State of the art paper

Addressing recurrent hypoglycaemia through thoracic surgical intervention: understanding Doege-Potter syndrome, a rarity in syndromes

Vasileios Leivaditis[1], Benjamin Ehle[2], Athanasios Papatriantafyllou[1], Francesk Mulita[3], Efstratios Koletsis[4], Georgios-Ioannis Verras[3], Konstantinos Tasios[3], Andreas Antzoulas[3], Nikolaos Charokopos[4], Manfred Dahm[1], Paraskevi F. Katsakiori[5], Konstantinos Grapatsas[6]

[1]Department of Cardiothoracic and Vascular Surgery, WestpfalzKlinikum, Kaiserslautern, Germany
[2]Department of Thoracic Surgery, Asklepios Lung Clinic Munich-Gauting, Gauting, Germany
[3]Department of Surgery, General University Hospital of Patras, Patras, Greece
[4]Department of Cardiothoracic Surgery, Patras University Hospital, Patras, Greece
[5]Health Centre of Akrata, Akrata, Greece
[6]Department of Thoracic Surgery and Thoracic Endoscopy, Ruhrlandklinik, West German Lung Centre, University Hospital Essen, University Duisburg-Essen, Essen, Germany

Corresponding author:
Dr. Francesk Mulita
Department of Surgery
General University
Hospital of Patras
Patras, Greece
E-mail: oknarfmulita@
hotmail.com

Abstract

Doege-Potter syndrome (DPS), a rare paraneoplastic phenomenon characterised by non-islet cell tumour hypoglycaemia (NICTH), presents clinicians with intricate diagnostic and therapeutic challenges. This comprehensive review consolidates current understanding, clinical presentations, diagnostic modalities, therapeutic interventions, and emerging trends in managing DPS. The pathophysiology of DPS revolves around dysregulated insulin-like growth factors (IGF), particularly IGF-2, produced by mesenchymal tumours, notably solitary fibrous tumours (SFT). Clinical manifestations encompass recurrent hypoglycaemic episodes, often distinct from typical hypoglycaemia, with implications for insulin and counterregulatory hormone levels. Diagnosis necessitates a multidisciplinary approach integrating biochemical assays, imaging studies, and histopathological confirmation of the underlying neoplasm. Surgical resection remains the cornerstone of treatment, complemented by adjunctive therapies to manage persistent hypoglycaemia. Prognosis is influenced by successful tumour resection and long-term surveillance for recurrence. A patient-centred approach, incorporating supportive services and multidisciplinary care, is essential for optimal outcomes in individuals affected by DPS.

Key words: Doege-Potter syndrome, non-islet cell tumour hypoglycaemia, paraneoplastic phenomenon, recurrent hypoglycaemia.

Introduction

Recurrent hypoglycaemia managed by general practitioners often stems from diverse factors such as diabetes medications, insulin miscalculations, inadequate dietary intake, heightened physical activity, alcohol consumption, insulin-secreting tumours, hepatic abnormalities,

Vasileios Leivaditis, Benjamin Ehle, Athanasios Papatriantafyllou, Francesk Mulita, Efstratios Koletsis, Georgios-Ioannis Verras, Konstantinos Tasios, Andreas Antzoulas, Nikolaos Charokopos, Manfred Dahm, Paraskevi F. Katsakiori, Konstantinos Grapatsas

endocrine imbalances, post-bariatric hypoglycaemia (PBH) after bariatric surgery, and renal dysfunctions. Some aetiologies necessitate hospitalisation for accurate diagnosis and management, including autoimmune conditions, hormonal deficiencies like Addison's disease, enzymatic deficiencies, severe hepatic or renal pathologies, anorexia, or septicaemia. Additionally, drug-induced hypoglycaemia may be encountered in specific cases [1–3].

Diagnosing hypoglycaemia in individuals without diabetes poses a challenge for endocrinologists. While surgical intervention is recognised in cases like pancreatic insulinoma for addressing recurrent hypoglycaemia, this review focuses on an uncommon condition, Doege-Potter Syndrome (DPS), in which comprehensive surgical resection acts as both an oncologic and therapeutic intervention for recurrent hypoglycaemia. This syndrome presents diagnostic complexities due to multifaceted clinical manifestations and its elusive nature [4].

Solitary fibrous tumours (SFT) are infrequent mesenchymal neoplasms, occurring at a rate of 2.8 per 100,000 [5]. Solitary fibrous tumours of the pleura (SFTP) are uncommon neoplasms primarily situated within the thoracic cavity, originating from submesothelial mesenchymal cells with fibroblastic characteristics. They constitute about 5% of pleural tumours, with approximately 1000 documented cases, although improved computed tomography (CT) imaging has led to increased diagnoses. Usually demonstrating a benign course, around 15–20% exhibit malignant behaviour, marked by recurrence and distant metastasis [6, 7]. Inversions on chromosome 12q13 induce repeated fusion transcripts linked to SFTPs. Notably, the NAB2-STAT6 gene fusion generates a chimeric protein (STAT6), representing a hallmark of SFTPs [8].

