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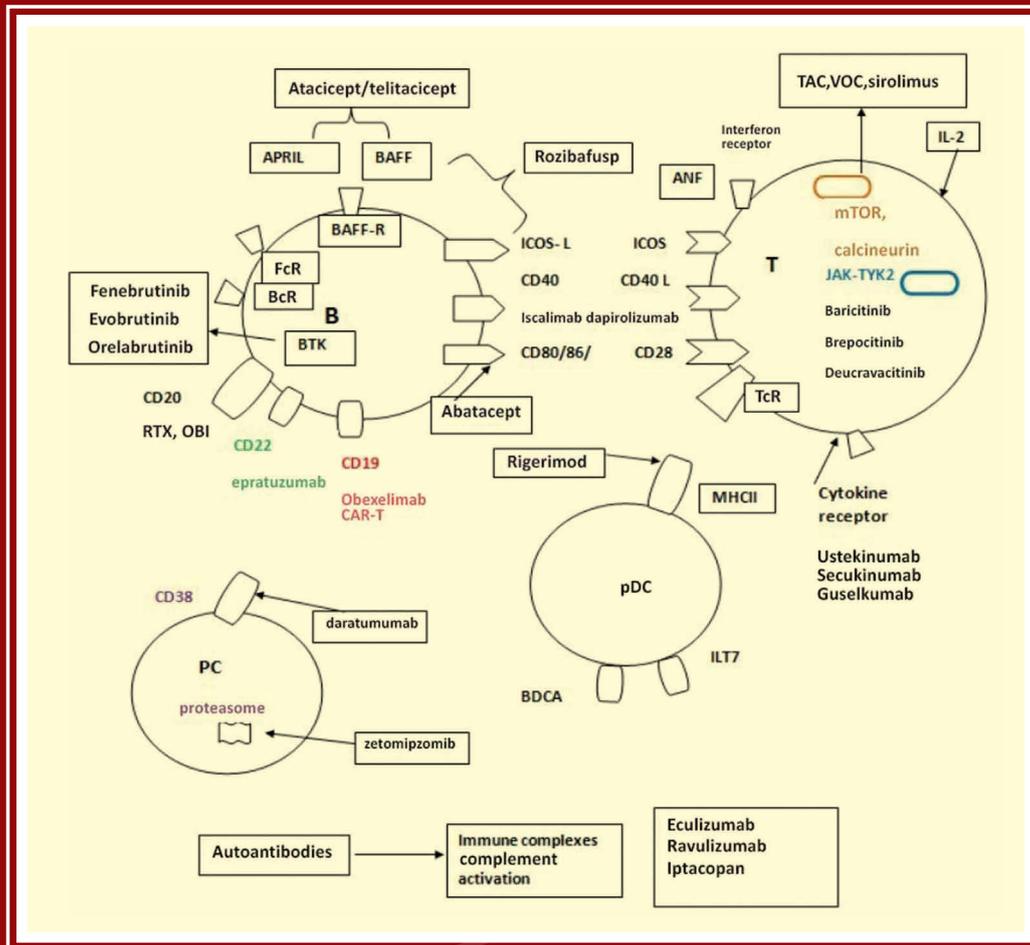
Medications and drug combinations in lupus nephritis

ACHAIKI IATRIKI

OFFICIAL JOURNAL OF THE MEDICAL SOCIETY OF WESTERN GREECE AND PELOPONNESUS (IEDEP)

GENERAL INFORMATION

ACHAIKI IATRIKI

Quarterly Official Journal of the
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CONTENTS

Dear colleagues,

In the current issue, the editorial by Zafeirati et al. describes the complex medical condition of adenomyosis, data related to its pathogenesis, clinical picture and diagnosis, and focuses on its impact on fertility. Moreover, this issue includes one original research article. The original research article by Kaliatzis et al. assesses the knowledge and practice of nurses regarding care of patients with spinal cord injury. Three review articles are also featured in the present issue. The first review, by Demertzis et al. offers valuable insights into the neuropsychiatric phenotypes of diseases causing parkinsonian syndromes, highlighting the need for a comprehensive delineation of neuropsychiatric symptoms as a core aspect of the phenotypes of parkinsonian syndromes and as a therapeutic challenge. The review by Pichlinski et al. explores how the COVID-19 pandemic affected pregnant women's acceptance of routine maternal vaccines and discusses further about the factors influencing decision making. The review by Mpounia et al. provides the current knowledge concerning the treatment management of lupus nephritis, presenting data from drugs either approved or under investigation.

Lastly, this issue includes the case report by Sotiropoulos et al. which presents an unusual case of a patient who developed euglycemic diabetic ketoacidosis (euDKA) in the context of post-ERCP cholangitis, bacteremia, and liver abscess, while receiving treatment with an SGLT-2 inhibitor.

Yours sincerely,

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Adenomyosis and infertility

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INTRODUCTION

Adenomyosis is a complex medical condition that affects a significant number of women around the world. It is characterized by an abnormal growth of endometrial tissue within the muscle wall of the uterus, causing symptoms in some of the women affected. In this editorial we explore the relationship of adenomyosis with infertility, shedding light on the most recent scientific data and the challenges ahead.

As time has gone by, adenomyosis has remained a histopathological diagnosis made after hysterectomy. During the last years, adenomyosis has been identified as a condition found in young fertile-age women due to the recent advancements in imaging studies. However, a common definition and classification system are still lacking. Despite the advances in technology that improved the performance of the diagnostic imaging, the awareness of the condition is still inadequate. The introduction of new medication and surgical techniques has allowed healthcare professionals to conservatively manage the disease.

Pathogenesis

The pathogenesis of adenomyosis is still unclear and cannot be understood by only a unique theory, since the phenotypes are heterogeneous and not clearly defined. Two main theories have prevailed over the years. The first being the tissue injury and repair theory (TIAR) which highlights the important role that tissue damage plays to the endometrial– myometrial interface and supports the common understanding that adenomyosis is associated with the risk factors of prior uterine surgery, previous caesarean section and

multiparity [1]. The second theory suggests that the disease arises de novo from metaplasia of embryonic or adult stem cells in the myometrium. However, this theory has not been sufficiently examined to draw any robust conclusions [1,2,].

Clinical picture

Despite its growing prevalence, adenomyosis is frequently underdiagnosed, contributing to delayed or missed opportunities for intervention. This disease often coexists with other gynaecological problems such as endometriosis and uterine fibroids, making diagnosis very challenging. The epidemiological profile of the condition has changed, and even though the most common risk factors include age of more than 40 years, multiparity, and prior uterine surgery, adenomyosis has been increasingly diagnosed in young women, in patients struggling with infertility, or in those with pain or abnormal uterine bleeding (AUB) or both [3,4].

Diagnosis and classification

The diagnostic investigation of adenomyosis should start with the suspicion of condition supported by the clinical presentation of relevant symptoms and signs. The confirmation of the presence of adenomyosis should be performed by the imaging techniques, which may also help to define the presence of comorbidities [5].

Pelvic ultrasound constitutes a straightforward, minimally invasive, and inexpensive examination. Ultrasonography aids to observe the size and shape of the uterus, the location of heterogeneous myometrium and the focal abnormal echotexture. It also evaluates the junctional zone (JZ) between the endometrium and the myometrium, which can appear uneven, poorly defined, and interrupted or absent. Lastly, it assesses the myometrial lesions; an affliction is considered localized

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if it is less than 50% of the volume of the uterus or it is considered diffuse if it is greater than 50% of the uterine volume [5]. The diagnosis of adenomyosis is often performed based on ultrasound (US) features, even though no agreement on US features for adenomyosis exists. The Morphological Uterus Sonographic Assessment (MUSA) consensus published in 2015 aimed to identify a standardized terminology for describing ultrasound images of normal and pathological myometrium [5,6].

MRI allows evaluation of the inner myometrium and observation of its thickness and nature of changes, which is considered the hallmark of adenomyosis [6]. Although pelvic MRI is more expensive and less available, it is a more reproducible examination, as the sensitivity, specificity, and positive and negative prediction values are high. Several classification systems based on MRI have been proposed in the literature. A classification system that has been proposed by Bazot et al., describes three types of adenomyosis by MRI. These include (i) Internal adenomyosis (focal, superficial and diffuse), (ii) adenomyoma and (iii) posterior or anterior external adenomyosis [5]. Another classification system that has been proposed by Chapron et al., defines two main adenomyosis subtypes: diffuse internal adenomyosis and focal adenomyosis of the external myometrium. In this classification, diffuse adenomyosis is defined by the association of two criteria. The first being a JZ of at least 12 mm and the second being a JZ/Myometrium ratio over > 40%. Focal adenomyosis is characterized by the presence of a poorly defined subserosal mass affecting the posterior or anterior wall of the myometrium, separated from the JZ by an area of healthy myometrium [5].

Impact on fertility

Adenomyosis has been considered for many years a uterine condition of multiparous women, although an increasing amount of evidence indicates an association with infertility and reproductive failure [7]. Currently, infertility is considered one of the possible clinical presentations of adenomyosis and several theories have been suggested to explain the underlying mechanisms. Calero et al in 2022, concluded that infertility may be due to several factors that impair adequate sperm mobility through the uterus and an impaired implantation of a product [8]. Furthermore, the inner myometrium and the JZ present with dysfunctional hyperperistalsis and increased intrauterine pressure. As a result, these structural myometrial abnormalities may cause a disturbance in normal myocyte contractility with subsequent loss of normal rhythmic contraction. Data suggests that in infertile women with adenomyosis, eutopic endometrium presents a wide variety of molecular alterations, thus causing a disruption in its receptivity capacity [9].

Treatment options

Management often involves a combination of medical and surgical approaches. Hormonal therapies such as progestins and gonadotropin releasing hormone agonists (GnRH), act by treating local hyperestrogenism and alleviating the most severe symptoms of adenomyosis such as heavy menstrual bleeding, dysmenorrhea, and pelvic pain [10]. Surgery options range from excising adenomyotic lesions to more extensive ones such as hysterectomy. The choice of treatment is usually individualized, taking into consideration the wish for fertility preservation, the severity of the symptoms and overall, the clinical condition of each patient [12].

Adenomyosis and IVF outcomes

There are conflicting results regarding the effectiveness of in vitro fertilization (IVF) in women with adenomyosis. Some studies show no difference in pregnancy rates, while others show a difference, but miscarriage rates appear to be higher. The reason for the conflicting results is because of the varying ovarian stimulation protocols used and a lack of proper description of the type and severity of adenomyosis [14,17].

Several researchers have examined the impact of adenomyosis on fertility by studying women who underwent IVF since this model provides more precise data on the effect of adenomyosis on embryo implantation. However, for the purposes of infertility research, it is essential to consider that adenomyosis often coexists with other gynecological disorders, including uterine fibroids and, notably, endometriosis, which are often associated with pelvic pain and dysmenorrhea. Consequently, the proportion of women with both diseases and the diagnostic criteria remain controversial. Since endometriosis has been linked to subfertility and reduced chances of conceiving through assisted reproductive technology (ART), it is critical to conduct studies that explore IVF outcomes in women with endometriosis only, adenomyosis only, and those with both pathologies [15,18,19].

Liang et al. conducted a retrospective cohort study in 2022 which revealed that adenomyosis has a negative effect on IVF-Embryo Transfer outcomes, increasing the risk of miscarriage, reducing live birth rates, and increasing obstetric complications [20].

Researchers conducted studies aiming to evaluate the effect of adenomyosis on the outcome of pregnancy in ICSI/FET cycles and the potential benefits of pre-treatment with GnRH agonist, conservative surgery, or a combination of both on pregnancy outcomes. It was shown that women with adenomyosis who underwent ICSI/FET cycles had lower clinical pregnancy rates, higher miscarriage rates, and lower rates of live birth and ongoing pregnancy compared to those without adenomyosis. However, there was a significant improvement in clinical pregnancy rates in patients who received pre-treatment with GnRH agonist, conservative surgery, or a combination of both. The GnRH agonist long protocol and conservative surgery with GnRH agonist pre-treatment were found to be beneficial [19]. However, further large-scale prospective comparative studies are needed to confirm these findings.

According to a few studies, patients with diffuse adenomyosis who underwent adenomyomectomy showed better fertility outcomes with increased clinical pregnancy rates and reduced miscarriage rates [19,20].

CONCLUSION

Over the past two decades, there have been significant advancements in the understanding of adenomyosis, and more clinicians are aware of this condition. Non-invasive diagnostic tools have allowed for accurate diagnosis without surgery. However, there is still much debate over diagnostic criteria, as imaging features have not been correlated with clinical presentation, and many patients are asymptomatic or have other gynecological issues that make diagnosis challenging. Various classifications have been proposed, but there is no shared language or uniformity. Current evidence is limited by poor quality studies, lack of strict imaging diagnosis, and absence of a classification according to disease extent. As our understanding grows, so too the potential for finding an optimal management strategy to alleviate symptoms and improve reproductive outcomes for women affected by this disease.

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Author Contributions: Both authors equally contributed to the literature review, the interpretation of the relevant data and the review of this editorial article, aiming to provide an insightful comprehension on adenomyosis and its impact on fertility.

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Knowledge and attitudes of nurses regarding patients with spinal cord injuries

Nikos Kalaitzis[1], Panagiotis Plotas[2], Nikos Stefanopoulos[3], Maria Lagadinou[4,5]

Abstract

Background and Aim: Traumatic spinal cord injury (SCI) affects 27–59 individuals per million globally, with a bimodal distribution, predominantly impacting young adults through motor vehicle accidents and older individuals through accidental falls. Significant efforts have been made to evaluate SCI severity and recovery potential, but there is a gap in knowledge about SCI and its related complications. This study aimed to assess nurses' knowledge and practice in caring for patients with spinal cord injury.

Methods: We provided a cross-sectional study which included 86 nurses of both genders. Our survey utilized a questionnaire developed by our research team, based on prior studies for collecting data on their experiences and challenges in caring for SCI patients.

Results: A significant number of participants reported that the greatest difficulties encountered involve the family environment of SCI patients. A statistically significant correlation was found between the work department and the quality of care provided to SCI patients. Nurses working in rehabilitation centers provided the best care (p<0.05) compared to those in Intensive Care Units (ICUs) and Emergency Departments. Additionally, there was a significant correlation (p = 0.03) between the nurses' educational level and their perception of providing optimal care to SCI patients.

Conclusion: While the age of professionals, frequency of caring for SCI patients, and nursing experience may influence attitudes towards SCI patients, the most reliable factors appear to be the nurses' educational level and the work department.

Key words: *Spinal cord; injury; psychological disorders; caregivers; attitudes*

INTRODUCTION

Spinal cord injury (SCI) refers to damage to any part of the spinal cord or nerves, often resulting in permanent changes in strength, sensation, and other body functions below the site of the injury [1]). SCI is classified into two types: complete and incomplete. Traumatic SCI occurs in 27–59 individuals per million population globally and exhibits a bimodal distribution, with peaks among young adults and older individuals, primarily due to motor vehicle accidents and accidental falls, respectively [2,3].

