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EDITORIAL

Prader-Willi syndrome: Making progress, one step at a time☆

Síndrome de Prader-Willi: avanzando paso a paso

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Prader-Willi syndrome (PWS) is a genetic neurodevelopmental disorder. It has an estimated prevalence of between 1:10,000 and 1:30,000 live births and is caused by a lack of expression of genes of paternal origin in the 15q11–q13 chromosomal region. Genetic subtypes can be paternal microdeletion (70%–75% of cases), maternal disomy (20%–25%), imprinting defect (1%–3%) or chromosomal translocations (less than 1%).[1]

The clinical manifestations of PWS include short stature due to lack of growth hormone (GH), kyphoscoliosis, hypopigmentation, hypogonadotropic hypogonadism, small hands and feet, narrow bifrontal diameter, inverted U-shaped mouth with thin upper lip, and eye abnormalities (myopia, strabismus or almond-shaped palpebral fissures). There is usually decreased foetal movement during pregnancy, neonatal hypotonia with suction difficulties in the perinatal stage, and infant lethargy, which improves with age. Additionally, exaggerated hyperphagia and lack of satiety are very characteristic, which leads sufferers to desperately search for food and eat anything (even if is in poor condition) and, over time, to morbid obesity with multiple associated comorbidities, with these being the main cause of mortality in this population.[2]

In recent decades, interest in understanding the syndrome and developing drugs that can reduce this exaggerated hyperphagia has led some pharmaceutical companies to focus their attention on including this type of patient in their clinical trials. Unfortunately, some drugs indicated for PWS failed to reach the market due to suspension of the trial because of side effects. One due to thrombosis and death from pulmonary thromboembolism (in the case of beloranib, an inhibitor of the enzyme methionine aminopeptidase-2[3]); others due to ineffectiveness (livolétide, a deacylated ghrelin analogue,[4] and carbetocin, an oxytocin analogue[5]). Others are still under development, such as controlled-release diazoxide choline,[6] intranasal oxytocin,[7,8] and drugs that inhibit the endocannabinoid CB1 receptor,[9] and once again there is a glimmer of hope.

The scientific community and clinical experts are working constantly to better understand the pathophysiology of this syndrome and to be able to give more precise action guidelines to improve the health and quality of life of these patients and their caregivers.

Our group is a reference in PWS both at a clinical and research level and has contributed to the knowledge of different aspects of the syndrome. Regarding hyperphagia, we have studied the role of hunger and satiety peptides, such as ghrelin, polypeptide YY (PYY)[10] and brain-derived neurotrophic factor (BDNF).[11] However, we have recently observed that, when analysing nine peptides in pre- and postprandial state in three groups of adult subjects (patients

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with PWS, patients with obesity and healthy controls) by means of cluster analysis, fasting peptides discriminate better than postprandial peptides, a hormonal pattern characteristic of this syndrome. This pattern consists of elevated levels of ghrelin, leptin, PYY, GLP1, GIP and suggests not only an excess of the hunger hormone (ghrelin), but also some resistance to the action of satiating hormones. Therefore, new drugs should be aimed not only at increasing these satiating hormones but also at modifying them to allow them to overcome this resistance.[12]

By investigating brain function in PWS patients using functional magnetic resonance imaging in relation to different aspects of the syndrome, in terms of food, we were able to observe that, while viewing images of spoiled food, cortical brain activity in areas related to visually evoked disgust (anterior insula, frontal operculum) was decreased compared to healthy controls. Moreover, there was little activity at the subcortical level in the limbic structures (hypothalamus, amygdala, hippocampus and periaqueductal grey matter), which are areas related to the instinct to react in this situation. This implies that patients with PWS can come to discern that the food is theoretically inappropriate, but they eat it anyway because their instinct does not lead them to avoid it.[13]

Regarding motor aspects, we observed a dysfunction at the level of the cerebellum to carry out complicated motor tasks that involve coordination,[14] as well as an alteration in the ability to imitate gestures with a relatively preserved visuospatial praxis, which did not correlate with any specific anatomical alteration at the level of the brain. Rather, it seems more related to diffuse cerebral dysfunction.[15]

The behavioural aspects have been widely described in a recent consensus.[16] The best known is obsessive-compulsive behaviour,[17] with an obsession with food and the repetition of certain acts such as scratching of the skin or anus. The alterations in functional brain connectivity observed that may explain this behaviour are broader and more subcortical than those of patients with classic obsessive-compulsive disorder.[18]

A novel aspect is evaluating these patients' awareness of the disease. Our group has validated a test for its evaluation[19] and has been able to observe that these patients are quite aware of the disease and the effects of the medication, but not of its social consequences. These aspects may be relevant for adherence to treatment and for their relationships with their companions and caregivers.[20]

The International Network for Research, Management and Education on adults with PWS (INfoRMEd-PWS), created in 2019, has contributed with several publications on different endocrinological aspects of PWS, such as central adrenal insufficiency,[21] hyponatraemia,[22] hypogonadism[23] or treatment with GH in adults.[24] In all of them an attempt has been made to provide a series of guidelines for the diagnosis and treatment of each of these anomalies.

A registry of patients with PWS in Spain has recently been started by the Spanish societies of Endocrinology and Nutrition (SEEN), Obesity (SEEDO) and Paediatric Endocrinology (SEEP), which we hope will be useful for future studies and clinical trials aimed at improving the quality of life of these patients.

To conclude, we would like to highlight the great work carried out by patient associations at the local level (Catalan, Valencian, Andalusian and Spanish) and the International Prader-Willi Syndrome Organisation (IPWSO), in supporting families and caregivers while at the same time always being willing to collaborate with the scientific community. Without this symbiosis it would be impossible to advance step by step in the treatment of this complex syndrome.

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