SFTs can also arise in extrathoracic locations, including but not limited to the meninges, soft tissues, retroperitoneum, and abdominal viscera. While thoracic SFTs comprise a significant proportion of reported cases, extrathoracic SFTs exhibit distinct characteristics, including variations in clinical presentation and behaviour [9, 10]. Notably, extrathoracic SFTs have been associated with a higher propensity for malignant behaviour compared to their thoracic counterparts. Studies have suggested that extrathoracic SFTs tend to present at more advanced stages and demonstrate increased rates of recurrence and metastasis. The underlying mechanisms driving the malignant behaviour of extrathoracic SFTs remain under investigation, with factors such as tumour size, histological features, and genetic alterations potentially contributing to their aggressiveness. Understanding the differences in malignant behaviour between thoracic and extrathoracic SFTs is crucial for appropriate clinical management and prognostication in patients with DPS [11, 12].

Hypoglycaemia associated with SFTP is attributed to the tumour's overproduction of high-molecular-weight insulin-like growth factor (IGF) 2 prohormone [13]. However, in some cases, IGF-2 levels may remain within the normal range. Approximately 4% of SFTPs are linked to DPS [14], with SFTP in the right haemothorax considered the primary cause of DPS [15]. However, several cases of extrathoracic solitary fibrous tumours have also manifested as DPS [16–19].

DPS, first independently described in 1930 by Karl Walter Doege (1867–1932), a German-American physician [15], and Roy Pilling Potter (1879–1968), an American radiologist, remains exceedingly rare, with fewer than 80 reported cases in the literature [15, 20–22]. Clinically, it often presents with symptoms like diaphoresis, tremors, anxiety, and loss of consciousness due to hypoglycaemia. Yet, a subset of patients might remain asymptomatic [20]. This article endeavours to consolidate current insights, unveil emerging paradigms, and navigate the intricate landscape of DPS.

Pathophysiology of Doege-Potter syndrome

DPS is a rare paraneoplastic syndrome characterised by non-islet cell tumour hypoglycaemia (NICTH). The pathophysiology primarily revolves around the dysregulation of IGF, particularly IGF-2, by certain mesenchymal tumours, notably SFTPs [1]. While SFTPs are often the main cause in DPS, other mesenchymal tumours can also be implicated. These neoplasms possess a unique ability to produce IGF-2 or its precursor molecules, which are then secreted into the circulation [2].

The insulin-like growth factor (IGF) system is a complex network of peptides and binding proteins that play pivotal roles in regulating growth, metabolism, and cellular proliferation. Central to this system are 2 main ligands, IGF-I and IGF-II, which share structural homology with insulin. IGFs exert their biological effects by binding to the IGF-1 receptor (IGF-1R), a transmembrane tyrosine kinase receptor, as well as insulin receptors (IR), initiating downstream signalling cascades [23]. Upon ligand binding, the IGF-1R autophosphorylates and activates various intracellular signalling pathways, including the PI3K-AKT and Ras-MAPK pathways, which regulate cell growth, survival, and metabolism. Additionally, IGFs can bind to insulin receptors, albeit with lower affinity, contributing to their metabolic effects. The actions of IGFs are tightly regulated by a family of IGF-binding proteins (IGFBPs), with IGFBP-3 being the most abundant in circulation. IGFBPs modulate the bioavailability and activity of IGFs by seques-

tering them in the extracellular environment and controlling their access to receptors. Furthermore, IGFBPs can potentiate or inhibit IGF actions, depending on the cellular context and interactions with other signalling molecules. Importantly, dysregulation of the IGF system, such as overproduction of IGFs or alterations in IGFBP levels, has been implicated in various pathological conditions, including cancer, metabolic disorders, and growth abnormalities [23, 24].

Under normal circumstances, around 70–80% of circulating IGF binds to IGFBP-3 alongside the acid labile subunit, forming an inactive complex. However, in the presence of "big" IGF-2, this complex formation becomes less effective. As a result, there is increased availability of IGF-2 to bind to IGF and insulin receptors, triggering glucose uptake into muscles, inhibiting gluconeogenesis in the liver, and suppressing lipolysis in adipose tissue. These mechanisms collectively contribute to the development of hypoglycaemia [20, 25].