Patients with SCI face increased risks of secondary health conditions, such as pressure ulcers, deep venous thrombosis, and urological complications. Efforts have been concentrated on evaluating SCI severity and predicting recovery potential. Healthcare providers play a crucial role in explaining and discussing these risks with SCI patients and their caregivers. Besides providing psychosocial support, discharge planning,

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and consulting with other caregivers as part of a team process, nursing staff are pivotal in educating patients and family members about the physiological changes resulting from traumatic SCI, including secondary complications. Despite these responsibilities, there is a notable gap in knowledge about SCI and its related complications [4].

Nurses are integral to the care of patients with acute traumatic spinal cord injuries throughout the entire care journey. While research on the experiences of nurses caring for these patients in acute settings is limited, numerous studies worldwide are exploring treatments and rehabilitation methods to help individuals with SCI remain productive and live independently [5,6].

Recognizing the challenges faced by nurses in provid-ing care for patients with life-changing injuries, this study aims to assess the knowledge and practices of nurses regarding the care of patients with spinal cord injury.

MATERIAL AND METHODS

We conducted a cross-sectional study in KAT Attica General Hospital from January to May 2023. The study involved nurses from the Emergency Department, Intensive Care Unit (ICU), and Rehabilitation Center. Participants were randomly selected without any exclusion criteria. Detailed information regarding the study aims and data confidentiality was provided to all potential participants. Nurses who consented to participate were required to complete an anonymous questionnaire.

Table 1. *The Questionnaire sheet that was distributed over the three groups of nurses (Rehabilitation Center, Emergency Department, Intensive Care Unit).*

No.	Question
1	Do you provide the same care to patients who suffer from acute organic psychosyndrome and patients who don't?
2	Do you teach the patient specific pain and stress management modalities after spinal column injuries?
3	Are there any practices nurses could do to help with the prevention of long-term post-traumatic stress for patients with spinal column injuries?
4	Do all patients with spinal cord injuries suffer from at least one post-traumatic stress reaction?
5	Do psychological transitions after an injury last more than physical symptoms?
6	Are there any practices the nursing staff could do to help with the prevention of long-term post-traumatic stress for patients with spinal column injuries?
7	Do you believe patients with spinal cord injuries receive the required care from you?
8	In your opinion, is it easy to train the family environment for the care of a patient with spinal cord injuries?
9	Do you believe that a family environment of a patient could meet the demands of his care after spinal cord and spinal column injuries?
10	Do you provide information to the patient's family about emotional or behavioral reactions which will show them that the patient might need extra care?
11	Do you teach the patient's family how to talk to him after a hard/painful/frightening experience?
12	Could nurses teach patients how to deal with difficulties and other matters that appear after a spinal cord injury?
13	Do you believe the nursing staff should focus on the treatment of patients with spinal cord injuries?
14	Do you teach a patient specific ways of dealing with pain and stress during a procedure that causes him these feelings?
15	Do you consider the special traits of each patient before planning his training?
16	Do you believe that personal hygiene of a patient with a spinal cord injury is effective in preventing infections?
17	Is your practice in prevention of decubitus ulcers effective?
18	Do you care about the correct nutrition and bowel function of the patient to prevent complications?
19	Do you use every available means you have, for patient's care?
20	Do you update in detail the patients about methods and ways you will follow?
21	Are the methods you use for dealing with a patient consistent with management protocols of the hospital where you work?

Our survey utilized a questionnaire developed by our research team, based on prior studies. The questionnaire was designed following a systematic review of all online medical search engines and was piloted with a small number of nurses before the study commenced to allow for necessary adjustments. Written in Greek, the questionnaire comprised two parts: Part A included four questions on demographic characteristics, work experience duration, and educational level and Part B consisted of twenty-one questions addressing knowledge and attitudes towards the care of patients with spinal cord injury and their caregivers. The answers were limited to "yes" or "no" (Table 1).

This study received approval from the Institutional Ethics Committee (University of Patras: 98828/19.12.2022, Referral Hospital: 1186/11.11.2022) and was conducted in accordance with the Guidelines of the Declaration of Helsinki. Participant anonymity was ensured throughout the study.

DATA ANALYSIS

Data were analyzed using the Statistical Package for Social Sciences (IBM SPSS software) version 27. A significance level of 0.05 was set for all analyses.

RESULTS

The study included 86 nurses from both genders. Table 2 represents the demographic characteristics of the participants, highlighting that the majority were women (75.6%).

Figures 1a and 1b illustrate the self-reported knowledge and attitudes of nurses towards patients with spinal cord injuries. It is remarkable that of all the negative answers, the higher percentages gathered those related to the family environment of patients with spinal cord injuries. The question "In your opinion, is it easy to train the family environment for the care of a patient with spinal cord injuries?" received the highest percentage of negative responses (57%). While a slightly lower percentage was gathered by the question "Do you believe that a family environment of a patient could meet the demands of his care after spinal cord and spinal column injuries?" (50%).

x² correlations between educational level and responses to each question

A statistically significant correlation (p = 0.03) was found between educational level and responses to Q7:

"Do spine and spinal cord injury patients consider themselves to be getting the best care they need from you?". Multiple correlations showed that more nurses with two years of training (76.5%) responded positively to this question compared to nurses with a master's degree (32%), while nurses with a university degree responded positively in 61.4% of cases. No other statistically significant correlations were reported. All measurements are shown in Table 3.

x² correlations between work department and responses to each question

A statistically significant correlation (p = 0.02) was found between the work department and responses to Q1: "Do you give the same care to patients with acute organic psychosyndrome as to patients without?". More nurses in the Intensive Care Unit (84.2%) gave a positive

Table 2. *Demographic characteristics (n= 86).*

	N	%
Sex		
Male	21	24.4
Female	65	75.6
Age (years)		
18-24	4	4.7
25-30	35	40.7
31-40	17	19.8
41-55	24	27.9
55+	6	7.0
Work Department		
Intensive Care Unit	57	66.3
Emergency Department	22	25.6
Rehabilitation Center	7	8.1
Work experience (years)		
0 - 1	4	4.7
2 - 5	36	42.4
6 - 10	12	14.1
> 10	33	38.8
Graduation Level		
Two years Nursing study	17	19.8
University education	44	51.2
MSc	25	29.1
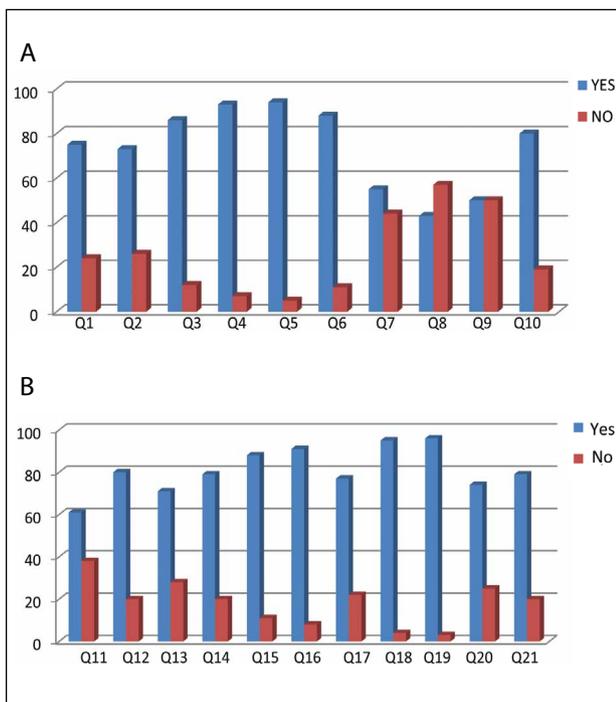
Figure 1a and 1b. Knowledge and attitudes of nurses on problems patients with spinal cord injuries confront.

answer compared to those working in the Emergency Department (54.5%). Another statistically significant correlation ($p < 0.05$) was found between the work department and responses to Q7. All nurses (100%) working in the Rehabilitation Center answered positively to that question, whereas those in the Intensive Care Unit responded positively in 49.1% of cases. No other statistically significant results were reported. All measurements are shown in Table 4.

DISCUSSION

To our knowledge, this is the first study in a Greek hospital that has formally assessed the awareness and knowledge of nurses regarding SCI patients. The sample size involved and response rate in the present study (n=86) were comparable to other foreign published studies.

Most of the participants demonstrated that spine and spinal cord patients get the best care they need. Similarly, there is a large body of literature related to rehabilitation nursing care for patients with SCI; however, little research focuses on how this care may influence outcomes, such as length of stay (LOS), complications, and quality of life [4]. It is well known that the delay in accessing

rehabilitation is associated with reduced quality of life and opportunity for independence [7]. McRae et al., reported that psychosocial and emotional adjustments are influenced by support received, especially from family members although increased caregiver burden has been identified in those caring for people with spinal injuries during and after rehabilitation [7].

Most of the participants answered that it is not easy to train the family environment of the spine or spinal cord injury patient in their care. Nevertheless, it is essential to maximally understand the capacity of family members in order to provide quality care to patients with SCI [8]. On the other hand, they answered that the family cannot cope with the demands of caring. Family caregivers are in touch with SCI patients and feel committed to them more than any other person [8]. Psychosocial support for patients and their families emerged as the most common component of care management for spinal cord injury groups. The provision of psychosocial support is important and may contribute to improved patient outcomes. In addition to supporting their patients physically and psychologically, family caregivers help patients accomplish their daily activities, reducing the care burden imposed on health systems, the need to use professional home care, and the rate of admission to nursing homes [8]. Decision makers who plan staffing for SCI rehabilitation centers should consider the time consumed for psychosocial support addressing both the patients and the family environment [4].

Most of the nurses with basic (two years) education (76.5%) and 61.9% of nurses with university education answered that spinal cord injury patients get the best care they need from them. This can be interpreted as the higher level of education and clinical experience might be associated with more time spent in interdisciplinary conferences on this category of patients [7]. Moreover, strengthening nursing in rehabilitation (through clinical experience and training) is a vital factor in delivering high-quality care and to ensure that rehabilitation can meet the needs of persons experiencing disability and achieve optimum health outcomes [8].

In our study, 100% of rehabilitation nurses answered that they give the best to patients with spinal cord injuries. It is important to create opportunities for nurses to specialize in rehabilitation nursing. Rehabilitation service providers should ensure that positions of

Table 3. *Correlations between educational level and responses to each question.*

Question	Two years of training	Master's degree	University degree	χ^2	p
Q1	64.7%	72.0%	81.8%	2.19	0.34
Q2	70.6%	76.0%	72.7%	0.16	0.92
Q3	76.5%	96.0%	86.0%	3.47*	0.17
Q4	100.0%	88.0%	93.2%	1.89*	0.39
Q5	94.1%	96.0%	93.2%	0.40*	1
Q6	22.4%	30.3%	47.4%	3.89*	0.12
Q7	76.5%[β]	32.0%[α]	61.4%	6.92*	0.03
Q8	52.9%	36.0%	43.2%	1.19	0.55
Q9	52.9%	48.0%	50.0%	0.1	1
Q10	94.1%	76.0%	77.3%	1.58*	0.30
Q11	64.7%	60.0%	61.4%	0.10	0.95
Q12	70.6%	91.7%	77.3%	3.28*	0.20
Q13	64.7%	75.0%	72.1%	0.54*	0.76
Q14	70.6%	68.0%	88.6%	5.02	0.08
Q15	22.4%	27.6%	50.0%	2.85*	0.24
Q16	21.5%	27.8%	50.6%	1.82*	0.44
Q17	94.1%	76.0%	72.7%	3.33	0.19
Q18	100.0%	96.0%	93.2%	0.89*	0.81
Q19	20.5%	30.1%	49.4%	1.81*	0.43
Q20	76.5%	68.0%	77.3%	0.77	0.68
Q21	82.4%	76.0%	79.5%	0.26	0.88

specialized rehabilitation nurses are included in the rehabilitation team. This approach will enable people experiencing disability to achieve optimal functioning, independent living and quality of life [7].

Spinal cord injuries have a large negative impact on patients' physical and mental health (organic psychosyndrome). Effective nursing measures are effective in the critical period of treatment and can prevent the recurrence of illness by paying close attention to the psychological and neuropsychiatric changes of SCI patients. Therefore, in the process of improved nursing measures humanized care and patient-centered care concepts should be adopted [10].

Our study has some limitations. Initially, it is geographically limited to only one General Hospital and not to other hospitals in the country. Still, the number of nurses enrolled is small. Finally, the questionnaires were completed on a voluntary basis and, therefore, some did not want to participate in the research.

Our questionnaire-based survey, which appears to be representative of the population of interest, identified significant differences in the attitudes toward patients with spinal cord injuries between nurses who work in the rehabilitation center, intensive care unit and emer-

Table 4. *Correlations between work department and responses to each question.*

Question	ICU	Emergency Department	Rehabilitation Center	χ^2	p
Q1	84.2%	54.5%$^\alpha$	71.4%	7.64	0.02
Q2	70.2%	77.3%	85.7%	1.01	0.60
Q3	91.1%	72.7%	100.0%	4.07*	0.11
Q4	93.0%	95.5%	85.7%	0.68*	1
Q5	94.7%	90.9%	100.0%	0.79*	0.75
Q6	89.5%	81.8%	100.0%	1.43*	0.55
Q7	49.1%	59.1%	100.0%$^\alpha$	6.92*	0.03
Q8	38.6%	45.5%	71.4%	2.73*	0.24
Q9	42.1%	59.1%	85.7%	5.54*	0.06
Q10	80.7%	81.8%	71.4%	0.67*	0.82
Q11	59.6%	63.6%	71.4%	0.40*	0.83
Q12	76.8%	81.8%	100.0%	1.65*	0.47
Q13	70.9%	68.2%	85.7%	0.68*	0.75
Q14	78.9%	72.7%	100.0%	2.02*	0.40
Q15	84.2%	95.5%	100.0%	2.02*	0.34
Q16	87.7%	100.0%	100.0%	2.91*	0.26
Q17	71.9%	86.4%	100.0%	3.45*	0.14
Q18	94.7%	95.5%	100.0%	9.32*	1
Q19	94.7%	100.0%	100.0%	0.98*	0.66
Q20	70.2%	77.3%	100.0%	3.04	0.22
Q21	77.2%	81.8%	85.7%	0.30*	0.92

gency department. Although the professionals' age, the frequency of caring for patients with SCI and the time of nursing experience may influence the nurses' attitudes towards SCI patients, the most reliable factors associated with the attitudes seem to be the nurses' level of education and work department.

