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Prevalence and course of endocrinopathy in POEMS syndrome

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Keywords:	POEMS syndrome, Endocrinopathy, paraneoplastic syndrome, Crow-Fukase syndrome, Takatsuki syndrome
Abstract:	Context. POEMS syndrome is a rare multisystem disorder characterised by polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma-proliferative disorder and skin changes among other features. Objective. To describe the prevalence and course of the endocrine dysfunction in the context of POEMS. Design. Cohort study with systematic review of the endocrinopathy in POEMS. Setting. 75 patients with POEMS were evaluated by the multidisciplinary team at our tertiary specialist centre. Patients. Endocrine data was available for 59 patients who attended the clinic from 06/1999 to 05/2018. Interventions. All patients had regular endocrine screening including testing for diabetes, pituitary and thyroid dysfunction and assessment of bone metabolism. Main Outcome Measure. Prevalence and survival time to develop endocrinopathy in POEMS. Results. Thirty-four (63%) patients presented with an endocrinopathy at point of POEMS diagnosis and 54 (92%) had at least one endocrine abnormality at follow-up. The median follow-up was 4.4[1.5, 7.9] years. The most common endocrine abnormality was hypogonadism in 68%, followed by hyperprolactinaemia (56%), hypothyroidism (54%), abnormal glucose metabolism (24%), adrenal insufficiency (17%) and high IGF-1 levels (15%). Spontaneous resolution of endocrine abnormalities at the end of follow-up was observed: 14% in hypogonadism, 42% in hyperprolactinaemia, 34% in hypothyroidism and 38% in high IGF-1 levels. Conclusions. Endocrinopathy was found in 63% of patients at diagnosis and in 92% of patients during follow-up in our cohort, therefore patients with POEMS should be systematically assessed for endocrinopathy. The most common deficiencies were hypogonadism and hypothyroidism, however normalisation of the endocrinopathy can occur so on-going treatment should remain under review.
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PRECIS: The precis is a brief description of your paper that will appear on the Table of Contents underneath your article title,	Description of the endocrine dysfunction in a cohort with POEMS syndrome, evaluated by a multidisciplinary team. All patients had regular screening of diabetes, pituitary, thyroid and bone metabolism.	

should your paper be accepted (see the current issue of JCEM for examples). The description should be **no longer than 200 characters, including spaces,** and should briefly explain what was done in your study and what was concluded. Please ensure that the precis does not simply repeat the article title.	
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We thank the editor and reviewers for their constructive comments, which have undoubtedly contributed to the improvement of the manuscript. Below we answer the queries received from the reviewers, and describe in detail the changes introduced.

Reviewer Comments:
Reviewer 1: Major Comments

1. The study was retrospective and from 2013 on prospective. The study was performed in a quaternary referral clinic. Therefore the study was susceptible to bias in data selection, analysis and conclusions.

We thank the referee for his/her comment. Due to the extreme rarity of POEMS syndrome, our quaternary referral patient dataset is likely to be the only one in the UK with a significant number of patients that allows a study of this nature. Also, our centre is unique as we have a multidisciplinary approach including endocrine specialist support. Nevertheless, we agree with the referee that our manuscript has inherent limitations due to its observational nature. Thus, we have emphasised this in the limitation section (page 14, lines 301-303: "part of the data was collected retrospectively, therefore it is susceptible to a selection bias. Due to the observation nature of the study, causal relationships cannot be stablished").

2. It is not mentioned that appropriate informed consent was obtained for the prospective part of the study.

We apologise for the lack of clarity and have added the following information into the material and methods section: ***"All the cohort have signed informed consent for POEMS data collection" (page 6, lines 94-95).***

3. Endocrine data were only available from 59 out of 75 patients. No standardized protocol was used to study the incidence and prevalence of the endocrinopathies. Nevertheless, the authors recommended that patients should be systematically assessed for endocrinopathy at each visit.

The referee raises an interesting point. We do have a systematic and standardised protocol at each visit for the endocrine assessment of patients with POEMS syndrome, which includes an order set of blood test and endocrine assessment by an SpR or above. We have clarified this point in the methods section (page 6, line 96-97).
In our experience, endocrinopathy can easily be misdiagnosed without a proper screening due to other symptoms (i.e. polyneuropathy) masking the endocrine disease. Of note, our results are in agreement with other studies regarding the high prevalence of endocrine abnormalities in context of POEMS; therefore, it seems reasonable to assess these patients systematically. Nevertheless, we have made a minor change in our conclusion (page 14, line 313).