IGFs, being peptide hormones with structural and functional similarities to insulin, include IGF-2, recognised as a critical mediator in DPS pathogenesis. In DPS, certain tumours produce excessive amounts of IGF-2 or its precursor proteins, deviating from its normal role in promoting cell growth, proliferation, and differentiation [1]. The surplus circulating IGF-2 activates the insulin receptor and insulin-like growth factor 1 receptor (IGF-1R) in an autocrine or paracrine manner. This activation promotes glucose uptake into tissues, enhances glycogen synthesis, inhibits gluconeogenesis, and stimulates cell growth and proliferation [4]. The elevated IGF-2 levels result in increased glucose utilisation and storage in peripheral tissues, leading to hypoglycaemia due to depleted circulating glucose. This dysregulated glucose metabolism and heightened glucose utilisation are the primary contributors to the observed hypoglycaemic episodes in DPS [4, 20].

Excessive IGF-2 production and subsequent hypoglycaemic episodes have systemic effects, leading to neurological manifestations such as confusion, seizures, and potentially coma. Prolonged and recurrent hypoglycaemic episodes can also impact various organ systems, potentially causing cardiac arrhythmias, neurocognitive impairment, and fatal outcomes if left untreated [13, 20].

Clinical features of Doege-Potter syndrome

DPS presents a diverse spectrum of clinical manifestations, posing diagnostic challenges due to its multifaceted and sometimes subtle symptoms. Patients may exhibit nonspecific signs such as weakness, fatigue, diaphoresis, and cognitive impairment, which can be mistaken for other conditions [1, 26].

Recurrent hypoglycaemic episodes stand as the hallmark feature of DPS, varying in severity and frequency. These episodes manifest as confusion, dizziness, diaphoresis, palpitations, and, in severe cases, seizures or loss of consciousness. Significantly, these occurrences transpire independently of meals or fasting [26].

A distinctive aspect of DPS is the incongruity between hypoglycaemia and insulin levels. Despite experiencing hypoglycaemia, DPS patients typically display low insulin and C-peptide levels, distinguishing it from insulinoma-induced hypoglycaemia. Additionally, counterregulatory hormonal responses (such as glucagon, cortisol, growth hormone) might be impaired or insufficient during hypoglycaemic events [24–27].

Crucially, as mentioned before, DPS is associated with mesenchymal tumours, particularly solitary fibrous tumours (SFTs) or other rare mesenchymal neoplasms. Assessing the patient's medical history for the presence of such tumours, even in asymptomatic cases, becomes pivotal in the diagnostic process [25–27].

In addition to DPS, it is noteworthy to mention Pierre Marie-Bamberger syndrome (PMBS), which can accompany some patients with SFTs [28]. PMBS, also known as clubbing-osteogenic hypertrophy of the ends of the fingers, is characterised by the enlargement of the fingertips, clubbing of the fingers, and hypertrophic osteoarthropathy [28, 29]. While not exclusive to SFTs, PMBS has been reported in association with SFTs, particularly those located in the pleura. The exact mechanisms underlying the development of Pierre PMBS in the context of SFTs remain incompletely understood, but it is believed to be related to the release of various growth factors and cytokines by the tumour. Recognition of PMBS in patients with SFTs is important for comprehensive clinical assessment and management [29, 30].

Diagnostic evaluation methods

Imaging techniques like computed tomography (CT) and magnetic resonance imaging (MRI) play a crucial role in identifying and characterising the primary tumour linked to DPS. These modalities aid in locating the mesenchymal tumour, assessing its size, extension, and potential involvement of adjacent structures, as well as detecting distant metastasis of SFTs [1, 3].

Biochemical evaluations involve measuring serum glucose levels during hypoglycaemic episodes, usually showing significantly reduced glucose levels, often dropping as low as 20 mg/dl. Additionally, assessments of insulin, C-peptide, IGF-1, IGF-2, and other pertinent hormonal levels help differentiate DPS from other hypoglycaemic disorders. These tests indicate recurrent or persistent hypo-

Vasileios Leivaditis, Benjamin Ehle, Athanasios Papatriantafyllou, Francesk Mulita, Efstratios Koletsis, Georgios-Ioannis Verras, Konstantinos Tasios, Andreas Antzoulas, Nikolaos Charokopos, Manfred Dahm, Paraskevi F. Katsakiori, Konstantinos Grapsatsas

glycaemic episodes, reflecting notably diminished glucose levels, typically below 10–25 pmol/l for insulin and < 0.1 nmol/l for C-peptide, aligning with the patient's profile under examination. Concurrently, diminished levels of growth hormone and IGF-1 are observed. Although IGF-2 levels generally remain within the normal range or may elevate, this leads to an increased IGF-2/IGF-1 ratio [31].