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Neuropsychiatric symptoms in parkinsonian syndromes: A narrative review

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Abstract

Parkinsonian syndromes, the most common of which are Parkinson's disease (PD), Dementia with Lewy Bodies (DLB), Progressive Supranuclear Palsy (PSP), Corticobasal Degeneration (CBD) and Multiple System Atrophy (MSA), manifest with motor symptoms, cognitive deficits and neuropsychiatric symptoms. This narrative review offers valuable insights into the neuropsychiatric phenotypes of diseases causing parkinsonian syndromes. Depressive symptoms, apathy and anxiety are common across these disorders. Conversely, hallucinations and delusions are significantly more characteristic of PD and DLB pathology. The involvement of diverse symptomatology renders treatment challenging, especially since interventions targeting specific symptoms can potentially exacerbate others. In particular, the pharmacological management of psychosis in PD and DLB presents a dilemma as treatment with antipsychotic agents that are included in the World Health Organisation (WHO) model list of essential medicines can in many cases aggravate motor symptoms, while cholinesterase inhibitors are commonly not reimbursed or entirely unavailable in low- and middle-income countries (LMIC). In addition, data on the efficacy of non-pharmacological interventions in managing neuropsychiatric symptoms in parkinsonian syndromes are succinctly presented. Our review highlights the need for a comprehensive delineation of neuropsychiatric symptoms as a core, albeit commonly neglected, aspect of the phenotypes of parkinsonian syndromes and as a therapeutic challenge.

Key words: *Parkinson's disease; dementia with lewy bodies; progressive supranuclear palsy; corticobasal degeneration; multiple system atrophy; behavioral and psychological symptoms in dementia*

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BACKGROUND

Parkinsonian syndromes are characterized by complex phenotypes which comprise but are not restricted to extrapyramidal symptoms, including bradykinesia, ataxia, resting tremor and rigidity [1,2]. These syndromes can encompass cognitive deficits, occurring in early or more advanced stages of the syndrome course, dysautonomia, gaze palsy, myoclonus, pyramidal tract signs and the alien limb phenomenon, as well as neuropsychiatric symptoms. The latter refer to symptoms like apathy, depressive mood, aggression, anxiety, irritability, appetite disturbances, delusions, disinhibition, hallucinations, euphoria [3,4]. Of note, neuropsychiatric symptoms are very common in the course of neurodegenerative diseases and pose a heavy burden to both patients and their care partners [5,6].

Parkinsonian syndromes are commonly caused by Parkinson's disease (PD) or by Parkinson-plus diseases [2], which are pathophysiologically classified either as alpha-synucleinopathies or tauopathies [1,7]. The most common Parkinson plus conditions are dementia with Lewy bodies (DLB), multiple system atrophy (MSA), corticobasal degeneration (CBD), and progressive supranuclear palsy (PSP) [7]. PD, DLB and MSA are characterized by inclusions formed by alpha-synuclein, i.e. Lewy bodies, while in CBD and PSP cytoskeleton proteins become abnormally phosphorylated, leading to the development of tau inclusions in neurons and glial cells [8,9].

Here, a succinct overview of neuropsychiatric symptoms in parkinsonian syndromes is provided. The terms neuropsychiatric symptoms, behavioural and psychological symptoms and non-cognitive symptoms of dementia are commonly interchangeably used. The objective of this narrative literature review is to synthesize the emerging literature detailing neuropsychiatric symptoms in parkinsonian syndromes. The review sheds light on neuropsychiatric symptoms that shape the clinical phenotypes of these syndromes. Additionally, it reports on strategies that have been developed for their management with special focus on low- and middle-income settings and on the World Health Organisation (WHO) recommendations for essential medicines for mental disorders [10].

Search strategy and eligibility criteria

A non-systematic approach was employed, searching the PubMed, PubMed Central, and Google Scholar databases from December 2022 to January 2023 for relevant articles. Search terms included: "neuropsychiatric symptoms", "behavioral and psychological symptoms", "non-cognitive symptoms", "depression", "anxiety", "aggression", "irritability", "appetite disturbances", "delusions", "disinhibition", "hallucinations", "euphoria" and PD, DLB, MSA, CBD or PSP. Eligible studies were studies published in English and which referred to people diagnosed with PD, DLB, MSA, CBD or PSP.

Parkinson's disease

PD is the second most common neurodegenerative disease, following Alzheimer's disease [11]. Its prevalence is expected to increase significantly over the following 20 years, propelled by the aging population and the advancements in clinical care and therapeutic strategies. In addition to motor symptoms, the clinical presentation of PD encompasses cognitive changes, behavioral/neuropsychiatric changes, and symptoms related to autonomic nervous system failures [12].

Depression is among the most common non-motor symptoms of PD. Approximately 40-50% of people with PD experience mild to severe depressive symptoms [13]. The point prevalence for major depression is reported to be 17% [14]. Clinical signs of depression in patients with PD include psychomotor retardation, decreased energy, fatigue, sleep- and appetite changes as well as mood alterations. Diagnosing depression in individuals with PD can be challenging due to the overlapping clinical presentations of the two conditions [15].

Depression has detrimental effects on quality of life, symptoms and the burden on care partners [15,16]. Besides the emotional toll associated with the confrontation with a progressive neurodegenerative disease leading to multifaceted disability, the development of depressive symptoms appears to be linked to neurobiological factors [13]. Of note, the onset of depressive symptoms can even precede motor symptoms. Thus, the neurodegenerative process may contribute to prodromal mood disturbances. Interestingly, in PD related brain pathological changes can extend beyond the midbrain and can include discrete loss of noradrenergic and serotonergic neurons, pertaining to mood regulation [13].

Treatment involves different strategies, depending on the severity of depressive symptoms. Pharmacotherapy of depressive symptoms in PD includes selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) (Table 1) [15,17]. SSRIs, especially citalopram and sertraline, are well tolerated and

Table 1. *Neuropsychiatric symptoms of Parkinsonian Syndromes and their treatment strategies.*

Parkinsonian Syndrome	Common Neuropsychiatric Symptoms	Current Treatment Strategies
Parkinson's Disease (PD)	Depression Anxiety	• Selective serotonin reuptake inhibitors (SSRIs) (e.g. citalopram, sertraline) • Tricyclic antidepressants (TCAs) (e.g. amitriptyline) • Cognitive-Behavioral Therapy (CBT)
	Psychosis	• Antipsychotics (e.g., quetiapine, clozapine) and/or Cholinesterase Inhibitors for acute psychosis • Modification of dopaminergic medication for chronic psychosis
	Impulse Control Behaviors (ICBs)	• Modification of dopaminergic medication
	Apathy	• Dopaminergic medication
	Rapid eye movement (REM) sleep behavior disorder	• Melatonin • Clonazepam
Dementia with Lewy Bodies (DLB)	Psychosis: • Recurrent complex visual hallucinations • Verbal and often incomprehensible auditory hallucinations • Delusional misidentification (e.g. Capgras syndrome) and paranoid delusions	• Cholinesterase inhibitors (e.g. rivastigmine, donepezil) • Antipsychotics (e.g. pimavanserin) should be used with considerable caution
	Depression	
	Anxiety	
	Apathy	
	REM sleep behavior disorder	• Melatonin • Clonazepam
	Hypersomnia	• Armodafinil
Progressive Supranuclear Palsy (PSP)	Apathy	• SNRIs (e.g., venlafaxine)
	Depression	• SNRIs (e.g. venlafaxine) • SSRIs (e.g. fluoxetine, paroxetine, sertraline, citalopram)
	Anxiety	• SSRIs
	Agitation	• Clozapine
	Irritability	
	Disinhibition	
	Sleep disturbances	• Mirtazapine, melatonin, clonazepam, zolpidem and trazodone
Corticobasal Degeneration (CBD)	Depression	• SSRIs
	Apathy	• SNRIs
	Anxiety	
	Frontal lobe dysfunction (e.g. compulsive behaviors, inappropriate behavior)	
Multiple System Atrophy (MSA)	Depression	• SSRIs
	Apathy	
	Anxiety	
	REM sleep behavior disorder	• Clonazepam

relatively safe for people with PD [16], while TCAs have more adverse effects and should be carefully used despite their high antidepressive efficiency. Of note both SSRIs and TCA amitriptyline are included in the 2023 WHO list of essential medicines and are expected to be available in all countries across the globe [10]. Serotonin norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs) and dopamine agonists have also been used in the treatment of depressive symptoms in PD [17]. Non-pharmacological interventions such as electroconvulsive therapy, transcranial brain stimulation and cognitive-behavioral therapy (CBT) were shown to be effective in managing depressive symptoms in PD [17]. In particular, CBT is very promising regarding working both with people with PD and their care partners, so that their distress is diminished [17,18].

Psychotic symptoms and Impulsive-compulsive Behaviors (ICBs) are further neuropsychiatric symptoms of PD. Psychosis in PD has been associated with older age and longer disease duration. In particular, the prevalence of psychosis increases from 3% around the time of PD diagnosis to 10% two years after the initial diagnosis [19]. In another study, in 82.7% of individuals with PD, psychosis spectrum symptoms were observed over a period of 36 months [20]. The point prevalence of psychotic symptoms in PD is 25–40%, while the cumulative incidence during the disease is 50–60% [14]. Even though visual hallucinations are the most common psychotic symptoms in PD, minor hallucinatory phenomena (sense presence, passage hallucinations, illusions), delusions and non-visual hallucinations may also exist [21]. In addition, ICBs have been reported in 3.5 to 43% of people with PD using dopamine replacement therapy, while people manifesting ICBs are more likely to use dopamine agonists than individuals with PD but without ICB [22]. Point prevalence of ICBs is estimated to be 14% and 5-year cumulative incidence 46% [14]. ICBs include among others hypersexuality, pathological gambling, excessive eating and buying, hoarding and the Dopamine Dysregulation Syndrome which is characterized by addictive behavior and excessive use of dopamine replacement therapy [23,24,25]. Both psychotic symptoms and ICBs in PD are pathogenetically linked to the treatment with dopamine agonists (DA) [16,26].

Regarding the management of psychotic symptoms in PD, it is important to differentiate the treatment strategy of an acute and potentially life-threatening PD psychosis, the onset of which is sudden, from a chronic setting. Acute psychotic symptoms are primarily managed with the treatment of the underlying cause, including general measures, treatment of specific triggers, adaptation of medication, and/or addition of cholinesterase inhibitors in cognitively impaired individuals with PD (rivastigmine, donepezil, or galantamine) and antipsychotics such as clozapine or quetiapine when not manageable with the previously mentioned steps [27]. Of note, quetiapine is considered a therapeutic alternative to risperidone in the 2023 WHO model list of Essential Medicines [10]. The treatment of chronic psychotic symptoms in Parkinson's Disease (PD) focuses on adjusting dopaminergic medication without worsening motor function or causing withdrawal symptoms from dopamine agonists. These withdrawal symptoms can include anxiety, dysphoria, fatigue, dysautonomia, sleep disturbances, generalized pain, and medication cravings. This severe and stereotyped withdrawal syndrome is specific to dopamine agonists and cannot be alleviated by levodopa or other PD medications [28,29]. The recommended order for reducing medication is as follows: anticholinergic agents, selegiline, amantadine, dopamine receptor agonists, COMT-inhibitors, and lastly levodopa [27]. If reduction of medication does not improve psychosis, the use of cholinesterase inhibitors or antipsychotic medication, similar to the treatment of acute psychotic symptoms, should be considered [27]. Pimavanserin, which acts as both an inverse agonist and antagonist at the 5-HT2A serotonin receptors, is approved by the U.S. Food and Drug Administration (FDA) for the treatment of PD psychosis and does not affect the motor symptoms of the disease [30].

In the lack of effective medications, managing ICBs in PD embodies a therapeutic challenge. Once again, a cautious reduction or discontinuation of dopaminergic agonists is recommended to minimize the risk of motor symptom deterioration or withdrawal symptoms. This careful balance aims to control both motor symptoms and aberrant behaviors [23]. Findings related to the efficacy of selective serotonin reuptake inhibitors, bupropion, antipsychotics, mood stabilizers, and zonisamide in managing ICBs in PD are conflicting, while a beneficial impact of amantadine on treating pathological gambling has been reported, even though amantadine has been associated with the presence of ICBs [31,32,33]. Non-pharmacological interventions which are increasingly receiving empirical support in the management of neuropsychiatric symptoms in dementia [34], may be encouraged in people with ICBs in PD, too.

Anxiety symptoms have a point prevalence of 30% in individuals with PD. They can present with many forms, including generalized anxiety disorder, acute stress disorder, panic attacks, phobias and post-traumatic stress disorder [16,35]. The treatment of anxiety symptoms relies on antidepressants such as SSRIs [36]. Fluoxetine or a therapeutic alternative to it (e.g. citalopram, escitalopram, sertraline) are included in the WHO list of Essential Medicines and are supposed to be available even in LMIC [10]. The use of benzodiazepines might be helpful, but their excessive use in people with PD should be avoided, due to the high risk of balance loss and falls [36]. CBT for the treatment of PD anxiety is also being reported [37].

The prevalence of apathy in PD is estimated up to 35-70% and might be present at the prodromal stage [14]. It includes lack of motivation and initiative and indifference. Although depression often occurs alongside apathy in Parkinson's disease, it is important to distinguish between these two symptom categories [38]. Numerous drugs are studied for their role in the management of apathy in PD but there is still no approved treatment [39]. Apathy might improve with dopaminergic medication, especially if it is associated with off periods or occurs during dopaminergic medication decrease [14].

Sleep can also be affected in PD, with a wide phenotypic spectrum, such as insomnia, daytime sleepiness, circadian disturbances and parasomnias [40,41]. Rapid Eye Movement (REM)-sleep Behavior Disorder (RBD) is a parasomnia highly associated with synucleinopathies and is characterized by loss of REM sleep muscle atonia, resulting in undesirable, recurrent complex motor or vocal dream enactment behavior [42]. Since RBD often occurs years before the onset of the motor symptoms and the diagnosis of PD, it could potentially be useful in early diagnosis and treatment of the disease [42]. Of note, medications (e.g. antidepressants including venlafaxine, mirtazapine, and selective serotonin reuptake inhibitors) used for managing neuropsychiatric symptoms can worsen RBD [42]. Treatment of RBD includes melatonin and clonazepam [43], which are not included in the WHO list of Essential Medicines resulting in care inequity. Pramipexole has been assessed in observational studies as a potentially effective treatment for RBD in individuals with Parkinson's disease, but it increases the risk of psychosis [44,45].

Dementia with Lewy Bodies

DLB is probably the second most common cause

of dementia, even though it largely remains underdetected or misdiagnosed [46,47,48]. Clinically, DLB manifests as progressive cognitive decline, along with recurrent complex visual hallucinations, REM sleep behavior disorder and one or more spontaneous cardinal features of parkinsonism namely bradykinesia, rigidity or rest tremor which occur after or simultaneously with the onset of dementia [49]. The cognitive deficits in DLB and in the oligosymptomatic, pre-dementia clinical entity of Mild Cognitive Impairment with Lewy Bodies (LB) mainly pertain to fluctuating attention/executive dysfunction and visual processing rather than memory and object naming [50].

