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Identifying co-morbidities and risk in people with epilepsy: The Maltese experience

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ABSTRACT

Background: People with epilepsy are at increased risk of multiple co-morbidities that may influence risk of adverse outcomes including impact on quality of life and premature mortality. These risk factors include potentially modifiable clinical characteristics associated with sudden unexpected death in epilepsy (SUDEP). For services to tackle risk, the clinical complexity of the target epilepsy population needs to be defined. While this has been comprehensively studied in large, economically developed countries little knowledge of these issues exist in small economically developed countries, like Malta (population: 500,000).
Methods: This was a single centre study focused exclusively on patients attending Gozo General Hospital (GGH) Malta. STROBE guidance for reporting cross sectional studies was used to design and report the study. This was a retrospective review of standard care and SUDEP and seizure risks provided to all adults (over 18 years) with epilepsy attending GGH (2018–2021).
Results: The review identified 68 people and 92% were compliant with their anti-seizure medication. A fifth (21%) had an intellectual disability. Despite only one patient having a psychotic illness, 19% were on antipsychotic medication. Only 18% of patients had a specific epilepsy care plan, 6% nocturnal surveillance and none had received advice on SUDEP.
Discussion: Patient outcomes may be improved with increasing rates of personalized epilepsy care plans, appropriate nocturnal surveillance and reducing the prescription of antipsychotic medication as it is associated with greater risk of mortality. Issues such as stigma and shame appear to play a significant role in small communities and their access to care.

1. Introduction

People with epilepsy are a complex and heterogeneous population with individual needs. [1] Epilepsy is associated with greater risk of a wide range of physical and psychiatric comorbidities. [2] Epilepsy is not a benign neurological condition. There is risk associated with seizures themselves (injury, hospitalization, impact on quality of life), and iatrogenic risk from misdiagnosis or adverse effects of treatment including anti-seizure medications (ASMs). [3,4] The most significant concern is risk of sudden unexpected death in epilepsy (SUDEP), the number one cause of death in epilepsy with an estimated pooled incidence of 1.4 per 1000 person-years. [5] There are specific risk factors for SUDEP, some static and others modifiable. [6] At the core of any treatment should be working collaboratively with the person with epilepsy and their support to reduce risk. Clinical complexity is associated with further increased risk of premature and potentially preventable mortality. The evidence suggests that in complex epilepsy populations, there may be specific risk factors to consider including polypharmacy (drugs other than ASMs), concomitant prescription for antipsychotic medications, and the level of multi-disciplinary support provided. [7] Recognition of these issues has

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recently led to the call for developing an integrated multidisciplinary service model for the care of people with complex epilepsy and other co-occurring conditions in the UK. [8] In order for services to work towards assessing risk and mitigation, we first need to understand how risk factors present in different populations.

While larger European countries (such as the UK, Germany, Netherlands, Scandinavia etc.) grapple with the recognized challenges of supporting and providing equitable care for this vulnerable population, there is little knowledge of the delivery of care to people with epilepsy within smaller European countries (defined as having populations $\leq$ 500,000) or of the specific and separate needs and challenges in relatively small populations.

The Maltese islands are the smallest member of the European Union with a population of 530,000. The islands are a high-income country based on the World Bank economic criteria, with a per-capita GDP of USD 25,370 in 2020, and a current average life expectancy of 82.6 years. Details of Maltese islands, health care system and epilepsy service are provided in supplementary information 1.

This is the first attempt to analyse in detail the clinical characteristics, seizure spectrum, and risk factors of epilepsy within an isolated, Southern Mediterranean, island community using Gozo, the second largest Maltese island (population 37,273) as a templar.

2. Methods

STROBE guidance for reporting cross sectional studies was used to design and report the study (supplementary information 2).

2.1. Data collection

This is a single centre study focused exclusively on patients attending Gozo General Hospital (GGH). The neurology service at this hospital has been run by a single consultant neurologist since 2018, ensuring a standardised approach to treatment in patients with epilepsy. The total caseload open to Neurology services were examined for eligible cases, and all included within the period studied. These were identified through manual searches of the Gozitan neurology patient database held by the consultant. Data were gathered retrospectively via review of patients' physical case notes (electronic health records are not yet available on the island). Pseudo-anonymised data (data that does not directly identify patient) on demographics, health background, epilepsy profile, medication, and risk factors for SUDEP and seizure harm using the evidence-based factors of the SUDEP and Seizure safety Checklist [9,10] were collected in a pre-designed data spreadsheet. As part of the Checklist, specific inquiry was made to see if there was a documented proof of providing an epilepsy care plan. An epilepsy care plan is a comprehensive, individualised plan that provides details of diagnosis, treatment, care and support. As recommended by the NICE (National Institute for Health and Care Excellence) Quality Standard QS211 that allows people to make informed choices wherever possible about their epilepsy and helps coordinate care between healthcare and other professionals in different settings.

In addition, medication compliance was determined using Serum ASM levels when these could be measured, feedback from patients and significant others such as family members.

The inclusion criteria were adults aged 18 years and over, with or without intellectual disabilities, who were known to, and being managed by, the local neurology services in GGH by December 2021. For people with intellectual disabilities, severity of their intellectual disability was coded as mild / moderate / severe based on the same rationale adopted in prior research. [3].

2.2. Statistical Methods

All analysis summarised the data collected and was descriptive in nature. Categorical variables were summarised by the number and percentage of subjects in each category. Continuous variables were described by the mean and standard deviation, if found to be approximately normally distributed, and by the median and inter-quartile range otherwise.