In many cases, the expression of IGF-2 does not notably rise. This is primarily due to IGF-2 levels commonly falling within the normal range in non-islet cell tumour hypoglycaemia (NICTH). Hence, the IGF-2/IGF-1 ratio serves as an indirect indicator of elevated IGF-2 concentrations, with a ratio surpassing 10 being clinically significant [13, 31]. Pre-pro-IGF-2 processing forms "big IGF-2" molecules, showing biological activity capable of inducing hypoglycaemia, even in the presence of normal IGF-2 levels. Serum primarily serves as the diagnostic medium for IGF-2 assessment, although both serum and plasma samples from patients were utilised for measurement, as documented in the literature [27, 32]. Thus, the most reliable indicator for diagnosing NICTH is the evaluation of the IGF-2/IGF-1 ratio. A normal ratio falls below 3, while a ratio exceeding 10 is widely acknowledged as indicative of NICTH [13].

Histopathological examination of the suspected tumour through biopsy or surgical resection remains the definitive method to confirm the diagnosis of DPS. Tissue analysis confirms the presence of a mesenchymal tumour, often a solitary fibrous tumour, supporting the link between the tumour and the hypoglycaemic syndrome. Specific pathological criteria outlined by the World Health Organisation (WHO) aid in ascertaining the malignancy of SFTs, encompassing elevated mitotic activity, increased cellularity, necrosis, haemorrhage, and pleomorphism [33, 34]. The conclusive identification and distinction of SFTP predominantly rely on pathology and immunohistochemistry, with positive indicators for vimentin, CD 34, and/or BCL-2, and non-reactivity for desmin and S-100 [35].

Therapeutic approaches in Doege-Potter syndrome

Surgical resection of primary tumour

The mainstay in managing DPS involves surgically removing the primary mesenchymal tumour, particularly SFTs, or other identified neoplasms linked to the syndrome [36]. The complete excision of the tumour aims to eradicate the source of IGFs or their precursors responsible for inducing hypoglycaemic episodes [20].

Surgical intervention can pose challenges, especially when dealing with large, invasive tumours or those affecting critical structures. Thorough preoperative planning is crucial to anticipate potential risks such as bleeding or damage to adjacent organs, ensuring successful tumour removal while minimising complications [7, 36].

Medical management of hypoglycaemia

A multimodal approach is often necessary to control hypoglycaemic episodes in DPS. Despite tumour removal, some patients may experience persistent or recurrent hypoglycaemia. Glucose infusion and vigilant monitoring are employed to manage hypoglycaemic episodes, maintaining adequate glucose levels without inducing hyperglycaemia [1, 20].

During acute episodes, immediate intervention involves oral or parenteral dextrose administration. For sustained management, pharmacological approaches may include corticosteroids, growth hormone, octreotide, or glucagon [20, 31]. Recombinant human growth hormone (GH) administered at doses ranging from 3 to 12 mg/day has demonstrated efficacy in managing hypoglycaemia [4].

Adjuvant therapies

In cases where complete tumour resection is unfeasible or for tumours at high risk of recurrence, adjuvant therapies like radiotherapy or chemotherapy might be considered. These additional treatments aim to diminish tumour size, prevent recurrence, or control tumour growth, although their effectiveness in DPS remains under ongoing research [5, 27].

Adjuvant chemotherapy could be contemplated; however, standardised chemotherapeutic indications or protocols are currently lacking, leading to debates regarding its efficacy [20]. Neo-adjuvant chemotherapy is discouraged due to the complexities and uncertainties in preoperative diagnosis [37, 38]. Radiotherapy exhibits potential benefits, especially when combined with surgical intervention and chemotherapy [20]. Other therapeutic modalities targeting distinct areas include radioembolisation employing labelled yttrium 90 (Y90) or utilising temozolomide/bevacizumab [39].

Hormonal manipulation

Some patients may require hormonal manipulation to counteract the effects of excessive IGFs and prevent hypoglycaemic episodes. Octreotide, a somatostatin analogue, has been used in specific cases to suppress IGF secretion and mitigate hypoglycaemia. However, its efficacy in DPS varies and necessitates further investigation [1, 13].

Long-term follow-up and monitoring

Following the initial intervention, ongoing surveillance is crucial to monitor for tumour recurrence, metastasis, or late complications associat-

Table I. Therapeutic approaches to Doege-Potter syndrome

Therapeutic approach	Description
Surgical resection	Complete excision of the primary mesenchymal tumour, particularly SFTs, aims to eradicate the source of IGFs or their precursors responsible for inducing hypoglycaemic episodes.
Medical management	Glucose infusion and vigilant monitoring are employed to manage hypoglycaemic episodes, maintaining adequate glucose levels without inducing hyperglycaemia.
	Pharmacological approaches may include corticosteroids, growth hormone, octreotide, or glucagon. Octreotide, a somatostatin analogue, has been used in specific cases to suppress IGF secretion and mitigate hypoglycaemia.
Adjuvant therapies	Radiotherapy or chemotherapy might be considered for tumours at high risk of recurrence, aiming to diminish tumour size, prevent recurrence, or control tumour growth.
Long-term follow-up	Ongoing surveillance is crucial to monitor for tumour recurrence, metastasis, or late complications associated with DPS.

ed with DPS. Regular imaging studies, biochemical assays, and clinical evaluations are essential for tracking disease progression and optimising management strategies for better outcomes [40].