Psychotic symptoms are prominent among individuals with DLB. Recurrent, complex, well-formed visual hallucinations, featuring people or animals are present in approximately 80% of people with DLB and are characteristic of LB pathology [49]. They can be accompanied by typically verbal and often incomprehensible auditory hallucinations and can sometimes co-occur with other disturbances of visual perception, such as passage hallucinations, sense of presence and visual illusions [49,50,51]. Of note, unimodal auditory hallucinations are uncommon. Auditory hallucinations in DLB are described as a "background soundtrack" accompanying visual hallucinations and their content as non-paranoid, non-imperative and mood-incongruent [51,52]. Interestingly, among people with DLB, female sex, visual hallucinations, hearing impairment, depression and delusions are risk factors for the development of auditory hallucinations [51]. Furthermore, the most common types of delusions in DLB are delusional misidentification (e.g. phantom boarder, delusional misidentifications of people, objects and reduplication of people) and paranoid delusions, particularly delusions of theft and persecution [52-53]. In addition, Capgras syndrome, characterized by the delusional belief that a person has been replaced by an identical imposter, is common in DLB and usually occurs in the presence of anxiety and visual hallucinations [54]. Delusions in individuals with DLB have been linked to poorer cognitive function and more severe neuropsychiatric symptoms [53].

The management of hallucinations and other psychotic symptoms in DLB may prove to be tantalizing for clinicians. Use of antipsychotics should be approached with considerable caution, due to the neuroleptic sensitivity of approximately 50% of people with LBD which represents a potentially fatal complication (Table 1)

[49,55,56]. In addition, exposure to dopaminergic therapy and anticholinergic medication within the frames of treatment of extrapyramidal symptoms may induce or exacerbate psychotic symptoms [49,55]. Interestingly, the cholinesterase inhibitors donepezil and rivastigmine are efficacious in improving cognition, reducing hallucinations and delusions and improving daily activities [55,56], with rivastigmine having been more extensively studied than donepezil. Moreover, pimavanserin is more effective and tolerable than quetiapine in managing psychotic symptoms [57]. Even though quetiapine and olanzapine are efficient in reducing hallucinations and delusions, individuals with DLB often do not tolerate them [57,58]. Treatment with the atypical antipsychotic risperidone appears to be inefficacious and even less tolerable [58]. Of note, a study across 40 nursing homes in Sweden revealed that more fluctuating cognitive deficits, visual hallucinations, and parkinsonian symptoms in DLB pertained to higher antipsychotic usage and were inversely related to anti-dementia medication [59]. These observations could imply a trend of the most vulnerable residents of the nursing homes to be treated with antipsychotics, which is in fact inappropriate given that they are at higher risk for adverse events such as parkinsonism, hypersomnia, sedation, extrapyramidal symptoms, delirium and increased mortality. In addition, it could indicate insufficient use of anti-dementia medication in older patients [59]. Despite the fact that expert opinion from Delphi consensus group and national guideline bodies have endorsed the use of rivastigmine and donepezil for neuropsychiatric symptoms in patients with DLB and the lack of evidence supporting the use of any antipsychotic drug in such patients [60], cholinesterase inhibitors are not included in the WHO model list of essential medicines, while in many LMIC no access to them is granted [61]. Thus, care inequities arise for people with psychotic symptoms in DLB across the globe.

Apathy, anxiety and depressive symptoms are common symptoms in people with DLB and embody supportive clinical features for DLB diagnosis [49]. For instance, depression is present in about a third of DLB patients [60]. Apathy, which is linked to faster cognitive decline [62,63], anxiety and appetite disturbances are useful predictors of conversion from MCI-LB to DLB [51,64]. Interestingly, anxiety may develop even four to five years before diagnosis and can manifest as panic attacks [65], while long-lasting, pervasive anhedonia [66] has been reported to be a characteristic depressive symptom of DLB, compared to other types of dementia

[67,68,69]. Of note, individuals with DLB are at higher risk of suicidal ideation compared to those with other types of dementia. Data on the use of antidepressants among individuals with DLB are limited to citalopram, which does not appear to be beneficial nor well tolerated [58]. In addition, there are concerns that antidepressants might affect sleep and worsen RBD [58].

Sleep disturbances are part of the LBD phenotype. RBD can occur even years before the onset of full-blown LBD [70]. People with DLB and/or their bed partners might experience serious injuries from limb movements or falls from bed during episodes of RBD, and commonly report vivid or violent dreams [71]. Interestingly, RBD in men develops at a younger median age than cognitive symptoms, whereas in women RBD and cognitive symptoms tend to emerge concurrently [72]. Moreover, hypersomnia is considered a supportive clinical feature for the diagnosis of DLB and is significantly more frequent and more severe in DLB and MCI-LB than in other neurocognitive disorders [71,73]. DLB and MCI-LB patients also exhibit a higher prevalence and severity of other sleep disorders, including insomnia, restless leg syndrome (RLS), periodic limb movements, sleep-related leg cramps, sleepwalking, and sleep-disordered breathing [71]. Retrospective case series in patients with RBD point to the usefulness of clonazepam, even though it should be prescribed with caution, since people with LBD are prone to gait disturbance, further cognitive decline, and are at high risk of falls [74]. Memantine, an NMDA receptor partial antagonist, is indicated for the treatment of moderate to severe dementia due to Alzheimer's disease. A 24-week randomized controlled study showed that memantine decreased physical activity during sleep in 20 patients with DLB, whereas the 22 patients in the placebo group worsened over the same period [75]. Limited data imply that armodafinil, which promotes wakefulness, may be a potential treatment for hypersomnia, while gabapentin may alleviate symptoms of restless leg syndrome [58].

Despite the weak evidence for people with DLB, non-pharmacological interventions (e.g. musical therapy and environmental modifications) are usually recommended as a first-line treatment for neuropsychiatric symptoms in DLB [60]. Non-pharmacological strategies which have been shown to be effective in individuals with Alzheimer's disease may be helpful in the management of neuropsychiatric symptoms in DLB. Nevertheless, no specific consensus exists, since these recommendations are mainly based on case reports and case series data [76].

Progressive supranuclear palsy

The key clinical features of progressive supranuclear palsy (PSP) are supranuclear gaze palsy, bradykinesia, rigidity, gait imbalance with frequent falls and subcortical and frontolimbic cognitive dysfunction [77]. The disease usually begins in the presenile period, with a mean age of onset at 63 years of age. Its prevalence is approximately 5/100.000 cases and it increases with age. Mean duration of illness is estimated at 5.9 years [77]. There are various clinical variants of the disease, the most important of which are: The classic phenotype, named Richardson syndrome (RS), PSP Parkinsonism (PSP-P), PSP-pure akinesia, PSP-corticobasal syndrome, PSP with frontal lobe cognitive or behavioral presentation, which includes the behavioral variant frontotemporal dementia (bvFTD) [77,78,79]. Depending on the distribution of tau pathological proteins, certain PSP phenotypes may resemble other disorders: PSP-P is similar to Parkinson's disease, PSP-PNFA resembles frontotemporal dementia, and CBS is akin to corticobasal degeneration. They differ from each other in terms of the severity and frequency of certain clinical and pathological features [77,79,80,81,82]. Patterns of neurocognitive deficits are executive dysfunction, apathy, bradyphrenia and disinhibition, decreased phonemic verbal fluency and impaired episodic memory to an extent similar to Parkinson's disease and frontotemporal dementia and less severe than in Alzheimer's disease [79,83,84,85,86,87]. Despite lack of consensus, the severity of executive dysfunction has been related to behavioral abnormalities (apathy in particular). Imaging reveals the characteristic "hummingbird sign" or "penguin sign". Atrophy of the midbrain results in a brainstem image (in the sagittal plane) in which the preserved pons form the "body of the bird" and the atrophic midbrain the "head" [88].

Neuropsychiatric symptoms may be the first signs of PSP, potentially leading to a misdiagnosis of the disease as a purely mental disorder rather than a neurodegenerative condition. Negative behavioral elements (apathy and depression) are more frequent than positive ones (irritability, impulsivity, and inappropriate social behavior) [77,83,84,87,89]. Of note, neuropsychiatric symptoms manifest in pathologically confirmed PSP at disease onset in 8% of individuals with the condition and in 60% of them 3 years after disease onset [77,90]. People with PSP are described as irritable, suspicious, arrogant, opinionated, and demanding, while a decrease in self-care and personal hygiene and a general feeling of anhedonia are also observed [77,84].

Apathy is the most common neuropsychiatric symptom in people with PSP [83,84,89,91]. A difficulty is observed in the processing of emotions, while individuals show a reduced ability to recognize emotions and look at faces, compared to healthy controls and individuals with PD patients [92,93]. Apathy is pathophysiologically related to dysfunction of the ventral prefrontal cortex (PFC) network which is particularly involved in reward and threat processing, as well as of subcortical regions of the thalamus and basal ganglia [77,87]. Since no disease-modifying treatments are available, the management of apathy may be based on non-pharmacological interventions, which include recreational activities and psychoeducation with the care partner's aid (Table 1) [94]. SNRIs, as for instance venlafaxine, as well as bupropion and amantadine could be prescribed [95]. In one case report, the use of zolpidem – a GABA agonist – greatly improved apathy [96].

Depression is also a prominent neuropsychiatric finding in PSP [77,83,84]. It usually manifests itself within one year from the time of diagnosis, but cases have been recorded where its appearance precedes the motor symptoms of the disease [97,98]. Its severity is not related to the severity of symptoms or cognitive impairment. Therefore, it remains unclear whether the genesis of depressive symptoms in PSP pertains to brain dysfunction or is the consequence of the effects of the disease itself (motor problems, loss of autonomy, difficulty in social life). The prevalence of depressive symptoms in PSP is approximately three times higher than in healthy controls [99]. Complicating the diagnosis of depression is the pseudobulbar affect (PBA), which in many ways mimics depressive symptoms and is present in approximately 50% of individuals with PSP, even though PBA can occur in other parkinsonian syndromes, too [100]. PBA is characterized by emotional lability and highlighted by a discrepancy between the emotional expressions of the individuals and their emotional experiences. Involuntary, sudden, and recurrent episodes of laughing and/or crying occur that tend to be inappropriate or disproportionate to the social context or stimuli [100]. Even though tricyclic antidepressants, like amitriptyline, have been used in the treatment of depression in PSP and they may even improve motor symptoms [101], they are not currently used because of their anticholinergic effects [101,102,103]. SSRIs (fluoxetine, paroxetine, sertraline, citalopram) and SNRIs (venlafaxine) are both effective at treating depressive symptoms in PSP and agents of the former category are included in the WHO

model list of Essential Medicines [95] but their use could paradoxically worsen symptoms of apathy [101]. Interestingly, transcranial magnetic stimulation was proven effective in one case of treatment-resistant depression [94]. Moreover, SSRIs, dextromethorphan and quinidine have been used to control PBA and abrupt laughing or crying episodes [101].

Sleep disorders are also common in PSP. Decreased sleep duration and quality have been observed, as well as RBD. Risk of obstructive sleep apnea and restless legs syndrome were also detected [104]. Lifestyle changes, such as stopping diuretics, avoiding amantadine administration late at night and increasing exercise during the day could improve the quantity and quality of sleep [94]. Agents like mirtazapine, melatonin, clonazepam, zolpidem and trazodone are currently used for treating sleep disturbances in PSP [95,101,103]. Mirtazapine is particularly potent in treating difficulties with sleep initiation.

Approximately one-third of individuals with PSP experience significant anxiety-, agitation-, irritability- and disinhibition symptoms [77,84,87]. Adjustment disorder with anxiety as well as generalized anxiety disorder have also been reported in a smaller proportion of people with PSP [77]. SSRIs are prescribed for alleviating depressive and anxiety symptoms. Clozapine is used to treat agitation symptoms in PSP despite uncertainties related to its beneficial effects [101].

Psychotic symptoms, such as hallucinations and delusions are rarely observed in PSP [95,101,105]. This is the reason why psychosis is the only group of neuropsychiatric symptoms that separates PSP from other parkinsonian syndromes, as it occurs with a much lower frequency in the former. For instance, the presence or absence of visual hallucinations can contribute to the differential diagnosis of the disease that causes the Parkinsonian syndrome [77]. In cases with psychotic symptoms, quetiapine or clozapine can be used [102].

A significant percentage of patients suffering from PSP seem to present with obsessive-compulsive personality disorder (OCPD) symptoms [106]. Such symptoms include preoccupation and insistence on details, rules, lists, order and organization, perfectionism, excessive conscientiousness, rigidity and stubbornness. A study comparing individuals with PSP and MSA found that more than one-third of patients suffered from OCPD, a rate significantly higher than that of individuals with MSA [106]. The presence of OCPD symptoms in these patients is probably attributable to a malfunction of the basal ganglia system, which includes the orbitofrontal circuits [106].

Non-pharmacological measures may prove useful in managing neuropsychiatric symptoms in PSP. Reduction of anticholinergic drugs, identification of potential distress causes and occupational therapy have been proposed as strategies contributing to the management of behavioral and psychological symptoms in PSP [95]. Person-centered, multidisciplinary approaches have been proposed so that neuropsychiatric symptoms of individuals with PSP are treated in a holistic and individualized way [101].

Corticobasal Degeneration

The most common CBD clinical phenotype is Corticobasal Syndrome (CBS) an akinetic-rigid parkinsonian syndrome with poor response to levodopa and a combination of asymmetric motor and non-motor symptoms which may be associated with cognitive-behavioral disorders such as apathy, depression, difficulty in performing commands, aphasia, apraxia and the alien limb phenomenon [95]. Neuropsychiatric disorders are common in CBD, clinically heterogeneous and may occur at the onset of the disease before motor symptoms. Thus, they are not of secondary importance in relation to motor impairment. They can be detrimental to the quality of life of both people with CBD and their care partners [107,108,109,110].

Depressive symptoms are the most common neuropsychiatric symptoms in individuals with CBD [90,107,108,109,110] and were shown to be more severe in CBD than in PSP or in Alzheimer's disease [89,111,112]. The prevalence of depressive symptoms in CBD seems to exceed 70%. Interestingly, a depressive profile dominated by high hopelessness predicted early-stage CBD with an accuracy of 70% [113]. People with CBS have higher prevalence of suicidal and death ideation than those with PD [114]. Anxiety symptoms are less prevalent than depressive symptoms in CBD, but they also appear to reduce quality of life. SSRIs are administered in the case of depression, while SNRIs are preferred for managing apathy [115].

Signs of frontal lobe dysfunction such as voracious appetite, inappropriate behavior, executive dysfunction, and impaired spontaneity have been reported in a few systematic studies and several case reports [109]. Of note, some of these manifestations were related to certain clinical phenotypes of pathologically confirmed CBD. In particular, phenotypes dominated by aphasia

and frontal symptoms included compulsive behaviors, socially inappropriate and disinhibited behavior, and a voracious appetite; Individuals with CBD exhibiting a predominantly frontotemporal dementia phenotype manifested irritability, aggression, and impaired judgment, while those with a CBS phenotype were more prone to depression [107].

Certain neuropsychiatric symptoms are less prevalent in CBD compared to other parkinsonian syndromes. For instance, the prevalence of RBD is remarkably lower in CBD than in other diseases causing parkinsonism. Nonetheless, there have been case reports in which insomnia and restless leg syndrome have been described in CBD [116,117,118]. In addition, the presence of hallucinations excludes CBD from the differential diagnosis [119]. Furthermore, photophobia is less common in CBD patients compared to those with PSP [116].