4. The included patients are phenotypically not well described. No information is presented about prevalence of polyneuropathy, organomegaly, monoclonal gammopathy and skin changes in the study population.

We agree with the referee's comment that this is an important point. All patients had monoclonal gammopathy at diagnosis and all patients except one had polyneuropathy. The one without neuropathy had Castleman variant POEMS. Thirty-five patients (59.3%) had

organomegaly and 41 (69.5%) skin changes**. **We have added this information in the manuscript (page 8, line 144-146). Nevertheless, the complete phenotype of the patient cohort, excluding the endocrine description, is the subject of a publication of the natural history of POEMS syndrome, to be published by or group shortly.

5. No information is reported about presenting symptoms of POEMS. How often was this an endocrinopathy/gyneacomastia?

This is a very interesting comment. Unfortunately, since endocrinopathy is minor criteria and since thyroid abnormalities are not sufficient to meet the minor criteria, we do not have reliable information about how many patients had endocrinopathy as a presenting symptom or gynecomastia. Even so, we know that 63% of patients had clinical evidence of an endocrinopathy at the point of POEMS diagnosis, but we cannot establish the order of appearance. This data is already in the manuscript (page 8, lines 146-147).

6. The prognosis of POEMS syndrome is dependent on the extent of the underlying plasma cell disorder and its response to treatment. However, the authors did not present any information about underlying plasma disorder, treatment regimens (how many participants were treated by melphalan/corticosteroids/radiotherapy) and responses to treatment.

We acknowledge that this is very important information, however this is not the scope of our manuscript, which aims to focus about the endocrine abnormalities. As we mentioned above, the complete phenotype including treatment and prognosis of the patient cohort is due to be published by our group.

7. Only nine of the thirty-three patients with hyperprolactinaemia underwent a pituitary or head MRI. The authors suggested that an indication to perform a MRI was only present if the hyperprolactinaemia was symptomatic or if prolactin was raised more than 3 times above the upper limit of reference. This is an arbitrary decision rule which is not well supported by arguments.

The referee raises an interesting point and we agree that this is an arbitrary criterion. In our study, the request of an MRI was dependent on the judgement of the clinician.
According to endocrine guidelines, MRI should be performed after detail clinical review, after excluding secondary causes of hyperprolactinaemia (i.e drugs) and in case of persistent hyperprolactinaemia; however, the significance and cause of hyperprolactinaemia is unknown in POEMS syndrome. Since there is not consensus for an existent cut-off for prolactin levels to request an MRI, we have deleted this cut-off criteria from our manuscript (page 12, line 252).

8. Page 11, lines 239-241; Since there were no differences between primary and central hypogonadism, the authors suggested that hyperprolactinemia was not the cause of hypogonadism. This is pure speculation. Did they measure levels of gonadotrophines in all participants with hypogonadism? What was their definition of primary and central hypogonadism?

We agree with the referee's comment and we have rephrased "69.2% patients with hyperprolactinaemia had hypogonadism, but there were no differences between primary and central hypogonadism; as hyperprolactinaemia was mild, this suggests the hyperprolactinaemia may not be the cause of the hypogonadism" (page 12, lines 246-248).

LH/FSH was measured in all subjects to differentiate between primary and secondary hypogonadism. We have added the definition of primary and secondary hypogonadism (page 7, lines 116-119).

9. IGF-I was increased while there was no evidence of increased activity of GH. How many of the participants were using corticosteroids with persistent high IGF-I?.

The referee raises an interesting point. Out of five patients with persistent high IGF-1, only one was on hydrocortisone 10/5/5 mg due to adrenal insufficiency. The rest of them were not on treatment with any type of corticosteroids. We have added this information in the manuscript (page 10, line 215-216).

Reviewer 2:
The study conducted by Caimari et al. reports the prevalence and course of endocrinopathy in POEMS. Although several limitations (which are addressed by the authors in the discussion) exist due in part to the retrospective nature of the work, the paper reports original data, with a significant number of patients, in a rare pathological condition. Text and figures are concise and well presented, an upmost need, to make this manuscript one of the reference on the topic of POEMS

We thank the reviewer for his/her valuable comment.

Prevalence and course of endocrinopathy in POEMS syndrome

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ABSTRACT

Context. POEMS syndrome is a rare multisystem disorder characterised by polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma-proliferative disorder and skin changes among other features.

Objective. To describe the prevalence and course of the endocrine dysfunction in the context of POEMS.

Design. Cohort study with systematic review of the endocrinopathy in POEMS.