The above main therapeutic approaches are summarised in Table I.

Prognosis and follow-up in Doege-Potter syndrome

Prognostic implications

The prognosis of DPS intertwines with diverse factors, including the extent of primary tumour removal, tumour biology, and the efficacy of treatments. Complete surgical excision of the mesenchymal tumour frequently leads to the resolution of hypoglycaemic episodes and a positive prognosis. Patients diagnosed early often achieve complete disease remission after tumour removal [41]. Nonetheless, incomplete resection or aggressive tumour behaviour may diminish the prognosis [1].

SFTs generally appear around the sixth decade, with approximately 78–88% displaying benign characteristics, although some may transform malignantly. Favourably, there is an 8% recurrence rate post-initial resection, often leading to complete recovery with additional surgery [22].

Recurrence rates and surveillance

Post-intervention, stringent long-term surveillance is pivotal to detect tumour recurrence, metastasis, or potential late sequelae of DPS. Routine imaging studies, like CT or MRI scans, coupled with biochemical assays, help identify any disease recurrence or progression [1, 6, 7]. For predicting the recurrence or metastasis of surgically removed SFTs, England's pathological criteria are extensively utilised [33]. These criteria consider the following:
- tumour size (> 10 cm),
- increased cellularity, > 4 mitoses per 10 high-power fields (HPFs),
- nuclear pleomorphisms,
- presence of tumour necrosis or haemorrhaging.

Even SFTs labelled as "benign" but not meeting England's criteria often recur. Recent studies have proposed additional risk factors, including extrathoracic location [40]. Moreover, SFTs associated with DPS demonstrate higher malignancy compared to those without the syndrome. Up to 60% of SFTs with DPS showed malignancy, contrasting with 5% to 10.4% in cases without the syndrome [20].

Late complications and long-term effects

Successful tumour resection may resolve hypoglycaemic episodes; however, residual tumour tissue or metabolic imbalances can cause persistent hypoglycaemia or functional deficits from initial hypoglycaemic events [13, 32].

Multidisciplinary follow-up care

Regular follow-ups with a multidisciplinary team consisting of endocrinologists, oncologists, surgeons, and other specialists are pivotal in managing DPS. These appointments focus on treatment response, monitoring for disease recurrence, addressing late effects, managing complications, and providing comprehensive support and care [1, 13].

Patient education and support

Patients with a DPS history need comprehensive education on the condition, potential complications, and the significance of ongoing monitoring. Encouraging lifestyle changes, like a balanced diet and exercise, supports overall health. The psychosocial impact on patients and families should be acknowledged. Providing psychological support, counselling, and access to support groups aids patients in coping with the challenges associated with DPS and its treatment [34].

Emerging trends and future directions in Doege-Potter syndrome

Advancements in imaging technologies, including positron emission tomography (PET) scans and

Vasileios Leivaditis, Benjamin Ehle, Athanasios Papatriantafyllou, Francesk Mulita, Efstratios Koletsis, Georgios-Ioannis Verras, Konstantinos Tasios, Andreas Antzoulas, Nikolaos Charokopos, Manfred Dahm, Paraskevi F. Katsakiori, Konstantinos Grapatsas

molecular imaging, hold promise in enhancing early detection, characterisation, and precise localisation of mesenchymal tumours associated with DPS. These modalities offer increased sensitivity and specificity, facilitating accurate tumour localisation and assessment of tumour biology [1, 34].

The use of fluorodeoxyglucose positron emission tomography (FDG-PET) in the evaluation of SFTs and associated syndromes is crucial for accurate diagnosis and management [42, 43]. However, it is essential to acknowledge the potential for false-negative results with FDG-PET, which may occur due to various factors. One such factor is the histological heterogeneity of SFTs, which can lead to variations in glucose metabolism and FDG uptake among different tumour regions. Additionally, small or well-differentiated tumours may exhibit low metabolic activity and, consequently, reduced FDG uptake, resulting in false-negative PET findings. Furthermore, the presence of necrotic or fibrotic areas within the tumour can also affect FDG uptake and contribute to false-negative results. Several studies have highlighted the limitations of FDG-PET in detecting SFTs, particularly in cases of low-grade or indolent tumours. Therefore, while FDG-PET remains a valuable imaging modality in the evaluation of SFTs, clinicians should be aware of its limitations and consider complementary imaging modalities and histopathological assessments for comprehensive diagnostic evaluation [43–45].