Treatment of neuropsychiatric symptoms of CBD is currently limited to symptomatic relief (Table 1) [95]. The management of neuropsychiatric symptoms includes reducing drugs that may exacerbate them, such as benzodiazepines and tricyclic antidepressants. Recently, a multidisciplinary approach to patients has been proposed to alleviate neuropsychiatric symptoms and improve the quality of life of both people with CBD and their care partners [120].

Multiple System Atrophy

Multiple System Atrophy (MSA) is a rare, sporadic, rapidly progressive neurodegenerative disorder [121]. Its clinical features are a combination of parkinsonian symptoms (bradykinesia, rigidity, postural instability, resting tremor), cerebral symptoms (ataxic gait with early falls, ocular movement abnormalities, pyramidal signs) and autonomic failure (orthostatic hypotension, urogenital/gastrointestinal dysfunction), which is an early manifestation of the disease and a sine qua non for its diagnosis [86,122,123,124,125,126]. There are two clinical subtypes of MSA: MSA-P with predominant parkinsonism and MSA-C with predominant cerebral symptoms. Both subtypes include dysfunction of the autonomic nervous system [86,125]. In MSA, impairment in visuospatial, constructional, and verbal functions is observed [87,125,127].

Even though neuropsychiatric symptoms have not been the focus of MSA research for many years, it has recently been found that these symptoms are not only very common in MSA, but also have a strong negative impact on the quality of life of individuals with MSA

and their care partners [86,123]. The most common neuropsychiatric symptoms in MSA are depression, apathy, anxiety disorders and RBD [126,127,128].

Depression is the most common neuropsychiatric symptom in MSA. It is estimated to affect as many as 80% of individuals with MSA [87]. It also varies in severity, spanning from mild to severe depression with suicidal ideation [86,87,128]. According to most studies, depression seems to be independent of the severity of the motor and autonomic dysfunction of MSA, suggesting that it is part of the spectrum of the clinical manifestations of the disease, rather than a consequence of other symptom groups [121,123,127]. Interestingly, people with MSA appear to be more severely affected by depression than individuals with PD or PSP [129]. Antidepressants, mainly SSRIs, are commonly used to treat depression, but are not effective for apathy, while tricyclic antidepressants are usually avoided in MSA as they worsen autonomic failure symptoms [86].

Apathy, anxiety and RBD can be present in MSA. Apathy is the second most common neuropsychiatric symptom in MSA [127,128]. Of note, the occurrence of apathy in the absence of depressive symptoms is reported to be lower in MSA compared to PSP [129]. Moreover, individuals with MSA exhibit more symptoms of anxiety compared to healthy controls. Nonetheless, anxiety symptoms are less common and less severe in MSA in comparison to PSP and PD patients [87]. RBD is the most common sleep disorder in MSA, while in some rare cases restless leg syndrome, sleep apnea and extremely vivid dreams have been reported [86,87,121]. Clonazepam may be used for RBD [87]. The management of neuropsychiatric symptoms of MSA is symptomatic (Table 1). Non-pharmacological interventions such as psychotherapy, physiotherapy and occupational therapy can be used to alleviate the symptoms of MSA and improve the quality of life of both people with the disease and their care partners [86,87,127].

CONCLUSIONS

To conclude, neuropsychiatric symptoms are present in all parkinsonian syndromes. They may contribute to the differential diagnosis of their cause, while they pose in many cases a heavy burden to people with such syndromes and their care partners and families. The impact of these symptoms on performance in activities of daily living is a research question warranting investigation. The management of neuropsychiatric symptoms in

parkinsonian syndromes embodies a daunting task, since it is purely symptomatic while people with these syndromes are very sensitive to the side effects of medications commonly used in treating neuropsychiatric symptoms and the access to modern antipsychotics and/or antidepressants is not always granted in LMIC. Finally, there is an urgent need for studies aiming at standardizing pragmatic and non-pharmacological interventions that are applicable even in primary healthcare settings to manage neuropsychiatric symptoms in parkinsonian syndromes. These interventions are crucial as they are commonly well tolerated, help manage symptoms, and improve quality of life.

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The impact of the COVID-19 pandemic on routine maternal vaccination acceptance; A mini review

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Abstract

In this mini review we aimed to identify how the COVID-19 pandemic affected pregnant women's acceptance of routine maternal vaccines and discuss further about the factors influencing decision making. The literature was reviewed from January 2020 to October 2023 in PubMed and Google Scholar, searching for relevant articles. The systematic review conformed to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines. The inclusion criteria were fulfilled by 12 studies conducted in several countries. Overall, a positive impact of the pandemic was suggested in seven articles, while four articles showed no alterations in pregnant women's opinions and attitudes towards routine maternal vaccines. Based on the results of this review, there is evidence that the COVID-19 pandemic may have had a positive impact on maternal vaccination acceptance. In order to effectively overcome the obstacle of vaccine hesitancy in the pregnant population, reliable professional information should be communicated targeting safety, effectiveness and availability of routine maternal vaccines.

Key words: *COVID-19; impact; routine maternal vaccination; acceptance*

INTRODUCTION

Routine maternal vaccination

The World Health Organization (WHO) as well as the Advisory Committee on Immunization Practices (ACIP) suggest that both the inactivated influenza vaccine and the Tdap (Tetanus, diphtheria and acellular pertussis) vaccine should be given as part of routine as antenatal care [1,2]. Additionally, the American College of Obstetricians and Gynecologists (ACOG) strongly recommends

COVID-19 vaccination during pregnancy [3]. All vaccines are effective and safe in protecting pregnant women, fetuses and infants up to six months of age from communicable and vaccine-preventable diseases (VPDs) [1,2,3]. Since fetuses and neonates have immature and relatively ineffective immune system, they receive passive immunity to potential pathogens by transplacental IgG transfer from the mother, which begins at about the 17th week of gestation, continues until birth and is followed by postnatal breast milk-derived antibody transfer. Consequently, there is a strong dependence of fetuses and newborn infants on maternal immunity which highlights the pivotal role of immunization of pregnant women [7,8].

During pregnancy, the human body faces several biological changes including alterations in metabolism, ventilation and tidal volume, blood pressure and vessel

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permeability, along with immunological regulations [5]. The latter are crucial for the selective suppression of Th1 cell-mediated immunity and up regulation of regulatory T-cells activity [11], which is a protective mechanism against recognition of antigens of the fetus and consequent miscarriage. However, this compromise of maternal immune response leads pregnant women to be more vulnerable to infectious diseases and to have greater chances of experiencing severe infection-related complications, compared to non-pregnant women [9,12]. One of the major epidemiological burdens is caused by influenza virus, which puts pregnant population at increased risk for severe disease and hospitalization, while complications in pregnancy, such as preterm delivery and small for gestational age infants, are more likely to happen [10,13,14].

Bordetella pertussis is the second pathogen against which there is a strong recommendation for routine maternal vaccination, affecting mostly neonates and young children, causing life-threatening clinical manifestations and raising mortality in infants up to 2 months of age [15,16]. Unless Tdap vaccine is administered during pregnancy especially in the third trimester, infants remain vulnerable to pertussis until their primary vaccination series. Thus, infants under six months of age are considered to be a high-risk population for severe pertussis infection [15,16,17]. Taking into consideration that young infants are also not included in influenza vaccination recommendations before that specific age, the imperative need for routine maternal vaccination to protect the youngest and most vulnerable infants from these preventable infectious diseases, is emphasized [18].

COVID-19, obstetric care and maternal vaccination

The COVID-19 pandemic, caused by the Severe Acute Respiratory Syndrome-Coronavirus 2, (SARS-CoV2) outbreak in December 2019 in Wuhan, China, had a massive impact on healthcare services globally. In particular, obstetric care, which usually includes routine visits for the best prenatal and postnatal outcome, faced significant challenges including remote counseling, monitoring and guidance of pregnant women, besides access to vaccination [19,20,21]. Apparently, healthcare practitioners had to lead the campaign of communicating the undoubtful benefits of immunization against COVID-19 not only for the mothers but also for their babies [2,4]. Thus, the experience of the pandemic demonstrated that

obstetricians' and midwives' recommendation for vaccination remained the most influencing factor to increase vaccine acceptance and outweigh hesitancy [22,23]. It is of note that the internet and social media were also significant sources of information about medical subjects, such as complications of COVID-19 during pregnancy and COVID-19 vaccine's safety and efficacy [24,25]. This review takes a comprehensive approach to clarify the impacts of COVID-19 pandemic on willingness and acceptance of routine maternal vaccination from pregnant women.

METHODS
Review methods and eligibility criteria

This systematic review was organized and conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [26]. We reviewed all the existing literature from January 2020 to October 2023, focusing on articles relative to the impact that the COVID-19 pandemic had on the acceptance of routine vaccination from pregnant individuals. All of them were written in the English language, while articles in other languages were excluded. Only full-text accessible articles were eligible for review, with particular interest in observational studies (Figure 1).

Information sources

PubMed and Google Scholar databases were thoroughly searched to select potential articles. The keywords and combinations of words used to select the relevant articles are the following: *COVID-19, pandemic, pre-pandemic, post-pandemic, impact, influence, affected, vaccines, vaccination, immunization/immunization, pregnancy, routine maternal, antenatal, pregnant, Tdap, pertussis, influenza , acceptance, accepted, willingness.* By screening the references of included articles using 'the snowball method', additional articles were retrieved. Duplicate publications were identified and excluded. Overall, we identified 274 potentially relevant studies (Figure 1) and screened all of them by title and abstract. Of these, we removed 61 duplicates, 196 studies that did not clearly relate the COVID-19 pandemic with routine maternal vaccination, one study published in Spanish and three studies that we did not have full access to the content but were excluded from the abstract. As the grey literature and national reports were not eligible for inclusion, another study, published by the Canadian Government, was excluded. We, therefore, included 12 articles.
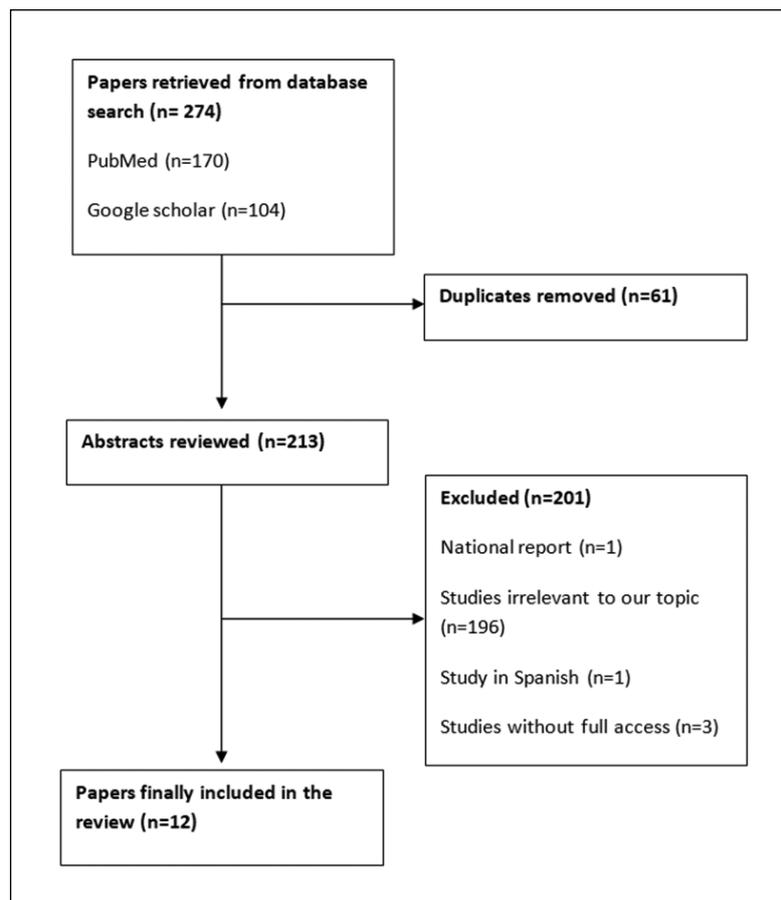
Figure 1. Study flowchart to identify and select eligible studies in the systematic review.

RESULTS

In total, the authors included 12 articles that specifically analyze, describe or refer to any potential impact that the COVID-19 pandemic may have had on routine maternal vaccination acceptance. In contrast to the limited number of articles, we tried to include studies conducted in a variety of countries, aiming to achieve a global approach (Table 1). Our main goal was to identify the effects of the pandemic on the perceptions of pregnant women for routine maternal vaccination. The majority of the reviewed articles were questionnaire-based.

Impact of the COVID-19 pandemic on the acceptance of routine maternal vaccination

During the pandemic pregnant women faced several unprecedented difficulties and changes in their standard prenatal care [18]. However, our review showed that their perceptions about routine maternal vaccination remained unchanged, as reported in four articles [31,33,37,38], or may have been positively affected by the pandemic, which is an interesting finding of seven articles [28,29,30,32,34,35,36]. In addition, a common conclusion of these articles was the fact that the COVID-19 pandemic raised awareness about the benefits of maternal vaccines and in general positively changed pregnant women's attitudes towards vaccination. One study in Turkey also highlighted a 28,9% decrease in maternal vaccine hesitancy during the COVID-19 outbreak [33]. On the other hand, a study from Pakistan showed a 28,8% decrease in Tetanus Toxoid maternal vaccination during the pandemic [27].

As far as immunization against influenza is concerned, the higher acceptance rate during the COVID-19 pandemic [30,32,34,36] and the observed positive link between COVID-19 and influenza vaccine uptake [32], may indicate that pregnant women's opinions regarding influenza viral infection and their willingness to receive the vaccine has been positively influenced by the pandemic.

