example, as used in Africa during the Ebola outbreak [16], may well change our approach to diagnosis, with whole genome sequencing being undertaken on any child with evidence of abnormality at birth [17]. As such techniques advance, the diagnosis could be made rapidly using one test rather than the possibility of having to repeat tests if the initial clinical diagnosis was incorrect. In this context, national or regional centers of excellence in rare disorders, such as proposed by the World Health Organization, will be essential. Such centers will need to be able to handle large complex datasets and to provide the necessary explanation of the findings to local health professionals. Where IPWSO can be of help is through projects such as ECHO®, where parents and local clinicians can be supported to develop the necessary skills to then deliver the care and treatment that is needed, ensuring a healthy and fulfilling life for the affected child.

Monitoring outcomes over time

Making the diagnosis is only the beginning of the journey and the care and support of people with PWS requires continued access to expertise, possibly over their lifetime. How can this be undertaken in a more effective and less costly manner, particularly in remote and sparsely populated rural areas? The use of wearable technologies and apps to monitor physical illnesses [18] and also mental states and behavior is one possibility. Such technologies can be extended to enable the integration of, for example, observational data (patient or informant input through an app) and physiological measurements including heart rate, physical activity and sleep. As systems develop, it will be possible to monitor a person's health daily to look for trends that may indicate the need for intervention. For people with PWS such systems could monitor blood sugar, where obesity may have led to diabetes mellitus or to monitor mental health. An important role for organization's such as IPWSO in the future may well be to use its detailed knowledge on the needs of people with PWS, working with its global partners to develop and evaluate novel methods for monitoring and managing the co-morbidities commonly associated with PWS.

Conclusions

Rare neurodevelopmental disorders such as PWS are complex, lifelong, and affect different organ systems, requiring the expertise of many disciplines during a lifetime.

The rarity of the disorder means that few in the relevant disciplines feel comfortable seeing people with PWS. For many in the world with PWS the already wide health inequalities will only get wider as the basics of care may not be available to them, let alone new therapies. In addition, the good health of people with PWS crucially depends on the quality of support and of social care if, as an adult, the person moves away from home. The prevention of obesity by managing the food environment, the effective management of behavior problems, and the detection of physical and mental ill-health depends on the skills of others. Through this paper we invite discussion on the solutions to the challenges faced by people with rare neurodevelopmental syndromes and their families globally. We argue that international charities such as IPWSO, together with regional and international rare disease organizations, are central to achieving an early diagnosis and universal access to knowledge and treatments as and when they are approved and thereby greater global equality.

Acknowledgements

We would like to thank the Trustees and members of the IPWSO advisory Boards and Committees for their support and for their ideas and enthusiasm. Special thanks to the many people with PWS and their families from all over the world who share their stories with us. AH would

also like to thank Professor Lucy Raymond, University of Cambridge, for the many informal discussions they have had on advances in genetics and their relevance to a rare disorder, such as PWS. IPWSO is supported by its National Association members, by the USA Friends of IPWSO, and by donations from individuals and project grants from pharmaceutical organizations and others. In recent years IPWSO has received particularly generous support from Jean Phillips-Martinsson, its Founder and Honorary President. Without these funds we would not be able to offer the support that we offer - thank you.

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