Setting. 75 patients with POEMS were evaluated by the multidisciplinary team at our tertiary specialist centre.

Patients. Endocrine data was available for 59 patients who attended the clinic from 06/1999 to 05/2018.

Interventions. All patients had regular endocrine screening including testing for diabetes, pituitary and thyroid dysfunction and assessment of bone metabolism.

Main Outcome Measure. Prevalence and survival time to develop endocrinopathy in POEMS.

Results. Thirty-four (63%) patients presented with an endocrinopathy at point of POEMS diagnosis and 54 (92%) had at least one endocrine abnormality at follow-up. The median follow-up was 4.4[1.5, 7.9] years. The most common endocrine abnormality was hypogonadism in 68%, followed by hyperprolactinaemia (56%), hypothyroidism (54%), abnormal glucose metabolism (24%), adrenal insufficiency (17%) and high IGF-1 levels (15%). Spontaneous resolution of endocrine abnormalities at the end of follow-up was observed: 14% in hypogonadism, 42% in hyperprolactinaemia, 34% in hypothyroidism and 38% in high IGF-1 levels.

Conclusions. Endocrinopathy was found in 63% of patients at diagnosis and in 92% of patients during follow-up in our cohort, therefore patients with POEMS should be systematically

assessed for endocrinopathy. The most common deficiencies were hypogonadism and hypothyroidism, however normalisation of the endocrinopathy can occur so on-going treatment should remain under review.

PRECIS

Description of the endocrine dysfunction in a cohort with POEMS syndrome, evaluated by a multidisciplinary team. All patients had regular screening of diabetes, pituitary, thyroid and bone metabolism.

INTRODUCTION

POEMS syndrome is a paraneoplastic disorder secondary to a plasma cell dyscrasia (1). The first case of POEMS syndrome was reported in 1934, and the POEMS acronym was used in 1980 for the first time (1). This rare multisystem disorder is characterised by Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal plasma-proliferative disorder and Skin changes among other features (2,3). POEMS syndrome is also referred to as Crow-Fukase syndrome or Takatsuki syndrome (4).

The aetiology of POEMS syndrome is unknown, although an increase in plasma or serum levels of vascular endothelial growth factor (VEGF) is one of the biochemical typical features (4). The diagnosis is often delayed due to the rarity of the syndrome and patients are frequently misdiagnosed with other neurological disorders, most commonly with chronic inflammatory demyelinating polyradiculoneuropathy (5).

POEMS syndrome involves multiple organs, and therefore a multidisciplinary approach is usually necessary to treat this group of patients, including a thorough endocrine assessment.

Multiple endocrinopathies have been described in POEMS, however the pathogenesis underlying the endocrine abnormalities in POEMS syndrome is unknown. The endocrine dysfunction reported so far is diverse and includes both primary and secondary insufficiencies, such as hypothyroidism, adrenal insufficiency, hypoparathyroidism and hypogonadism (6) as well as excess of hormones with hyperprolactinaemia and hyperparathyroidism (7,8). Pituitary tumours have been described (9), but this could be an incidental finding as the prevalence of these tumours is approximately 20% in the general population (10).

There is a significant risk of morbidity from unrecognised endocrinopathy in these patients, especially if there is a lack of a multidisciplinary approach. Little is known about the course and severity of the endocrine dysfunction in POEMS. Here we describe the endocrinopathy at diagnosis and during follow-up in the largest reported European cohort of patients with POEMS syndrome seen at a single specialist centre.

MATERIAL AND METHODS

Seventy-five patients were identified fulfilling the internationally accepted POEMS diagnostic criteria (see Table 1), attending a quaternary referral clinic at University College London Hospital (UCLH), from 1999 to May 2018 referred from other centres in the UK and Ireland. Endocrine data was available from 59 patients who attended the joint haematological / neurological /endocrine clinic. Endocrine data was collected initially retrospectively from medical notes and prospectively from 2013. All the cohort have signed informed consent for POEMS data collection. All patients had at least six monthly regular endocrine screening including diabetes, pituitary, thyroid and bone metabolism, including clinical assessment and an order set of blood test according to our protocol. Those patients with only endocrine screening at diagnosis, without endocrine follow-up, or followed in another hospital were excluded from this study. Other non-endocrine features and treatment of this cohort of POEMS syndrome patients has been described elsewhere (Keddie et al, manuscript in progress).

Definition of variables

POEMS syndrome was diagnosed when patient fulfilled the diagnostic criteria (5) (Table 1). The date of diagnosis was defined as the date of confirmation of POEMS syndrome. Last follow-up was defined as the last hospital appointment in our institution.