Of note, two articles found that the maternal atti-

Table 1. *Studies referring any impact of the Covid-19 pandemic on routine maternal vaccination acceptance.*

Reference	Country /year of publication	Study Type	Number of participants (if any)	Main findings
Chandir et al	Pakistan (2020)	Retrospective data-analysis study	-	A 28,8 % decrease in maternal Tdap vaccine was observed due to missing follow-up appointments during the spread of Sars-Cov-2.
Anderson et al	UK (2021)	Qualitative interview study	n=31	The pandemic had elevated the importance of routine maternal vaccines.
Cavaliere et al	Italy (2021)	Cross-sectional study	n=195	The COVID-19 pandemic raised awareness and had a positive impact on attitudes towards immunization during pregnancy.
Wang et al	China (2021)	Multicentre cross sectional study	n=2568	The higher acceptance rate of influenza vaccine during the Covid-19 pandemic may indicate raised awareness of pregnant women towards protection through vaccination.
Saleh and Halperin	Israel (2022)	Online questionnaire-based study	n=410	The pregnant women participating in this survey did not change their approach towards influenza vaccination despite the 2nd and 3rd wave of COVID-19.
Pisula et al	Poland (2022)	Cross-sectional study	n=515	The increase in vaccination acceptance might be influenced by the pandemic; positive link between COVID-19 and influenza vaccine uptake.
Gencer et al	Turkey (2022)	Cross-sectional study	n=152	The COVID-19 pandemic caused a decrease in vaccine hesitancy in 28,9% of the participants; no effect to 50,6 % and positive effect to 44,1% for future vaccinations.
Lumbreras Areta et al	Switzerland (2022)	Multicentre-prospective survey-based study	n=951	Comparing the findings of this survey during the pandemic (2021) with the maternal vaccination rates in 2019, those of influenza were significantly higher indicating increased vaccine awareness during the pandemic. Tdap rates were similar during both seasons.
Bruno et al	Italy (2022)	Repeated cross-sectional study	n=104/n=241	The pandemic may have positively affected pregnant women's opinions about vaccination.
Shamoun et al	USA (2022)	Retrospective descriptive cross-sectional study	n=293/n=185	The pandemic had a positive impact on influenza vaccination rates in the pregnant population. No difference in Tdap vaccination rates.
Kim and Kim	Korea (2023)	Cross-Sectional study	n=351	The Covid-19 pandemic did not affect or increased the uptake of influenza vaccine in pregnant women.
Zimmerman et al	USA (2023)	Qualitative study	n=42	The COVID-19 pandemic had not affected the perceptions towards vaccination in pregnancy (67%)- 19% positive impact.

tudes towards Tdap remained unchanged and similar to pre-pandemic years [34,36]. One article reported negative impact [27], in contrast with the conclusion of a study from the USA that showed greater acceptance of maternal tetanus vaccine, compared with other vaccines [38].

The pivotal role of healthcare practitioners

Among the reviewed articles mentioned above, one study from the USA showed that 79%-81% of the participants were more inclined to receive influenza and Tdap vaccines if their doctor recommended them to do so [38], while two more studies stated that a medical recommendation would make mothers more positive to receive the vaccines [29,36]. In addition, a Polish study reported that the majority of its participants would prefer to receive better and more detailed information about maternal influenza vaccination from their healthcare practitioners, even though they were not offered the vaccine during their pregnancies [32]. Moreover, an Italian survey, comparing beliefs of pregnant women before and after the pandemic, found that in both periods the most trusted source of information about vaccines were institutional sources and healthcare providers [35]. With regards to influenza, a Korean survey found that trust in healthcare professionals was significantly higher in pregnant women vaccinated against influenza [37], whereas a study from Israel highlighted that although pregnant women's trust in healthcare practitioners is a fundamental factor for vaccine compliance, their recommendations for flu vaccine were ignored during the pandemic [31].

Factors that influence maternal vaccination uptake

Except from the recommendation from a healthcare practitioner, other factors determining the decision for vaccination in pregnancy, as highlighted during the pandemic, include mother's level of education with women with higher academic degrees being more inclined to get vaccinated [31,34,55], ethnicity [57], younger maternal age [55,57] and working status [56] along with average income per family member [32]. Additionally, what the COVID-19 pandemic definitely clarified was the power of influence of the internet and social media on public opinion about medical issues, such as vaccine confidence [24]. In particular, one article in this review mentioned that non-institutional websites with COVID-19 related content received significant attention during the pandemic [35]. Also a study from Turkey related vaccine hesitancy with fear derived from negative news from social media [33], while another study characterized the Internet as the main source of information about the pandemic [32].

DISCUSSION

In the era of COVID-19, vaccination in general and particularly during pregnancy was a widely discussed topic. The fact that pregnant women were excluded from clinical trials of COVID-19 vaccines and the consequent lack of evidence about safety and efficacy regarding this population, led them to question the need of vaccination [24,32,42,46,47,48,59]. As far as general population is concerned, the pandemic had also indirect effects on routine immunization programs by disrupting healthcare services, causing a worth-mentioning decline in childhood vaccination [49,50,51]. However, the experience of the pandemic resulted in raised awareness about routinely used vaccines and motivated people to search for more information about immunization [52].

Inevitably though, vaccine hesitancy remained one of the most critical obstacles to overcome, in order to minimize the mortality and the morbidity caused by vaccine-preventable diseases [53]. While pertussis, influenza and SARS-Cov2 vaccination during pregnancy protects not only pregnant women but also their fetuses and infants, strategies to decrease maternal hesitancy are of paramount importance [54].

A relationship of trust between pregnant women and health-care practitioners, such as obstetricians-gynecologists, midwives or general practitioners plays a pivotal role in the decision for vaccination [58]. The COVID-19 pandemic emphasized the health-care practitioners' responsibility for raising awareness about the availability, the indications and the benefits of routine maternal vaccination, along with addressing every question and concern about safety is of great significance [29,36,38,59].

This review article tried to identify how pregnant women's perceptions about routine maternal vaccination were affected by the COVID-19 pandemic, during which the subject of immunization was put in the center of interest and this area is obviously still evolving yet more data is to come.

Conclusions and future perspectives

Although there is yet limited data in the field, there is evidence that the COVID-19 pandemic has not altered and may have had a positive impact on maternal vaccination acceptance. However, further research and actions are needed and global harmonized vaccination strategies for pregnant women should be implemented. The pandemic reminded the international medical community that the role of health care practitioners, especially obstetricians and midwives, for raising public awareness about the risk of infectious diseases during pregnancy and the necessity of vaccination, is of paramount impor-

tance. In order to effectively overcome the obstacle of vaccine hesitancy in the pregnant population, reliable professional information should be communicated targeting the efficacy, the safety and the availability of routine maternal vaccines. Interestingly, the number of the available maternal vaccines will increase in the future, while the new maternal Respiratory Syncytial Virus (RSV) vaccine is already licensed [60] and others are yet to come. The lesson learnt from the COVID-19 pandemic could contribute to raise vaccine acceptance for future vaccines in pregnancy.

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Treatment of lupus nephritis: A glance into the future

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Abstract

Lupus nephritis is a severe manifestation of systemic lupus erythematosus that may be fatal. International guidelines have suggested immunosuppressive treatments with satisfactory results on kidney function of patients with lupus nephritis. Yet, it remains a difficult to treat manifestation as it may be unresponsive to existing therapies. Moreover, patients may show intolerance to drugs, or a flare may always come up despite the initial response. Cyclophosphamide or mycophenolate mofetil in combination with high doses of steroids are acceptable treatments to induce remission of the most severe histopathologic types of nephritis. Calcineurin inhibitors such as Tacrolimus may be an alternative, safe and effective treatment option. Maintenance of remission is achieved by mycophenolate mofetil or azathioprine or tacrolimus. Newer medications show promising results; Obinutuzumab an anti-CD-20 monoclonal antibody, voclosporin a new calcineurin inhibitor and Belimumab an anti-BAFF monoclonal antibody have displayed great effects on preserving Glomerular Filtration Rate and reducing proteinuria in patients with lupus nephritis. Anifrolumab, an anti - interferon receptor antibody also is one of the agents that target molecules implicated in pathogenesis of lupus nephritis. There are numerous studies that have highlighted several treatments as efficacious in lupus nephritis and others still ongoing whose results are expected with great interest.

Key words: *Systemic lupus erythematosus; lupus nephritis; induction and maintenance remission therapy; molecules targeted*

INTRODUCTION

Systemic lupus erythematosus (SLE) is a worldwide known multiorgan systemic disease. It has a preference for young women and several races. Among the organs that may be severely affected in patients with SLE, the kidneys are to be referred on top. Lupus nephritis (LN) may present early, up to the first 5 years after lupus diagnosis at nearly 2/3 of newly diagnosed patients [1]. LN is more common in African Americans, African-Caribbean, Hispanics and Asians. LN that may progress to end stage renal failure (ESRD) is observed mostly in African Americans and non-white populations. LN is associated with more cardiovascular events observed and increased morbidity and mortality as well.

Treatment of SLE is defined by targeting cells of innate and adaptive immunity that may be implicated in pathogenesis of the disease, like B lymphocytes, T lymphocytes, plasmacytoid dendritic cells (pDCs) or long-lived plasma cells (PCs) through surface molecules or innate pathways [2,3]. Antimalarials, glucocorticoids (GCs) and cytostatic agents that inhibit cell division are used to treat lupus manifestations.

The treatment of LN needs to be initiated at once in order to preserve renal function and save the kidney of a patient with LN before it is too late [1-3]. The approved medications that rheumatologists have been using aggressively so far are in accordance with international guidelines -either a kidney biopsy has been performed or not- in order to achieve remission of LN. Usually high doses of GCs are administered in combination with

immunosuppressive cytostatic agents such as cyclo-phosphamide (CYC) [4, 5, 7-10] and mycophenolate mofetil (MMF) [6,7-10]. In addition, calcineurin inhibitors (CNIs) are an alternative therapy like tacrolimus (TAC), cyclosporine A (CsA) and the newer voclosporin (VOC) [1,2]. The CNIs inhibit calcineurin, which is responsible for activating the transcription of IL-2 in lymphocytes, thus suppressing T lymphocytes. In addition, CNIs restore the actin cytoskeleton and ameliorate podocyte injury in this way, having an antiproteinuric effect as a consequence. Table 1 shows the main immunosuppressants used for LN, their targets and their effects on proteinuria and glomerular filtration rate (GFR).

After remission has been achieved, MMF may be given to preserve remission of LN. Alternatively, Azathioprine (AZA), a purine analogue that interferes with DNA replication and purine synthesis in T and B lymphocytes may be used for maintenance therapy or small dosages of CNIs like TAC or CsA may be used as well [7-10].

There are also non immunosuppressive interventions to treat LN such as Angiotensin-converting enzyme inhibitors (ACEs), Angiotensin receptor blockers (ARBs) and sodium-glucose transport protein 2 inhibitors (SGLT2i).

The aim of treatment selected depends on outweighing the effectiveness vs. toxicity of the medications. The patients should achieve complete or partial response through certain parameters chosen such as GFR and levels of proteinuria. In case there is no response or there is intolerance of the medications, the treatment should be altered. The recurrence of nephritis should be acknowledged rapidly in order to treat aggressively and save as many nephrons as possible. For all these reasons, quite a few agents are being investigated. This review refers to old and new treatments of LN with more emphasis on newer treatments and their result on LN.

Induction and maintenance therapy for LN approved so far

LN is subdivided in 6 subtypes in accordance with the histopathologic findings of the kidney biopsy in patients with lupus [11, 12]. The biopsy classification of lupus nephritis according to the International Society of Nephrology/Renal Pathology Society criteria (ISN/RPS 2003) [11] is depicted in table 2. Classes I and II of glomerulonephritis (GN) are non-proliferative types with a relatively better prognosis, while classes III and IV are proliferative types and more severe that need to be aggressively treated. Class V is a membranous type that can be diagnosed as pure membranous type in biopsy or in coexistence with classes III or IV, therefore in the second case the treatment should target the active or chronic proliferative lesions. Class VI is a sclerosing type involving >90% of glomeruli which are globally sclerosed with residual activity, so no immunosuppressive treatment could be efficacious. The guidelines that European Alliance of Associations for Rheumatology- European Renal Association-European Dialysis and Transplant Association (EULAR- ERA- EDTA) [7], American college of Rheumatologists (ACR) [8], Kidney Disease: Improving Global Outcomes (KDIGO) [9] and, Asia Pacific League of Associations for Rheumatology (APLAR) [10] follow

Table 1. *Medications approved and tested for treatment of LN.*

drug	Target	Effect on proteinuria	Effect on GFR
CYC	T,B cells	↓	↑
MMF	T , cells	↓	↑
CNIs	T cells , podocytes	↓	↑
BEL	BAFF of B cells	↓	↔
RTX	CD20 of B cells	↓	↑
OBI	CD20 of B cells	↓	↑
VOC	T cells, podocytes	↓↓	↔
ANF	type I interferon receptor subunit 1	↓	↔

Main immunosuppressive medications, their target and their effect on proteinuria and GFR in patients with LN.

Symbols: ↓ = reduced, ↔ = not reduced, ↑ = improved

Abbreviations: LN: lupus nephritis, GFR: glomerular filtration rate CYC: cyclophosphamide. MMF: mycophenolate mofetil, CNIs: calcineurin inhibitors, BEL: Belimumab, RTX: Rituximab, OBI: Obinutuzumab. VOC: Voclosporin, ANF: Anifrolumab BAFF: B cell activating factor

Table 2. *Classification of Lupus Nephritis ISN/ RPS 2003.*

Classification of LN ISN/ RPS 2003	
Class I	Minimal mesangial lupus nephritis
Class II	Mesangial proliferative lupus nephritis
Class III	Focal proliferative glomerulonephritis (<50% of glomeruli)
Class IV	Diffuse proliferative glomerulonephritis (≥50% of glomeruli)
Class V	Membranous glomerulonephritis
Class VI	Advanced sclerosing glomerulonephritis

Abbreviations: (ISN/ RPS): International Society of Nephrology/ Renal Pathology Society criteria

to achieve and sustain remission according to the type of nephritis are included in table 3.

All patients with a diagnosis of SLE have already been taking hydroxychloroquine (HCQ). In case of presentation of kidney involvement, CYC [4, 5] or MMF [6] in combination with high dosage of corticosteroids is considered to be the first line medication option for induction therapy in severe LN. CYC is administered intravenously (IV) at 500-1000mg/m^2 every month for six monthly cycles or at 500mg every two weeks for six cycles, the three-month EUROLUPUS scheme called [13]. MMF is preferred to CYC in women in reproductive age at a dosage of 3g/d. It is important to point out that MMF at a smaller dosage of 2 g/d is more commonly used in Asiatic patients with LN because of the smaller weight of this population and of lesser risk for infections.

CNIs, like TAC are more effective in type V membranous LN. TAC is also considered as a rescue therapy in Asian patients with refractory LN. TAC combined with a small dose of MMF for 12 months has been proven a good alternative treatment for non-responding patients with LN to standard treatments [14]. Another randomized controlled study (RCT) proved non inferiority of TAC vs. IV CYC, with a complete or partial response rate of 83.0% (117 of 141 patients) in the TAC group and 75.0% (93 of 124 patients) in the IV CYC group at 24 weeks after treatment [15]. In addition, kidney function and immunological parameters of patients in both groups were similar and serious adverse events were observed in 18.5% of patients in the TAC group and in 24.6% in the CYC group.

GCs are used combined with immunosuppressive therapy in a large dosage of three consecutive pulses of 1 gr methylprednisolone / d IV at the initiation of treatment. Then, prednisone is given orally at 0.3–0.5 mg/kg/day for one month and tapered to ≤7.5 mg/day at an interval of three to six months (EULAR–ERA–EDTA) [7]. All guidelines tend to agree and have similarities in reducing the dosage of IV pulses of methylprednisolone and in tapering as soon as possible the oral dosage of prednisone to the smallest dosage ≤7.5 mg/d at least in 3 months after the induction therapy [7-10]. This seems highly important if we take into account the serious adverse effects that the long use and high dose of GCs might provoke.

