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CLINICAL COMMENTARY

Comorbidities in patients with Unverricht–Lundborg disease (EPM1)

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Background: Unverricht-Lundborg disease (EPM1) typically leads to accumulating disability. Disability may also be caused by comorbidities but there are no data available on these.

Aims of the Study: To investigate the frequency of comorbidities in EPM1.

Methods: Comorbidity data of a previously described cohort of 135 Finnish patients with EPM1 were retrieved from neurological, surgical (including subspecialities), internal medicine (including subspecialities) and intensive care patient charts of the treating hospitals.

Results: Mean follow-up time was 31.4 years (SD 12.4 years, range 6.8–57.8 years), during which at least one comorbidity was observed in 107 patients (79%) and three or more in 53 (39%). The most common diagnostic categories were external injuries, mental and behavioural disorders and endocrine, nutritional and metabolic diseases. The most common single comorbid diagnosis was a fracture of the ankle (in 19% of all patients). The second most common single comorbid diagnosis in the cohort was diabetes (in 13% of all patients), and the third was depression, recorded for 13% of the cohort. Malignancies and cardiovascular end-organ damage were rare, whereas phimosis/paraphimosis appeared more common than in general population.

Conclusions: Patients with EPM1 often have comorbidities. Trauma and mental health risks should be especially followed and acted upon. Further studies are needed to more accurately comorbidity risks, characteristics and patient needs.

KEYWORDS
clinical neurology, comorbidity, epileptic syndromes, hereditary disorders, rare epilepsies

1 | INTRODUCTION

Progressive myoclonic epilepsy-1A (EPM1) (OMIM #254800), or myoclonic epilepsy of Unverricht and Lundborg, is a rare neurodegenerative disorder. Its most common manifestations are myoclonus, seizures, ataxia and cognitive decline.[1–4] The disorder is caused by cystatin B (*CSTB*) gene mutations and inherited recessively.[4] *CSTB* codes a small protein called Stefin B/cystatin B that functions as an intracellular thiol protease inhibitor. It has been isolated from human spleen and liver and shows biased expression in oesophagus and urinary bladder but is widely distributed. Current information points to it having a role in protecting against the proteinases leaking from lysosomes, but its function is inadequately understood.

The clinical course of EPM1 is variable but and early retirement.[1,2,5] Beyond the nervous system, abnormal skeletal findings have been reported,[6] but little information is available concerning

the occurrence of comorbidities in patients with EPM1. The prognosis is highly variable but, on average, the patients have poorer survival compared to matched controls.[5] Identifying and treating possible co-occurring diseases could provide a way to improve the prognosis. We therefore investigated the occurrence of comorbid diseases and injuries in a population-based cohort of EPM1 patients.

2 | METHODS

The ascertainment and characteristics of the study cohort have been described previously. Briefly, national mandatory registries, patient records and laboratory data were used to identify the 135-person (54% women) cohort of persons with EPM1 in Finland between 1 January 1998 and 31 December 2016.[5] Comorbidity data were obtained from neurological, surgical, internal medicine and intensive care patient records obtained from the treating hospitals. The occurrence of comorbid diagnoses was initially analysed by chapters and blocks (A-Q, S and T) in the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10). The blocks with the highest frequencies of diagnoses and some individual diagnoses of particular interest are presented in more depth. The distribution of continuous variables was assessed with Shapiro–Wilk and Kolmogorov–Smirnov tests which were used to choose either Mann–Whitney U test or independent samples *t*-test to analyse patient characteristics. Analyses were conducted using IBM SPSS Statistics for Windows, Version 27.0.

3 | RESULTS

In the 135 patients of the cohort, mean follow-up time was 31.4 years (SD 12.4 years, range 6.8–57.8 years) At least one comorbidity was observed in 107 patients (79%) and three or more in 53 (39%). The total number of comorbid diagnoses was 326 (median per patient 2, IQR 1–3, range 0–11). The most common ICD-10 chapters were XIX (Injury, poisoning and certain other consequences of external causes), V (Mental and behavioural disorders) and IV (Endocrine, nutritional and metabolic diseases; Table 1).