We defined endocrine abnormality at diagnosis if the patient presented before or at the moment of POEMS syndrome diagnosis with one or more of the following comorbidities: diabetes mellitus (DM), thyroid disease, hypogonadism, adrenal insufficiency, hyperprolactinaemia, hypo/hyperparathyroidism. We defined endocrinopathy at follow-up if the patient newly presented with any of those abnormalities during follow-up, in addition to abnormal IGF-1 levels.

New primary hypothyroidism was defined as two separate thyroid stimulating hormone (TSH) levels above the reference range (0.27-4.20 mIU/L). DM and pre-diabetes were diagnosed according to the ADA criteria (11). Hyperprolactinaemia was defined when at least two prolactin levels were above the reference range (324 pmol/L for men and 496 pmol/L for

women). Hypogonadism in men was defined when testosterone level at 9 am was below the reference range on at least two occasions (7.6 mmol/L) with elevated LH/FSH in primary hypogonadism and low or normal LH/FSH in secondary hypogonadism. Hypogonadism in women was defined when amenorrhoea was present with low oestrogen, and abnormally low LH/FSH levels in secondary hypogonadism or high LH/FSH levels in primary hypogonadism. Women with amenorrhoea, high LH/FSH levels and above 45 years old were considered to be in the menopause and were thus not considered as having pathological hypogonadism. Adrenal insufficiency was defined as clinical symptoms of hypoadrenalism and basal cortisol below 100 nmol/L in the absence of exogenous corticosteroid administration or abnormal short synacthen test. High IGF-1 levels were considered when IGF-1 was elevated above the age adjusted reference range at least on two occasions.

Statistical analysis

The Shapiro-Wilks test was used to assess normal distribution for continuous variables. Normally distributed variables were expressed as mean and standard deviation (SD) and were analyzed with the Student t-test. Median and interquartile range (IQR) were used to describe non-normally distributed variables. These variables were analyzed with the Mann-Whitney U-test. Qualitative variables were expressed as percentage and analyzed with the chi-square test to compare two or more groups. Kaplan Meier (KM) curves were calculated for each endocrine dysfunction to estimate their survival time. Patients with endocrinopathy at diagnosis were excluded for KM calculation. $P<0.05$ was taken as significant.

RESULTS

Baseline characteristics

Fifty-nine patients had endocrine follow-up. All patients fulfilled the minimum criteria for POEMS diagnosis (Table 1). Thirty-nine patients were male (66.1%) and the median age of diagnosis was 52.5 [38.6, 63.3] years with no differences between gender (53.3 [40.6,73.4] years for men vs 47.8 [37.4,72.8] years for women, p=0.147). Five patients (9.6%) were active

smokers at diagnosis and 23.1% were ex-smokers. The median follow-up was 4.4 [1.5, 7.9] years.

All patients had monoclonal gammopathy at diagnosis and all patients except one had polyneuropathy. The one without neuropathy had Castleman variant POEMS. Thirty-five patients (59.3%) had organomegaly and 41 (69.5%) skin changes. Thirty-four (63%) patients had clinical evidence of an endocrinopathy at the point of POEMS diagnosis. Endocrine abnormalities at presentation are described in Table 2. Two patients presented with an empty sella, one with panhypopituitarism with ACTH, TSH, FSH/LH deficiency and hyperprolactinemia, and the other with normal pituitary function but with primary hypothyroidism and type 2 DM.

Endocrine abnormalities at follow-up

Fifty-four patients (91.5%) had an endocrinopathy at some point during follow-up (25.4% with one endocrine abnormality, 23.7% with two, 28.8% with three, 8.5% with four, 3.4% with five and 1.7% with six abnormalities). None of our patients developed hypo- or hyperparathyroidism during follow-up. The next sections describe the endocrine abnormalities with their relevant treatment, ranked by their frequency (summarized in Table 3).

Hypogonadism

Thirty-nine (68.4%) patients presented with hypogonadism by the end of follow-up. Ten (50%) women were considered to be menopausal and therefore were not included as having pathological hypogonadism. When studied by gender, 29 (78.4%) men and 10 (50%) of women were diagnosed with hypogonadism. From those, 16 (41%) had central hypogonadism and 23 (59%) primary hypogonadism. Out of these 23 patients, 14 (60.9%) developed primary hypogonadism after receiving melphalan treatment as preconditioning for autologous stem cell transplant. The median time to develop hypogonadism after diagnosis of POEMS syndrome was 3 [0.9, 5.9] years (Figure 1A). Hypogonadism spontaneously resolved in five (13.5%) patients: three with central hypogonadism and two with primary hypogonadism.