Since remission of LN has been achieved, induction therapy is continued for three to five years aiming mainly to reduce the number of flares and the extent of kidney damage. MMF is used at a dosage of 2 g or 1 g/d. AZA in a dosage of 2g /kg or Leflunomide (LEF) or low dose of CNIs like TAC or CsA are alternative agents [7, 9,10]. A recent trial compares administration of LEF vs. AZA [16] for maintaining remission in LN. Kidney flares were similar between the two groups compared: 15.7% in the LEF group vs.17.8% in the AZA group. The non-inferiority of LEF vs. AZA taking into account the safety of the drug makes LEF a good alternative for remission maintenance therapy.

WIN-LUPUS is a multicentre RCT [17] in which patients with LN that had achieved remission were randomized in two groups: 1) one group that continued immunosuppressive therapy with AZA or MMF plus HCQ (n=48) and 2) the other group that did not continue immunosuppressive therapy (n=48). The discontinuation of immunosuppressive therapy was non inferior for renal relapse rate for two or three years compared to the continuation of immunosuppressive therapy. Only severe renal or extra renal SLE flares were less frequent in patients who continued to take immunosuppressive therapy vs. patients that did not continue immunosuppressants (5/40 vs. 14/44 patients, p=0.035).

Newer medications for therapy of LN

Biologic agents other than the immunosuppressants described above have been used in cases of LN. Rituximab (RTX), one of these agents is a monoclonic antibody (mAb) against CD-20 of B lymphocytes thus inducing B cell depletion. RTX has been an excellent rescue therapy in refractory cases of LN. RTX administered in combination with GCs and immunosuppressive agents as CYC and MMF in patients with LN had as a result a significant improvement in 24-h proteinuria

Table 3. *International Recommendations for the treatment of lupus nephritis.*

LN	EULAR–ERA–EDTA 2019	ACR 2012	KDIGO 2021	APLAR 2021
Induction therapy Class III/IV ±V LN	**First line**: GCs + MMF (2–3 g/day) or low-dose IV CYC	GCs + MMF (2–3 g/day), or high-dose IV pulse CYC (low-dose for white Europeans)	**First line**: GCs (lower dose) + MMF (2–3 g/day), or low-dose IV CYC	**First line**: GCs + MMF (2 g/day), or high-dose IV CYC
	Second line: (i) MMF + CNI (TAC) (for nephritic range proteinuria); (ii) high-dose IV CYC (for high risk of kidney failure)		**Second line**: (i) MMF + CNI (TAC); (ii) high-dose IV CYC, or oral CYC	**Second line**: low-dose IV CYC, or TAC
Induction therapy Class V LN	**First line**: MMF (2–3 g/day	GCs + MMF (2–3 g/day)	GCs + MMF, or CYC, or CNIs, or AZA, or rituximab	**First line**: GCs + MMF (2 g/day), or high-dose IV CYC
	Second line: (i) IV CYC; (ii) CNI (TAC); (iii) CNI (TAC) + MMF (particularly for nephritic range proteinuria)			**Second line**: low-dose IV CYC, or TAC
Maintenance therapy	MMF (1–2 g/day) , or AZA (2 mg/kg/day) + prednisone (2.5–5.0 mg/day) for 3–5 years	MMF (1–2 g/day), or AZA (2 mg/kg/day) ± low-dose GCs	**First line**: MMF for at least 3 years **Second line**: AZA, or CNI (TAC)	**First line**: MMF or AZA for 5 years **Second line**: low-dose CNI (TAC)

Abbreviations: (EULAR- ERA- EDTA):European Alliance of Associations for Rheumatology- European Renal Association-European Dialysis and Transplant Association, (ACR):American college of Rheumatologists, (KDIGO): Kidney Disease: Improving Global Outcomes, (APLAR):Asia Pacific League of Associations for Rheumatology, LN: lupus nephritis, GFR: glomerular filtration rate, IV: intravenously, CYC: cyclophosphamide, MMF: mycophenolate mofetil, GCs: glucocorticoids, AZA: Azathioprine, CNIs: calcineurin inhibitors, TAC: Tacrolimus , BEL: Belimumab, RTX: Rituximab, OBI: Obinutuzumab. VOC: Voclosporin, ANF: Anifrolumab, BAFF: B cell activating factor

at 12 months (4.41 g. baseline vs. 1.31 g. post-therapy, p=0.006[18]. RTX has given equally great results in LN when co administered with MMF even in the absence of oral GCs [19].

BEL is a mAb against B-cell activating factor (BAFF), therefore it is another molecule targeting B cells. Although at first approved for active non renal lupus, the past few years has presented satisfactory results to control LN as an add-on agent to standard-of-care (SOC) therapy for LN. BEL in the BLISS-LN study showed that BEL when added to SOC either MMF and GCs or

EUROLUPUS CYC followed by AZA in a period of 108 weeks was superior to placebo added in SOC in the control group [20]. More specifically, the BEL group had a primary efficacy renal response 43% vs. placebo 32%, p=0.03 and a complete renal response 30% vs. placebo 20%, p= 0.02. These were reflected by non worsening of GFR and reduction of renal flares or renal damage in the reported time interval. The adverse events between the two groups taking and not taking BEL were similar implying a good safety profile for BEL.

Obinutuzumab (OBI) is a newer and more drastic

B-cell depleting agent that targets CD20 in a more efficacious manner. The phase II RCT (NOBILITY) displayed that OBI when added to MMF and GCs was superior to placebo for the achievement of complete and overall renal responses at week 52 [21]. Complete renal response was succeeded with OBI at week 52 (35%) vs. (23%) with placebo, p=0.115) and at week 104 (41%) vs. (23%), p=0.026. OBI was associated with improvements in GFR and lowering of proteinuria and was safe enough according to the observed serious adverse effects, infections or deaths. Phase III RCT (REGENCY NCT04221477) is expected upon completion to evaluate the addition of OBI vs. placebo in patients with class III or IV lupus nephritis (LN) already on SOC with MMF plus CS [22].

A newer CNI called Voclosporin (VOC) has been recently approved for the treatment of LN. Its pharmacokinetic and pharmacodynamic profile makes therapeutic drug monitoring unnecessary. VOC is not able to act when GFR is ≤45 ml/min/1.73 m^2.

In the AURORA 1 study, a multicenter double-blind phase III study, patients with LN class III, IV, or V or combination of these classes already on therapy with MMF 1 g twice daily, were randomly assigned (1:1) to receive oral VOC (23·7 mg twice daily) vs. placebo for 52 weeks; meanwhile oral steroids were attempted to be rapidly tapered to low dose [23]. Complete renal response at week 52 was achieved in more patients in the VOC group than in the placebo group (73 [41%] of 179 patients *vs* 40 [23%] of 178 patients, p=<0·0001. Adverse events, even serious ones, were presented at a similar rate between the two groups.

The AURORA 2 phase III study displayed equally satisfactory results at three years of treatment with VOC vs. placebo as well [24]. Complete renal response was achieved in 59% of the VOC group vs. 39% of the placebo group. Proteinuria was more rapidly and persistently reduced in the VOC group while kidney function was almost preserved in a good level in both groups.

Anifrolumab (ANF), a mAb to type I interferon receptor subunit 1 was approved after TULIP2 phase III RCT study for the treatment of medium / severe SLE [25]. TULIP-LN study evaluates the addition of ANF in patients with active Class III/IV LN already on MMF and GCs [26]. One hundred forty-seven patients were assigned to receive ANF 1:1:1 basic scheme monthly ANF IV 300 mg, or an intensified scheme ANF 900 mg ×3 at first for 4 weeks and 300 mg thereafter, or placebo. The primary endpoint of this study which was the relative difference in the mean change of 24-hour urine protein-creatinine ratio (UPCR) from baseline to week 52 was not met. The percentage of patients who had a complete renal remission (which required inactive urinary sediment) at week 52 was greater in the intensified ANF group than the placebo group 40.9% vs. 13.3%, and lower in the basic scheme ANF group than in the placebo group 7.0% vs. 13.3%. Response rates were higher with ANF IR vs. placebo as early as week 12 and remained higher over time. The patients who had a sustained oral glucocorticoid dosage tapering ≤7.5 mg/day were more in the ANF intensified group compared to the placebo group (55.6% vs. 33.3%) as well. Herpes zoster infections had higher incidence in the ANF groups, but a larger study is warranted to make more safe conclusions for the drug.

Regulatory T cells (Tregs) have been found lessened and less functional in SLE. IL-2 is a cytokine that promotes expansion of Tregs, so administration of low dose IL-2 seems promising for treatment of SLE and LN. A double-blind placebo-controlled trial of He et al. compared 60 patients with active SLE, 30/60 received low dose IL-2 and the rest 30/60 received placebo on top of SOC treatment for 12 weeks and were observed for a total interval of 24 weeks [27]. At week 12 and at week 24 the Systemic Lupus Erythematosus Responder Index (SRI-4) response rates were higher for IL-2 vs. placebo, p= 0.052(week 12) and p=0,027 (week 24), respectively. Seven out of 13 patients with LN achieved complete remission by taking low dose IL-2 compared with 2 out of 12 patients with LN in the placebo group, p=0.036.

Studies of combining medications for LN

An interesting study was conducted to evaluate the effect of OBI with MMF and no oral steroids co administration vs. MMF plus oral steroids co administration (NCT04702256) [28].

In the CALIBRATE study, the authors tried to assess the efficacy of BEL added after the administration of RTX and CYC in patients with refractory lupus nephritis vs. placebo added after this combination of RTX and CYC [29]. The clinical outcomes between the two groups were not outstanding. The number of total B cells and autoreactive B cells compared to baseline was unsurprisingly reduced in the BEL group.

The BEAT-LUPUS study in a similar way compared RTX as induction therapy followed by BEL four to eight weeks after the first RTX infusion in patients with refractory SLE (only 38 % of patients had LN) vs. RTX, followed by placebo for 52 weeks [30]. The BEL group had a bigger reduction of B cells, of anti -ds-DNA Abs titles and of severe disease flares.

Refractory LN

A kidney response -as it is defined according to worldwide criteria- may not be achieved despite all immunosuppressive drugs approved so far have been administered. Therefore, LN is considered resistant after we have excluded the patient's tolerance and good adherence [31]. Rescue therapies include LEF, intravenous immunoglobulin/plasma exchange (especially for patients at high risk for infection or recurrent infections), anti plasma cell therapies like Bortezomib, a proteasome inhibitor and anti-CD38 a mAb followed by RTX or BEL, autologous stem cell transplant, chimeric antigen receptor (CAR)-T therapy or anti-complement therapy.

There are a couple of studies published for cases of patients with refractory lupus. Two patients only, one with LN and the other with hemolytic anemia with unsuccessful treatments in the past, were treated with daratumumab, a mAb that targets CD38 of long-lived PCs [32]. The results were remarkable, as disease activity scores were reduced in both patients; proteinuria was diminished in the first patient and preservation of kidney function was achieved too. In the second one hemoglobin and platelet levels were restored. The addition of BEL in these 2 patients helped to sustain the satisfactory effect and outcome of daratumumab depleting PCs, which in cases of multiple myeloma is rather transient.

Another therapy that has been tested for lupus refractory cases is CAR T cells. Despite their use in cancer and other hematologic diseases, the use of CAR T cells that target CD19, a specific marker of B lymphocytes, has shown promising results in mouse models of lupus and patients with SLE. T cells from patients with SLE are transduced with a lentiviral anti-CD19 CAR vector, are then expanded and reinfused after immunodepletion. Five patients with refractory lupus to previous immunosuppressive therapy were enrolled to this CAR-T cell treatment. A significant depletion of B cells was observed as well as an improvement of clinical symptoms, of laboratory and immunological tests [33]. All patients had severe proteinuria that was astonishingly decreased to normal levels. Disease remission was maintained for almost 8 to 12 months after CAR T cell administration with a great tolerance.

No RCTs of rescue therapies for LN have been performed. Mostly observational uncontrolled studies for refractory disease have been published. The groups of patients selected lack homogeneity in clinical picture, in disease activity and in previous treatment administered.

Non immunosuppressive treatments in LN

We should not disregard the avoidance of smoking, exercise, the control of high blood pressure, the treatment of diabetes mellitus, hyperlipidemia and metabolic derangements. Renin–angiotensin–aldosterone system inhibitors may offer renoprotection and amelioration of proteinuria in patients with LN [34, 35].

SGLT2i has been highly expressed in kidney podocytes. SGLT2i might reverse the damage of podocytes through inhibition of NLRP3 inflammasome-mediated inflammation and through inhibition of mammalian target of rapamycin complex 1 (mTORC1) signaling as histopathologic findings suggest [36, 37]. Their use has been displaying promising results in LN in animal models and patients with LN. For instance, empagliflozin reduced the titre of anti-ds-DNA Abs in mrl/lrp mice and improved proteinuria kidney function and abnormal histologic findings in mices' glomeruli [38]. A retrospective study showed that administration of SGLT2i in 9 patients with LN for more than 2 months had a significant decrease of their proteinuria and improvement of their kidney function [38].

DISCUSSION

LN is a severe manifestation, and the initiation of therapy is considered emergent to prevent a fatal outcome. Lots of therapies have been proved to be lifesaving for the kidneys of patients with LN. Except the cytostatic agents [3-10], B-cell targeted therapies with mAbs show hopeful results in treating LN such as BEL, RTX and OBI [18-22,28-30]. VOC the newest CNI is also a promising factor [23,24].

It should be emphasized that there are a lot of agents under experimental use that target one or more molecules involved in the pathogenesis of LN [1-3]; these agents are depicted in figure 1. The results of a few ongoing clinical trials of these agents are expected in the near future. Surface antigens and growth factors of B cells as CD19, CD22, B cell receptor (BCR), Fc Receptor (FcR), a proliferation-inducing ligand (APRIL) and Bruton's tyrosine kinase (BTK) are therapeutic targets as well. Co-stimulatory molecules may be targeted also like anti- inducible T cell co-stimulator ligand (ICOS)/ ICOS ligand (L) or anti-CD40/CD40L. Double-action mAbs should not be missed like anti BAFF/ anti- APRIL (atacicept, telitacicept), peptide conjugate anti - BAFF and anti- ICOSL and finally mAb against BAFF -R and FcR (lanalumab).