TABLE 1 The frequencies and proportions of all comorbidities by category in the cohort

Disease category (ICD-10 block)	No. diagnoses	Proportion of all diagnoses (%)
Infectious diseases (A&B)	3	1
Neoplasms (C-D48)	9	3
Diseases of the blood and blood-forming organs (D50-D89)	3	1
Endocrine, nutritional and metabolic diseases (E)	52	16
Mental and behavioural disorders (F)	62	19
Diseases of the nervous system (G)	5	2
Diseases of the eye and the ear (H)	3	1
Diseases of the circulatory system (I)	37	11
Diseases of the respiratory system (J)	5	2
Diseases of the digestive system (K)	27	8
Diseases of the skin and subcutaneous tissue (L)	4	1
Diseases of the musculoskeletal system and connective tissue (M)	29	9
Diseases of the genitourinary system (N)	15	5
Pregnancy, childbirth and the puerperium (O)	0	0
Certain conditions originating in the perinatal period (P)	0	0
Congenital malformations, deformations and chromosomal abnormalities (Q)	3	1
Injury, poisoning and certain other consequences of external causes (S&T)	69	21

3.1 | Trauma

The most common single comorbid diagnosis in the entire cohort was a fracture of the ankle of which there were 27 in 25 individuals (19% of the entire cohort, 52% men). There was no difference in EPM1 onset age between patients with an ankle fracture and those without ($p = .69$). Fracture of the wrist or the hand had been diagnosed in seven patients (5% of the cohort), a fracture of the foot below the ankle in six (4%) and a traumatic brain injury or its sequelae also in six patients (4%). There had been three fractures of the antebrachium, two of the collarbone and two hip fractures but none of the knee, the elbow or the upper arm. In total, there were 48 bone fracture diagnoses in 27 individuals (19% of the cohort).

3.2 | Mental and behavioural disorders

The third most common single comorbid diagnosis in the cohort was depression, which had been recorded for 17 patients (13% of the cohort, 59% women). The age of EPM1 onset did not differ between patients with depression and those without ($p = .11$). Alcoholism was observed in 13 patients (10%) and abuse of other substances in three. Personality disorders had been diagnosed in eight patients (6%) and anxiety disorders in four. At least one diagnosis of a mental

or a behavioural disorder (ICD-10 block F) was observed in 39 individuals (29% of the cohort).

3.3 | Endocrine and metabolic disorders

The second most common single comorbid diagnosis in the cohort was diabetes, observed in 18 patients (13% of the cohort, 67% men). No difference in EPM1 onset age was observed between patients with diabetes those without ($p = .96$). Hypothyreosis had been recorded in 12 patients (9% of the cohort, 83% women), obesity in 11 (8%) and hypercholesterolemia in six (4%). An endocrine or metabolic diagnosis had been recorded in 41 individuals (30% of the cohort) with nine patients (7%) having more than one.

3.4 | Cardiovascular disorders

Hypertension had been diagnosed in 15 patients (11%) and atrial fibrillation in three. Two patients had a diagnosis of coronary disease, but no myocardial infarctions were observed. Cardiac insufficiency had been diagnosed in two patients and a pulmonary embolism in also two. There had been three ischemic strokes but no haemorrhagic ones. There had been one case of hypertensive encephalopathy in a patient whose hypertension appeared to be familial and malignant.

3.5 | Miscellaneous disorders of interest

There had been seven patients (5%) with a malignant neoplasm of which three had been of the breast, two of the colon, one of the thyroid and one of the adrenals. Osteoarthritis had been diagnosed in eight patients (6%). Seven patients (5%) had gallstone disease and one had a pancreatitis as a complication. Five patients (8% of the cohort's men) had been diagnosed with and operated for phimosis/paraphimosis, all in the adult age. Specific diagnoses of infectious disease were few. However, in many admissions infection had been suspected but the diagnosis was uncertain.

4 | DISCUSSION

This study showed that comorbidities are common in patients with EPM1 with 60% of the patients having at least two such diagnoses. The most common comorbidities were trauma, mental health disorders and endocrine disease, especially diabetes. Malignant neoplasms and cardiovascular end-organ damage were rare.

Cystatin B is associated with bone metabolism and particularly osteoclast function.[7,8] Moreover, patients with EPM1 have abnormal skeletal features that are probably associated with the *CSTB* mutation.[6] The current data showed that bone fractures are very common among patients with EPM1 with 19% of the cohort having had at least one recorded. Interestingly, almost all of the fractures were of the ankle or the small bones of the hand and foot with very few fractures of the larger bones, such as the femur. In general, as ataxia, myoclonus and balance impairment are central features of EPM1, and *CSTB* has a role in bone metabolism falls, and fractures are to be expected. These risks should therefore be regularly assessed.