Regarding testosterone replacement, of the 29 men with hypogonadism, 14 (48.3%) did not receive any treatment. Seven (24.1%) were treated with testosterone injections and 8 (27.6%) with testosterone gel. From those treated with testosterone, six (37.5%) developed polycythaemia after testosterone replacement, in comparison to three (6.8%) that did not receive testosterone replacement (p=0.024). Five were on testosterone injections (testosterone enanthate or a combination of testosterone propionate, testosterone phenylpropionate, testosterone isocaproate and testosterone decanoate) and one on testosterone gel.

Hyperprolactinaemia

Thirty-three (55.9%) patients developed hyperprolactinaemia although six of these were treated with a drug with the potential to induce hyperprolactinaemia. Nine patients underwent a pituitary or head MRI. Of these, eight had a normal pituitary MRI and one presented with an empty sella. The median peak prolactin was 1.9 [1.5, 2.2] times above the upper limit of the normal range, adjusted by gender.

Twenty-seven patients (69.2%) with hyperprolactinaemia had hypogonadism, without differences between central and primary hypogonadism (10 (62.5%) vs 17 (73.9%) respectively, p=0.447).

The median time to develop hyperprolactinaemia during follow-up was 2.8 [0.9, 6.2] years (Figure 1B). No patient received treatment with a dopamine agonist and in 14 (42.4%) patients, the prolactin level normalised by the end of follow-up.

Thyroid disease

Thirty-two (54.2%) patients were diagnosed with hypothyroidism: 17 (53.1%) with clinical primary, 14 (43.8%) with subclinical primary and 1 (3.1%) with central hypothyroidism. The median TSH value for patients with primary hypogonadism at diagnosis was 10.1±5 mIU/L (normal range 0.27-4.20 mIU/L) and all patients requiring treatment were treated with levothyroxine once a day (median dose 62.5 [37.5, 106.3] mcg). Hypothyroidism developed

after 2.64 (0.6- 4.9) years (Figure 1C). Hypothyroidism spontaneously resolved in 11 (34.4%) of these patients, three with clinical and eight with subclinical hypothyroidism.

Abnormal glucose metabolism

Fourteen (23.8%) patients presented with abnormal glucose metabolism, eight (13.6%) with DM (seven type 2DM and one with steroid-induced DM), and six (10.2%) with pre-diabetes.

Patients with DM were treated with diet alone in one patient, four with oral hypoglycaemic drugs and three with insulin with/without oral hypoglycaemic drugs. Patients developed abnormal glucose tolerance after 3.4 [0.9, 6.1] years from the diagnosis of POEMS (Figure 1D). DM resolved in the one patient with steroid-induced diabetes.

Adrenal insufficiency

Ten (17%) patients presented with adrenal insufficiency at the end of follow-up. Five had primary adrenal insufficiency, one central and four with secondary cortisol deficiency due to long-term steroid treatment. None of the patients recovered from adrenal insufficiency at the end of follow-up. The median time to develop cortisol deficiency was 3.6 [1.4, 6.8] years (Figure 1E).

IGF-1

Eight (14.8%) patients had high IGF-1 levels on at least two different occasions. Only one patient had acromegalic features. The IGF-1 mean in these patients was 1.3±0.2 times above the upper limit of the normal range, adjusted by age. The median time to develop high IGF-1 level at follow-up was 4.3 [1.4, 8] years after diagnosis of POEMS syndrome (Figure 1D). Five patients with persistent high IGF-1 level had screening for growth hormone (GH) excess with a 75g Oral Glucose Tolerance Test (OGTT). In all of them GH was adequately supressed, therefore excluding acromegaly and in only one patient was on treatment with corticosteroids (hydrocortisone 20 mg) due to adrenal insufficiency. The patient who had acromegalic features underwent a pituitary MRI, which did not demonstrate any pituitary lesion. In three (37.5%) of those patients IGF-1 level normalised at the end of follow-up.

DISCUSSION

We have reviewed the course of endocrine dysfunction in a large group of patients with POEMS syndrome. To our knowledge, this is the largest series that systematically reviews the endocrinopathy in this rare condition. It uses endocrine data collected initially retrospectively and later prospectively during follow-up. Our cohort is characterized by diverse endocrinopathy, mostly with more than one endocrine diagnosis, and combining primary and secondary insufficiencies as well as excess of hormonal secretion.