Other treatments approved or under investigation
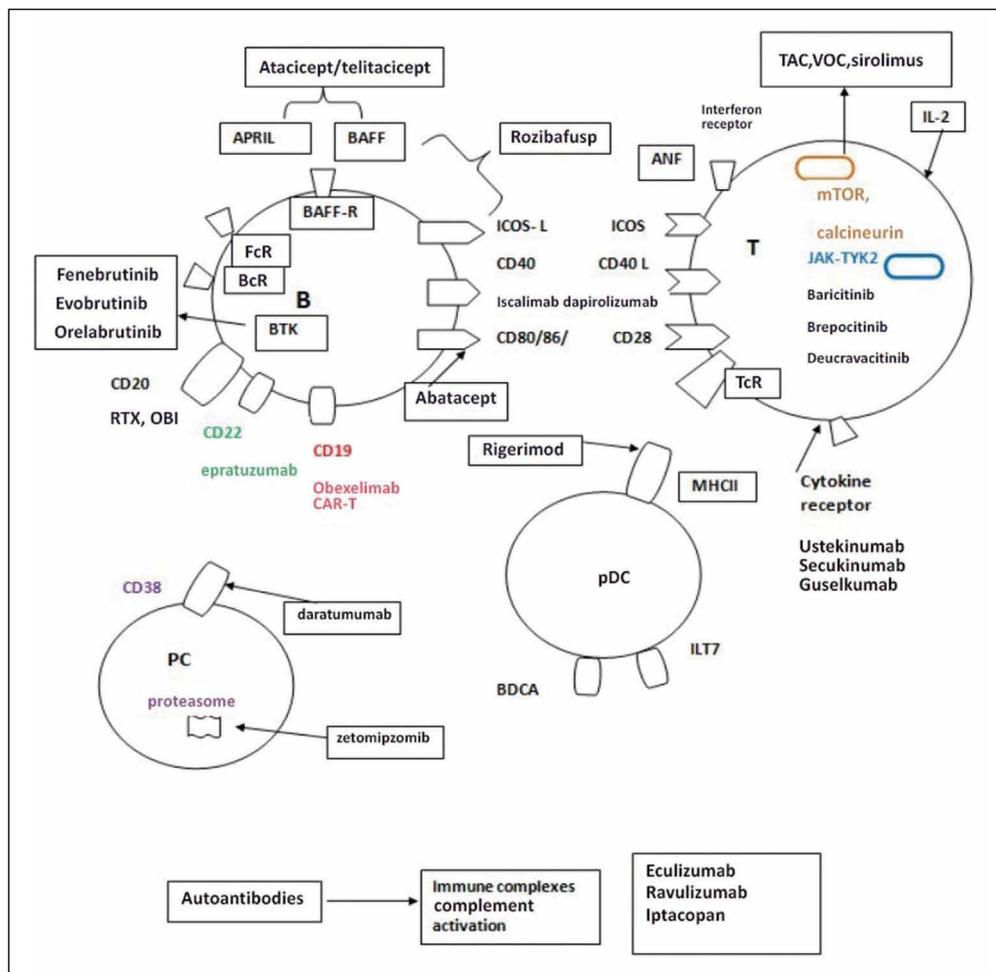
Figure 1. medications and drug combinations with few trials or uncompleted trials in LN. Targets of surface molecules or inner molecules of B, T cells, pDCs and PCs in patients with LN that have been approved or are under investigation are depicted in the above scheme.

Abbreviations: (pDCs): plasmacytoid dendritic cells, (PCs): plasma cells LN: lupus nephritis, TAC: Tacrolimus, BEL: Belimumab, RTX: Rituximab, OBI: Obinutuzumab. VOC: Voclosporin , ANF: Anifrolumab, Tc R:Tcell receptor, BcR: B cell receptor, FcR: Fc Receptor BAFF: B cell activating factor, APRIL: A proliferation-inducing ligand, MHC II: major histocompatibility complex II, (CAR)-T: chimeric antigen receptor, BDCA: Blood Dendritic Cell Antigen, JAK: Janus kinase ,TYK 2: tyrosine kinase-2, ILT7: immunoglobulin-like transcript 7, BTK: bruton tyrosine kinase, ICOS: Inducible T cell co-stimulator, ICOS-L: Inducible T cell co-stimulator-Ligand, mTOR: mammalian or mechanistic target of Rapamycin

are IFN-I signaling inhibition as ANF does [25,26], complement system inhibition like eculizumab, ravulizumab and other drugs targeting many of the molecules - key points in the pathogenesis of SLE. Targeting intracellular proteins of T cells like mTOR inhibitors e.g. sirolimus may be effective, too. pDCs may be targeted with mAbs against surface molecules like blood dendritic cell antigen 2 (BDCA2)/ daxcilimab, immunoglobulin-like transcript 7 (ILT7)/ litifilimab or MHCII / rigerimod are a few of them. Moreover, long lived PCs are targeted with proteasome inhibitors or mAbs against their surface molecules [32]. There are also mAbs against cytokines and their receptors like IL-2, IL-12, IL-23 (secukinumab

and ustekinumab) that have been tested in lupus [1-3]. In the end, the results of interventions in intracellular downstream signaling pathways, like JAK and TYK2 pathways are expected with great interest.

The basic research and understanding of pathogenesis of SLE has been dramatically improved and aided the treatment of the severe manifestations of the disease, such as LN. The biopsy findings and further classification of GN types with additive findings of activity or chronicity of lesions of kidneys as well as molecular profiling of patients with LN may be a further stepping stone for choosing the proper therapy for each patient. The biopsy still remains a prerequisite to settle

the diagnosis of LN and thus to select the appropriate treatment even though biomarkers of serum and urine have been tried to replace it.

CONCLUSION

There are numerous treatments to induce and preserve LN remission. The old medications used so far are quite effective, but the unresponsiveness and the recurrence of LN forces the rheumatologists to shift towards more precise therapies. Research focuses on targeting more specific molecules of immune cells involved in the pathogenesis of LN. The first results are quite encouraging so far, but bigger and better designed studies are required to make more safe conclusions for treating LN.

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A case of euglycemic diabetic ketoacidosis in the context of post-ERCP cholangitis, bacteremia and liver abscess in a patient receiving an SGLT-2 inhibitor

Christos Sotiropoulos, Christos Konstantakis, Georgios Theocharis, Christos Triantos, Konstantinos Thomopoulos

Abstract

Background: Euglycemic diabetic ketoacidosis (euDKA) is a rare yet serious side effect of SGLT-2 inhibitors. It is typically triggered by acute illness (such as infections), reduced food and fluid intake, decreased insulin doses, or alcohol consumption.
Case Presentation: We present a case of a 53-year-old patient, with a history of type 2 diabetes mellitus treated with Empagliflozin, who presented with abdominal pain and jaundice. Ultrasound revealed a dilated biliary tract and an ERCP identified a stenosis in the intrapancreatic segment of the bile duct. Histological analysis suggested adenocarcinoma and an abdominal CT scan showed a hypodense lesion in the head of the pancreas. Postoperatively, the patient developed euglycemic diabetic ketoacidosis and a Pseudomonas aeruginosa microbemia. Due to persistent fever, a follow-up CT scan was conducted, revealing a liver abscess, which was subsequently drained under CT guidance.
Conclusions: Euglycemic diabetic ketoacidosis is a rare but serious condition and its atypical presentation necessitates a high level of vigilance from physicians, as early detection and treatment are crucial for quickly and safely restoring acid-base balance.

Key words: *Euglycemic diabetic ketoacidosis (euDKA); post-ERCP cholangitis; SGLT-2 inhibitors*

INTRODUCTION

SGLT-2 inhibitors have gained great importance in recent years due to their cardioprotective and nephroprotective properties in patients with type 2 diabetes mellitus. A rare but serious side effect of SGLT-2 inhibitors is the euglycemic diabetic ketoacidosis (euDKA), which is usually triggered by acute disease, reduced food and fluid intake, reduced insulin doses, or alcohol consumption [1-4].

CASE PRESENTATION

We report a 53-year-old patient with a history of cholecystectomy, dyslipidemia and type 2 diabetes mellitus under treatment with Metformin 1000 mg 1x2 and Empagliflozin 25 mg 1x1, who was admitted to the hospital due to right upper quadrant abdominal pain with accompanying jaundice and the following laboratory test values: AST: 2338 U/l, ALT: 1508 U/l, γ-GT: 2020 U/l, ALP: 483 U/l, TBL: 2.65 mg/dl, DBL: 2

.22 mg/dl, Ca 19-9: 1181.86 U/ml. Physical examination showed no pathological signs, while intrahepatic and extrahepatic bile duct dilatations were revealed by abdominal U/S. The patient underwent ERCP (Figure 1A) where a stenosis in the intrapancreatic segment of the bile duct with prestenotic dilatation was revealed, a cytological smear was taken (histological examination: adenocarcinoma) and a fully covered metal stent of 6 cm length was inserted through the stenosis, while abdominal CT (Figure 1B) revealed a hypodense lesion (d. 3cm) in the head of the pancreas and portal vein thrombosis. Postoperatively (in the 1st 24-hours), the patient presented with febrile right upper quadrant abdominal pain, nausea, vomiting, lethargy, tachypnea and tachycardia with an accompanying increase in inflammatory markers and cholestatic enzymes, with normal serum glucose (Glu: 180 mg/dl). Blood cultures and arterial blood gasses were obtained where metabolic acidosis was found (pH: 7.21, HCO3:

13 mmol/l, Lac: 0.8 mmol/l) with an increased anion gap (25 mmol/l), while the general urine test analysis showed ketonuria (ketone > 43 mg/dl). The patient was administered intravenous antibiotic treatment for Gram (-) and anaerobic microbes and treatment of euglycemic diabetic ketoacidosis with an insulin pump with co-administration of glucose solution and intravenous administration of crystalline fluids and potassium replenishment. The SGLT-2 inhibitor was discontinued. The patient showed progressive improvement with gradual recovery of acidosis and anion gap with undetectable urinary ketones. Microbemia due to *Pseudomonas aeruginosa* was detected from the blood cultures, where the antibiotic treatment was modified based on the antibiogram; however, due to lack of apyrexia, an imaging re-evaluation with CT scan was performed, where a liver abscess was detected (Figure 1C). Eventually, liver abscess was treated with drainage under CT guidance (Figure 1D).
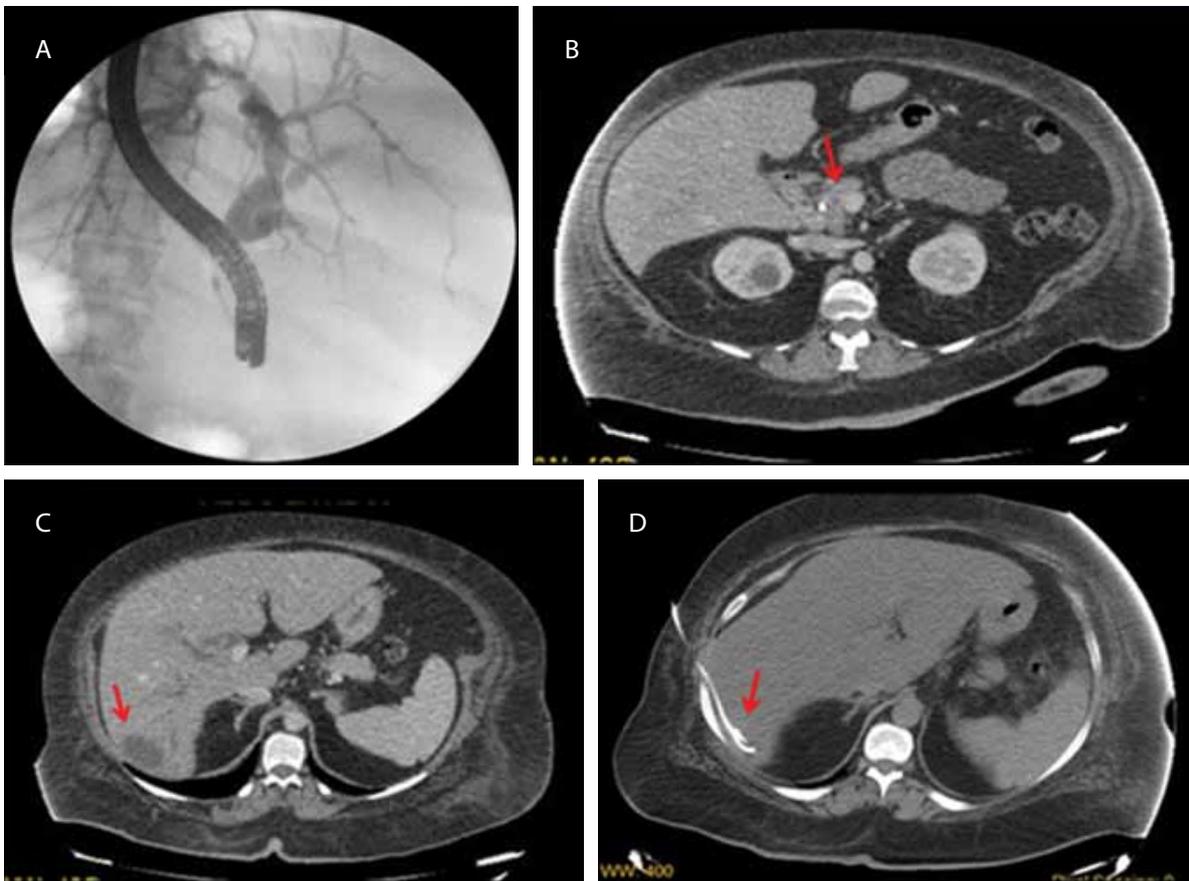

Figure 1 A. ERCP cholangiogram revealing a stenosis in the intrapancreatic segment of the common bile duct with prestonotic dilatation. B. Abdominal CT scan showing a hypodense lesion (d. 3cm) in the head of the pancreas and portal vein thrombosis. C. Liver abscess. D. Liver abscess drainage.

DISCUSSION

SGLT-2 inhibitors have become increasingly significant due to their cardiovascular and renal protective effects in diabetes [1]. In 2015, the US Food and Drug Administration (FDA) issued an official warning advising cautious use of SGLT-2 inhibitors due to the potential risk of euglycemic diabetic ketoacidosis (euDKA) [1]. While the introduction of SGLT-2 inhibitors in diabetic patients can lead to euDKA, the precise mechanism behind this phenomenon remains unclear [1]. Several contributing factors associated with SGLT-2 inhibitors in exacerbating euDKA include infections, acute pancreatitis, post-surgery recovery, malignancy, and reduced oral intake [1]. The primary hypothesized mechanism is outlined as follows [2]: SGLT-2 inhibitors induce significant glucosuria, lowering plasma glucose levels and stimulating glucagon secretion [2]. With glucose being the primary trigger for insulin release, plasma insulin levels decrease notably [2]. Conversely, plasma glucagon levels rise due to reduced insulin secretion and possibly decreased SGLT-2 mediated glucose transport into α-cells [2]. The diminished insulin to glucagon ratio triggers lipolysis and increases lipid oxidation, leading to ketoacidosis [2]. Insulin plays a pivotal role in regulating lipid metabolism [2]. Diabetic ketoacidosis is recognized as a contributor to hypertriglyceridemia [2]. Insulin deficiency prompts heightened lipolysis in adipose tissue, resulting in increased release of fatty acids [2]. Elevated free fatty acid delivery to the liver boosts very-low-density lipoprotein (VLDL) production [2]. Insulin deficiency also reduces lipoprotein lipase activity, which normally breaks down triglycerides in lipoproteins [2]. The combination of elevated serum VLDL and reduced lipoprotein lipase activity contributes to hypertriglyceridemia, further exacerbating ketoacidosis [2].

CONCLUSIONS

Euglycemic diabetic ketoacidosis is a rare but serious complication of SGLT-2 inhibitor administration, often with a multifactorial etiology. Its atypical appearance requires a high level of awareness from physicians as early recognition of this complication can quickly and safely restore acid-base balance.

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