In addition to FDG-PET, the use of tyrosine-PET has emerged as a promising imaging modality for the evaluation of SFTs. Tyrosine-PET exploits the increased amino acid metabolism characteristic of many tumours, offering advantages over FDG-PET, particularly in cases of low-grade or indolent tumours with limited glucose metabolism [46, 47]. By targeting amino acid transporters and protein synthesis pathways, tyrosine-PET can provide complementary information to FDG-PET, potentially enhancing the detection and characterisation of SFTs. Therefore, considering the evolving role of tyrosine-PET in tumour imaging, its incorporation into the diagnostic algorithm for SFTs warrants further investigation and discussion [47].

Exploration of molecular profiling and identification of specific DPS-related biomarkers could provide insights into tumour behaviour, potential therapeutic targets, and prognostic indicators. Analysing genetic and molecular signatures of mesenchymal tumours might guide personalised treatment strategies and predict treatment response [40]. Patients diagnosed with malignant SFTs, especially those with pleural effusion, often face heightened recurrence rates, resulting in mortality within approximately 2 years for the majority of cases [22].

As our understanding of the molecular pathways involved in DPS expands, targeted therapies aimed at specific molecular aberrations or immunotherapeutic approaches may emerge as potential treatment options [40]. Investigational studies focusing on IGF pathways or employing immunomodulatory agents show promise in mitigating the hypoglycaemic effects of DPS. Utilising tyrosine kinase inhibitors, such as imatinib, in DPS management may improve tumour control in cases with inoperable tumours and severe hypoglycaemia [20, 48].

The development of comprehensive, multimodal treatment approaches that integrate surgery, targeted therapies, adjuvant treatments, and novel therapeutic agents represent a promising strategy in optimising DPS management. Tailored combinatorial strategies based on individual patient profiles may enhance treatment efficacy and outcomes [34].

Establishing comprehensive longitudinal studies and disease registries dedicated to DPS can offer valuable insights into disease epidemiology, natural history, treatment outcomes, and long-term follow-up data. Large-scale data collection and analysis would lead to a better understanding of the disease spectrum and assist in refining treatment approaches [20, 34].

Prioritising patient-centric care models that address the holistic needs of individuals affected by DPS is crucial. Encouraging collaboration among multidisciplinary teams, academic institutions, and research consortia is essential in advancing the field of DPS. Collaborative efforts enable resource pooling and expertise sharing, and foster innovative research initiatives aimed at improving diagnostics, therapeutics, and patient outcomes.

Conclusions

Our findings advocate for vigilance when faced with recurrent episodes of hypoglycaemia of unknown origin, warranting thorough tumour screening. Specifically, in cases of SFT, considering DPS as a potential differential diagnosis for tumour-induced hypoglycaemia is crucial. The primary treatment of choice remains complete surgical resection of the tumour, offering promising prospects for mitigating the hypoglycaemic effects and positively impacting patient outcomes. This review aims to offer a comprehensive insight into the complexities of DPS, highlighting the challenges in its diagnosis and management, and emphasizing the necessity for collaborative efforts among multidisciplinary teams. It underscores the significance of ongoing research and innovative approaches to navigate the intricacies associated with this rare paraneoplastic syndrome.

Conflict of interest

The authors declare no conflict of interest.

References

1. Torres Gómez A, GarcíaAlabarce AM, García Castro JM, Navas Bueno B, Rueda Villafranca B, Fernández JL. Doege-Potter syndrome. Endocrinol Diabetes Nutr 2023 Oct 17:S2530-0180(23)00135-X.

2. Wang C, Cao T, Hu G, et al. Recurrence of solitary fibrous tumor of the pleura with hypoglycemia (Doege-Potter Syndrome): a case report description. Front Oncol 2023; 13: 1245289.

3. Featherstone I, Hosie A, Siddiqi N, et al. The experience of delirium in palliative care settings for patients, family, clinicians and volunteers: a qualitative systematic review and thematic synthesis. Palliat Med 2021; 35: 988-1004.

4. Corsano C, Paradiso M, Laudadio ED, Sollitto F, Lamacchia O. A case report of doege-potter syndrome: a rare cause of hypoglycemia in a patient without diabetes. J Clin Med 2023; 12: 3984.

5. Kiely NP, Sinha R, Tang K, Wan KM. Doege-Potter syndrome: a systematic review of the literature and case presentation of a rare pelvic malignant solitary fibrous tumour. BMJ Case Rep 2021; 14: e242447.

6. Chick JF, Chauhan NR, Madan R. Solitary fibrous tumors of the thorax: nomenclature, epidemiology, radiologic and pathologic findings, differential diagnoses, and management. AJR Am J Roentgenol 2013; 200: W238-48.