In the literature, endocrine dysfunction has been reported in 58-80% of patients (2,7). This is similar to our study, although we report a significant increase in the diagnosis during follow-up (63% at presentation vs 91.5% at follow-up), suggesting that the endocrine screening during follow-up is essential in these patients.

Hypogonadism

The most frequent endocrine abnormality was hypogonadism (68.4%), but hyperprolactinaemia (55.9%) and hypothyroidism (54.2%) were also common in our cohort, as previously reported (4,7,12). Although, most patients did not have clear causes for the development of hypogonadism, some alternative or additional factors could play roles in development. Firstly, these patients were frequently ill at presentation, with a possible underlying diagnosis of hypothalamic hypogonadism, described in context of severe illness (13,14). Secondly, some of the patients developed primary hypogonadism in the context of melphalan treatment (an alkylating agent known to cause gonadal toxicity)(15), and therefore hypogonadism may not be directly related to POEMS. The combination of these three precipitating factors probably explains why hypogonadism is the most common endocrinopathy in POEMS.

Hyperprolactinaemia

Hyperprolactinaemia was the second most common endocrinopathy in our cohort (55.9%), and only a few patients had treatment with drugs that could induce hyperprolactinaemia. In our

cohort the frequency of hyperprolactinaemia is higher than previously reported and we hypothesise that this is the direct result of a systematic screening of these patients (7).

69.2% patients with hyperprolactinaemia had hypogonadism, but there were no differences between primary and central hypogonadism; as hyperprolactinaemia was mild, this suggests the hyperprolactinaemia may not be the cause of the hypogonadism. We hypothesise that empty sella could also be an expression of endocrine abnormality in POEMS, although an incidental finding cannot be excluded as there are no other cases reported so far. Given only the mild increase in prolactin in most of our patients we suggest that a pituitary MRI should only be requested if the hyperprolactinaemia is persistent or symptomatic.

Hypothyroidism

Hypothyroidism was the third endocrine disease in frequency in our cohort (54.2%). Most of our patients (except one with panhypopituitarism), presented with primary hypothyroidism, and half of them had subclinical hypothyroidism. Mild elevation of TSH has been reported in other series (4,7,16). Although hypothyroidism is not considered as part of the POEMS criteria diagnosis, the prevalence of thyroid disease in POEMS is by far much higher in POEMS patients than in general population (17).

Glycaemic control

Patients with type 2 DM accounted for 13.6% in our cohort, however abnormal glucose metabolism reached 23.8% when pre-diabetes was also considered. The prevalence does not differ when compared with general population, although the prevalence of type 2 DM varies by region, age and ethnicity, amongst other factors (18). As type 2 DM has a high prevalence in the population, caution should be taken when considering it as part of the POEMS syndrome, especially if no other endocrine organs are affected and this is the reason why DM is not included in the POEMS diagnostic criteria. Treatment of abnormal glucose metabolism should be in line with usual recommendations.

Adrenal insufficiency

Adrenal insufficiency was significant in our cohort (17%). In this group, those who had long term steroid treatment had cortisol deficiency secondary to treatment for POEMS syndrome. However, five of 59 patients (8.5%) had primary adrenal insufficiency. Different from the natural course of other endocrinopathies, adrenal insufficiency was permanent in every patient in our cohort.

IGF-1 levels

We report for the first time that patients with POEMS syndrome present with elevated IGF-1 levels. In those with persistent high IGF-1, the OGTT, a measure of GH suppressibility, revealed a normal GH-IGF-1 axis. Of note, the increase of IGF-1 was mild in all patients. The significance of this finding is unclear and difficult to explain, especially taking into account that IGF-1 levels are usually low in the context of severe illness (19) and that IGF-1 concentrations are reduced in patients with multiple myeloma (20). Although our patients have hepatomegaly, we have not found any evidence that hepatomegaly is associated with increased IGF-1 production.

Interestingly, the prevalence of endocrine abnormalities increased during follow-up. The median time to develop any abnormality ranged from 2.6 to 4.3 years after POEMS presentation. This could indicate that the endocrine organ damage continues after controlling the disease. This data was unexpected as it is well described that other features of POEMS syndrome, such as polyneuropathy, improve after treatment (21). On the other hand, we found that endocrine dysfunction can be reversible in POEMS syndrome: 42.4 % patients with hyperprolactinaemia, 34.4% of patients with hypothyroidism and 37.5% in high IGF-1 levels demonstrated a transient abnormality. Of note, our patients were characterized by presenting multiple but mild endocrinopathies.