Mental and behavioural problems were also very common with nearly a third of the patients having at least one block F diagnosis and 13% diagnosed with depression. The 10% cumulative prevalence of alcoholism in patients with EPM1 did not appear higher than in general population as excessive drinking is unfortunately still quite common in Finland.[9] Nevertheless, there is cause for concern as alcohol abuse of EPM1 patients often occurred during the second decade of life with a concurrent clinical worsening. This suggests that many patients with EPM1 need more robust psychological and social support, especially during adolescence.

Endocrine and metabolic disturbance was common in these patients, and diabetes appeared more common than in the general Finnish adult population, although underdiagnosis may confound results.[10,11] The cumulative prevalence of hypothyroidism appeared almost threefold compared to its one-year prevalence in the general population.[12] The reasons for this are unclear but since *CSTB* is expressed in the thyroid, a causal association seems possible. The recorded prevalence of obesity, on the other hand, was markedly lower than in the Finnish general population.[13] It is noteworthy that *CSTB* is quite actively expressed in fat tissue.

Neoplasms and cardiovascular diseases were rare. In contrast, the 8% occurrence of phimosis/paraphimosis among adult men was clearly higher than the general population rate of 3.4% for phimosis and 1% for paraphimosis.[14,15] Again, the reasons for this are unclear especially as lichen sclerosis, diabetes or obesity were not more common than in the general population.

Our data were retrospective and hospital-based. The proportions are therefore bound to be minimum estimates as many diseases, such as diabetes, are managed in primary healthcare in Finland. This is, perhaps, best highlighted by the fact that we observed no diagnoses of osteoporosis even though fractures were common. Naturally, this could also be due to possible underdiagnosis of the condition in this population. Data on the time of diagnosis were often unavailable, so age-specific burdens cannot be assessed and direct comparisons with general population made. The search also included only those hospitals that treated these patients for EPM1 so, for example, possible fractures treated at lower-level hospitals or health centres were missed. Furthermore, only some specialities were included and at least gynaecological disorders and obstetric/puerperal diagnoses were probably mostly missed. Moreover, identifying and classifying acute infections based on this data proved too inaccurate, especially considering that swallowing difficulties are common in EPM1 and patients usually die of pneumonia.[5] In all, this study should be viewed as a first glance on the subject that warrants a prospective cohort study.

In conclusion, comorbidities are common in patients with EPM1, and especially, the risk of trauma and mental health disorders should be acknowledged clinically. These and other comorbidities, especially endocrine and metabolic conditions and any propensity to

infections, also need to be investigated in more detail, preferably in prospective patient cohorts. Comparative data concerning comorbidities in somewhat similar chronic neurological diseases such as juvenile myoclonic epilepsy are also needed.

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CONFLICT OF INTEREST

Jussi Sipilä has received honoraria (Merck, Pfizer, Sanofi), a consultancy fees (Rinnekoti Foundation, Medaffcon), travel grants and congress sponsorship (AbbVie, Orion Pharma, Merck Serono, Sanquin, Lundbeck, Novartis) and holds shares (Orion Corporation). Reetta Kälviäinen has received grants from the Academy of Finland and Saastamoinen Foundation, speaker's honoraria from Eisai, Omamedical, Orion, Sandoz, Sanofi, and UCB and honoraria for membership of the advisory boards of Angelini Pharma, Eisai, GW Pharmaceuticals, Marinus Pharmaceuticals, Orion, Takeda and UCB.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from Findata. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from https://findata.fi/ with the permission of Findata.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/ane.13706.

ETHICS APPROVAL

This registry-based study was approved by THL (THL/1613/5.05.00/2017) and Statistics Finland (TK-53-1280-18). In addition, regional permits were required by some hospital districts, and they were obtained accordingly. Since the study involved no contact with patients, ethical committee approval was not needed. This was a retrospective register study, and thus, no informed consent was required, and the participants were not contacted. The legal basis for processing personal data is public interest and scientific research (EU General Data Protection Regulation 2016/679 (GDPR), Article 6 (1)(e) and Article 9 (2)(j); Data Protection Act, Sections 4 and 6).

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