7. Schmid S, Csanadi A, Kaifi JT, et al. Prognostic factors in solitary fibrous tumors of the pleura. J Surg Res 2015; 195: 580-7.

8. Smrke A, Thway K, Huang P, Jones RL, Hayes AJ. Solitary fibrous tumor: molecular hallmarks and treatment for a rare sarcoma. Future Oncol 2021; 17: 3627-36.

9. Huang SC, Huang HY. Solitary fibrous tumor: an evolving and unifying entity with unsettled issues. Histol Histopathol 2019; 34: 313-34.

10. Kayani B, Sharma A, Sewell MD, et al. A review of the surgical management of extrathoracic solitary fibrous tumors. Am J Clin Oncol 2018; 41: 687-94.

11. Yin H, Ye D, Zhu Y, Geng C. Solitary fibrous tumor of the great omentum: a case report and literature review. Curr Med Imaging 2022; 18: 417-20.

12. Alexiev BA, Finkelman BS, Streich L, et al. Solitary fibrous tumor of thoracic cavity, extra-thoracic sites and central nervous system: clinicopathologic features and association with local recurrence and metastasis. Pathol Res Pract 2021; 224: 153531.

13. Bodnar TW, Acevedo MJ, Pietropaolo M. Management of non-islet-cell tumorhypoglycemia: a clinical review. J Clin Endocrinol Metab 2014; 99: 713-22.

14. Reuvers JR, van Dorp M, Van Schil PE. Solitary fibrous tumor of the pleura with associated Doege-Potter syndrome. Acta Chir Belg 2016; 116: 386-7.

15. Castaldo V, Domenici D, Biscosi MV, et al. Doege-Potter syndrome; a case of solitary fibrous pleura tumor associated with severe hypoglycemia: a case report in internal medicine. Endocr Metab Immune Disord Drug Targets 2023; 23: 1562-9.

16. Rötgens J, Lapauw B, T'Sjoen G. Doege-Potter syndrome in a patient with a giant abdominal solitary fibrous tumor: a case report and review of the literature. Acta Clin Belg 2023; 78: 358-64.

17. Taliente F, De Rose AM, Ardito F, Giuliante F. Solitary fibrous tumor of the liver with Doege-Potter syndrome:

an exceptional finding. Discovering the role of blood glucose levels and insulin growth factor II. Clin Res Hepatol Gastroenterol 2022; 46: 102051.

18. Deguchi Y, Komuta W, Watanabe T, et al. Successful surgical treatment of a recurrent pelvic solitary fibrous tumor of uterine origin accompanied by Doege-Potter syndrome: a case report. Am J Case Rep 2022; 23: e936806.

19. Doege KW. Fibro-sarcoma of the mediastinum. Ann Surg 1930; 92: 955-60.

20. Han G, Zhang Z, Shen X, et al. Doege-Potter syndrome: a review of the literature including a new case report. Medicine 2017; 96: e7417.

21. Piórek A, Kowalski D, Płużański A, et al. Solitary fibrous tumour along with non-small-cell lung cancer and Doege-Potter syndrome. Kardiochir Torakochir Pol 2019; 16: 49-51.

22. Gohir Q, Ghosh S, Bosher O, Crawford E, Srinivasan K, Moudgil H. Pleural-based giant solitary fibrous tumour with associated hypoglycaemia: unusual presentation with pulmonary hypertension in a patient with Doege-Potter syndrome. Clin Med (Lond) 2023; 23: 518-20.

23. Talia C, Connolly L, Fowler PA. The insulin-like growth factor system: a target for endocrine disruptors? Environ Int 2021; 147: 106311.

24. Miller BS, Rogol AD, Rosenfeld RG. The history of the insulin-like growth factor system. Horm Res Paediatr 2022; 95: 619-30.

25. Zapf J, Futo E, Peter M, Froesch ER. Can "big" insulin-like growth factor II in serum of tumorpatients account for the development of extrapancreatic tumor hypoglycemia? J Clin Invest 1992; 90: 2574-84.

26. Naito A, Nwokolo M, Smith EL, et al. Personality traits of alexithymia and perfectionism in impaired awareness of hypoglycemia in adults with type 1 diabetes – an exploratory study. J Psychosom Res 2021; 150: 110634.

27. Khowaja A, Johnson-Rabbett B, Bantle J, Moheet A. Hypoglycemia mediated by paraneoplastic production of Insulin like growth factor-2 from a malignant renal solitary fibrous tumor – clinical case and literature review. BMC Endocr Disord 2014; 14: 49.

28. Solsi A, Pho K, Shojaie S, Findakly D, Noori T. Doege-Potter syndrome and pierre-marie-bamberger syndrome in a patient with pleural solitary fibrous tumor: a rare case with literature review. Cureus 2020; 12: e7919.