Patients received endocrine treatment according to current medical guidelines and generally wellbeing improved in these patients (author's observation). We observed that patients with hypogonadism treated with testosterone had a high risk of polycythaemia. Polycythaemia itself is a feature commonly found in active/unremitted POEMS (2). Therefore, this cohort has a predisposition to develop polycythaemia, also a well-known side effect of testosterone treatment. In our experience, patients who received testosterone injections had higher chance of polycythaemia compared to those treated with gel, and the level of polycythaemia occasionally required cessation of testosterone treatment.

This study has some limitations. Firstly, part of the data was collected retrospectively, therefore it is susceptible to a selection bias. Due to the observation nature of the study, causal relationships cannot be stablished. Secondly, due to its observational nature several questions cannot be addressed. These include the cause of the endocrine dysfunction in POEMS syndrome, how and why the endocrine disease can be reversible and why the patients present either hormonal insufficiency or hypersecretion, such as high IGF-1 levels. We will address these questions with studies of a different design. Finally, due to the high incidence in the general population of some of the endocrine diseases such as hypothyroidism or Type 2 DM, the incidental co-association of these abnormalities cannot be excluded, but is recognised. We believe that this study has highlighted several issues, which contribute to the knowledge of this rare but challenging clinical situation.

In conclusion, endocrinopathy in POEMS was found in 63% of patients at diagnosis and in 91.5% of patients during follow-up in our cohort. We therefore suggest the following recommendations for patients with POEMS syndrome in addition to the multidisciplinary haematological and neurological care.

1) POEMS syndrome involves multiple organs, and a multidisciplinary approach should include an endocrinologist.

2) Patients should be systematically assessed for endocrinopathy at each visit and be offered endocrine treatment as indicated.
3) Normalisation of the endocrinopathy occurred in a proportion of patients, so on-going treatment should remain under review.
4) Adrenal insufficiency was permanent and patients will need education and advice regarding life-long steroid sick day rules.
5) Patients on testosterone replacement therapy should be monitored for polycythaemia.

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FIGURE LEGENDS

Figure 1. Time to develop endocrinopathy in patients with POEMS syndrome.

Figure 2. Endocrinopathy at follow-up and transient endocrine abnormalities.

Black columns indicate the percentage of endocrinopathies at follow-up. Grey columns indicate the percentage of patients that normalise the endocrine dysfunction.

Table 1. Diagnostic criteria for POEMS syndrome (5)**.**

Mandatory Major Criteria
Polyneuropathy (typically demyelinating)
Monoclonal plasma cell proliferative disorder (almost always λ)
Other Major Criteria (one required)
Castleman disease
Sclerotic bone lesions
Vascular bone lesions
VEGF elevation
Minor criteria (one required)
Organomegaly
Extravascular volume overload
Endocrinopathy*
Skin changes
Papilledema
Thrombocytosis, polycythaemia
Other useful features
Clubbing, weight loss, hyperhidrosis, pulmonary hypertension/ restrictive lung disease, thrombotic diathesis, diarrhoea, low vitamin B12.

* Due to the high prevalence of diabetes mellitus and thyroid abnormalities, this diagnosis alone is not sufficient to meet this minor criterion.

Table 2. Endocrine abnormalities in POEMS syndrome at diagnosis and follow-up.

Clinical characteristic	Total cohort N= 59	Men N=39	Women N=20	p-value
Endocrine dysfunction at diagnosis*	34 (63%)	21 (61.8%)	13 (65%)	0.812
Thyroid disease	20 (36.4%)	12 (34.3%)	8 (40%)	0.672
Hypogonadism	20 (36.4%)	16 (45.7)	4 (20)	0.057
Diabetes Mellitus	4 (7.3%)	4 (11.4%)	0	0.116
Hypoparathyroidism	0	0	0	NA
Addison disease	3 (5.5%)	1 (2.86%)	2 (10%)	0.262
Hyperprolactinaemia	13 (24.1%)	7 (20.6%)	6 (30%)	0.435
Endocrine dysfunction at follow-up	54 (91.5%)	35 (89.7%)	19 (95%)	0.375

*IGF-1 levels were not assessed at POEMS diagnosis.

Table 3. Endocrine abnormalities in POEMS syndrome at follow-up.