29. Koliakos E, Chappalley D, Kalogiannis E, Sgardello S, Christodoulou M. Pierre-Marie Bamberger syndrome leading to the diagnosis and surgical treatment of a localized lung cancer. Cureus 2023; 15: e48991.

30. Boyer-Duck E, Dajer-Fadel WL, Hernández-Arenas LÁ, Macías-Morales MP, Rodríguez-Gómez A, Romo-Aguirre C. Pierre-Marie-Bamberger syndrome and solitary fibrous tumor: a rare association. Asian Cardiovasc Thorac Ann 2018; 26: 154-7.

31. Pelosof LC, Gerber DE. Paraneoplastic syndromes: an approach to diagnosis and treatment. Mayo Clin Proc 2010; 85: 838-54. Erratum in: Mayo Clin Proc 2011; 86: 364.

32. Moreira BL, Monarim MA, Romano RF, Mattos LA, D'Ippolito G. Doege-Potter syndrome. Radiol Bras 2015; 48: 195-6.

33. England DM, Hochholzer L, McCarthy MJ. Localized benign and malignant fibrous tumors of the pleura. A clinicopathologic review of 223 cases. Am J Surg Pathol 1989; 13: 640-58.

34. Travis WD, Brambilla E, Nicholson AG, et al.; WHO Panel. The 2015 World Health Organization Classification of Lung Tumors: impact of genetic, clinical and radiologic

Vasileios Leivaditis, Benjamin Ehle, Athanasios Papatriantafyllou, Francesk Mulita, Efstratios Koletsis, Georgios-Ioannis Verras, Konstantinos Tasios, Andreas Antzoulas, Nikolaos Charokopos, Manfred Dahm, Paraskevi F. Katsakiori, Konstantinos Grapatsas

advances since the 2004 classification. J Thorac Oncol 2015; 10: 1243-60.

35. Ali MI, Aftab G, Akram A. Solitary fibrous tumors of the pleura. Cureus 2021; 13: e12998.

36. Abu Arab W. Solitary fibrous tumours of the pleura. Eur J Cardiothorac Surg 2012; 41: 587-97.

37. Cardillo G, Lococo F, Carleo F, Martelli M. Solitary fibrous tumors of the pleura. Curr Opin Pulm Med 2012; 18: 339-46.

38. Robinson LA. Solitary fibrous tumor of the pleura. Cancer Control 2006; 13: 264-9.

39. Savu C, Melinte A, Posea R, et al. Pleural solitary fibrous tumors-a retrospective study on 45 patients. Medicina (Kaunas) 2020; 56: 185.

40. Ronchi A, Cozzolino I, Zito Marino F, et al. Extrapleural solitary fibrous tumor: a distinct entity from pleural solitary fibrous tumor. An update on clinical, molecular and diagnostic features. Ann Diagn Pathol 2018; 34: 142-50.

41. Donato BB, Sewell MA, Sen A, Beamer SE. Doege Potter syndrome presenting as multiple fibrous tumours of the chest. Interact Cardiovasc Thorac Surg 2022; 35: ivac089.

42. Lococo F, Cafarotti S, Treglia G. Is 18F-FDG-PET/CT really able to differentiate between malignant and benign solitary fibrous tumor of the pleura? Clin Imaging 2013; 37: 976.

43. Zhao L, Wang H, Shi J. 18F-FDG PET/CT characteristics of solitary fibrous tumour of the pleura: single institution experience. Ann Nucl Med 2022; 36: 429-38.

44. Lococo F, Rapicetta C, Ricchetti T, et al. Diagnostic pitfalls in the preoperative 18F-FDG PET/CT evaluation of a case of giant malignant solitary fibrous tumor of the pleura. Rev Esp Med Nucl Imagen Mol 2014; 33: 109-11.

45. Shinya T, Masaoka Y, Sando M, et al. Imaging an intrapulmonary solitary fibrous tumor with CT and F-18 FDG PET/CT. Radiol Case Rep 2019; 14: 755-8.

46. Inoue T, Koyama K, Oriuchi N, et al. Detection of malignant tumors: whole-body PET with fluorine 18 alpha-methyl tyrosine versus FDG--preliminary study. Radiology 2001; 220: 54-62.

47. de Boer J, Jager PL, Wiggers T, et al. The therapeutic challenge of a nonresectable solitary fibrous tumor in a hypoglycemic patient. Int J Clin Oncol 2006; 11: 478-81.

48. Paz-Ibarra J, Lu-Antara J, Uscamayta BE, et al. Imatinib use in the management of a patient with Doege-Potter syndrome. Endocrinol Diabetes Metab Case Rep 2023; 2023: 22-0360.