Endocrine abnormality N=59	Prevalence n (%)	Time of onset median years [IQR]	Treatment n (%)	Transient n (%)
Hypogonadism	39 (68.4)	3 [0.9, 5.9]	15 (51.7)	3 (13.5)
Hyperprolactinaemia	33 (55.9)	2.8 [0.9, 6.2]	0	14 (42.4%)
Thyroid disease	32 (54.2%)	2.6 [0.6-4.9]	14 (43.8)	11 (34.4%)
Abnormal glucose metabolism	14 (23.8)	3.49 [0.9-6.1]	8 (57.1)	0
Adrenal insufficiency	10 (17)	3.6 [1.4-6.8]	10 (100)	0
High IGF-1	8 (14.8)	4.3 [1.4-85]	0	3 (37.5)

Figure 1

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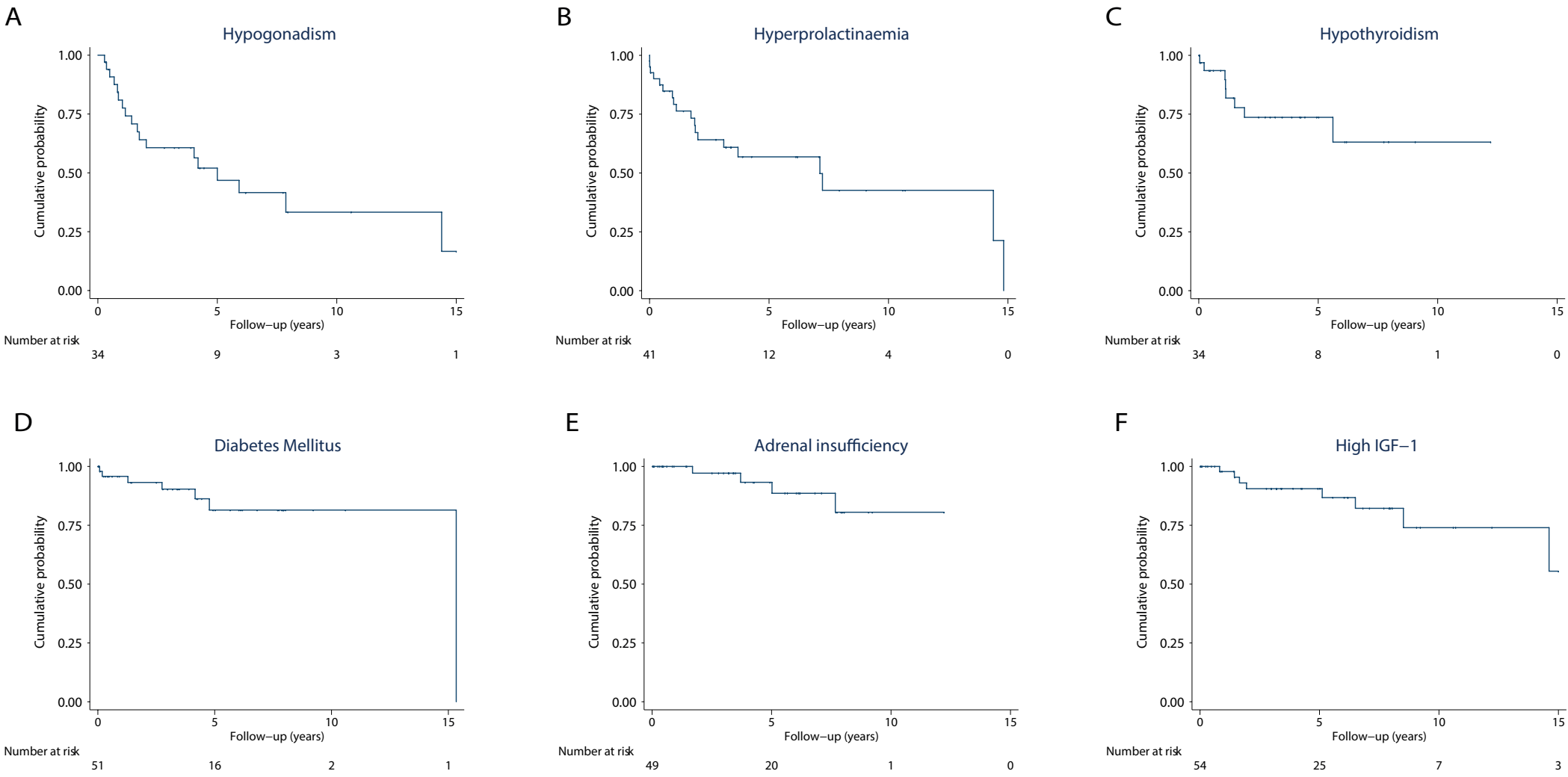

Figure 2