2.3. Study registration and ethical approval

The project was registered as an internal service evaluation and was approved by the information governance structures in GGH. No direct patient identifiable data was collected, and individual data were pooled in a single anonymised dataset (data set with no specific identifiable individual personal or clinical characteristics) prior to sharing outside the hospital for analysis.

3. Results

Data were collected from all 68 subjects with epilepsy open to the GGH neurology services. This is the total caseload for the one Consultant neurologist at Gonzo.

Demographic and core clinical characteristics of the group are summarised in Tables 1 and 2. The mean age of the group was found to be 45 years, 39 (57 %) of whom were male. The median age of first diagnosis of epilepsy was 17 years and 35 (52 %) had been diagnosed with epilepsy for over 15 years. Seven (10 %) had reported routine alcohol use and one of recreational drugs. Forty (59 %) had physical co-morbidities (neurological). Patients with 'physical findings' included those with post-stroke epilepsy and CVE-related physical signs, patients with cerebral palsy / brain trauma + epilepsy and the related physical signs, a patient with epilepsy following measles encephalitis with severe physical and cognitive deficits, and patients with suspected but unidentified genetic disorders with abnormal physical traits and examination (spasticity, paraparesis, incoordination, dysarthria, and others).

Of the study cohort 14 (21 %) had an intellectual disability. These were equally distributed amongst the mild (n = 4), moderate (n = 4), and severe (n = 4), level intellectual disability was unknown for two participants. Known genetic conditions was identified in three (4 %) i.e. Tuberous Sclerosis Complex (n = 1) and Trisomy 21 (n = 2). Autism spectrum disorder was reported in three (4 %), ADHD in one and psychosis in one person.

3.1. Seizure profile (Table 3)

The most common type of seizure was a generalised seizure, which 43 (64 %) people had. Seven (10 %) had more than one type of seizure. Over half of subjects had reported no seizures in the last year (median number of seizures in last year was zero). One or more tonic clonic seizure in the last year was reported by 15 (22 %).

Table 1
Demographics of all people with epilepsy open to GCH.

Variable	n	Category	Summary
Current age	68	–	45.4 ± 17.6 {17, 81}
Sex	68	Female	29 (43 %)
		Male	39 (57 %)
Time since diagnosis	67	<5 years	15 (22 %)
		5–15 years	17 (25 %)
		>15 years	35 (52 %)
Age at diagnosis	65	–	17 [6, 37] {0.1, 79}
Alcohol use	68	No	61 (90 %)
		Yes	7 (10 %)
Drug use	68	No	67 (99 %)
		Yes	1 (1 %)

Summary statistics are: mean ± standard deviation {range}, median [inter-quartile range] {range}. or number (percentage).

Table 2
Concurrent conditions.

Variable	n	Category	Number (%)
ID	68	No	54 (79 %)
		Yes	14 (21 %)
ID severity (known)	12	Mild	4 (33 %)
		Moderate	4 (33 %)
		Severe	4 (33 %)
Genetic findings	68	No	65 (96 %)
		Yes	3 (4 %)
Physical findings*	68	No	28 (41 %)
		Yes	40 (59 %)
ASD	68	No	65 (96 %)
		Yes	3 (4 %)
ADHD	68	No	67 (99 %)
		Yes	1 (1 %)
Psychotic	68	No	67 (99 %)
		Yes	1 (1 %)

(*) Specific neurological signs and symptoms (spasticity, paraparesis, incoordination, dysarthria, cognition etc).

Table 3
Seizure information.

Variable	n	Category	Summary
Seizure type(*)	68	Generalised	43 (64 %)
		Focal	7 (10 %)
		Other type	10 (15 %)
		>1 seizure type	7 (10 %)
Current seizure freq. (**)	66	–	0 [0, 1]
Seizures in last year (**)	68	–	0 [0, 1]
Tonic clonic seizure in last year	68	0	53 (78 %)
		1	13 (19 %)
		2+	2 (3 %)

(*) Classified by seizure type not seizure disorder.Generalised seizures = All generalised seizure types. Focal seizures = All focal seizure types. 'Other' =all other seizure types/unidentified. > 1 seizure type indicates patients manifesting both generalised and focal seizures. Patients with single seizures, non-epileptic fits and faints are excluded.
(**) Figures expressed as number of seizures per year.

3.2. Medication (Table 4)

The group had a median of three medications, with a median of one anti-seizure medication (ASM). Twenty (30 %) were on Central Nervous System (CNS) acting medication, with 13 (19 %) on antipsychotics (as defined by NICE:https://bnf.nice.org.uk/treatment-summaries/psychoses-and-related-disorders/#antipsychotic-drugs). Sixty (92 %) patients were compliant with medications.

3.3. Epilepsy risk factors (Table 5)

Four (6 %) had status epilepticus within the last five years and eighteen (26 %) had an emergency admission or paramedic callout within the last 5 years. None had documented evidence of SUDEP discussion, 56 (82 %) did not have an epilepsy care plan and only four (6 %) had nocturnal surveillance of any form.

Table 4
Medications.

Variable	n	Category	Summary
Number of medications	68	–	3 [1,5]
Number of ASMs	68	–	1 [1,2]
Antipsychotics	68	No	55 (81 %)
		Yes	13 (19 %)
CNS acting meds	68	No	48 (71 %)
		Yes	20 (29 %)
Compliant to meds (*)	65	Not compliant	5 (8 %)
		Compliant	60 (92 %)

Summary statistics are: median [inter-quartile range] or number (percentage).
(*) Omitting subjects not on regular medication

4. Discussion

4.1. Intellectual disability, neurodevelopmental disorders, genetics

In the included epilepsy cohort 21 % had a diagnosed intellectual disability. This is consistent with wider epidemiological findings, with a typical distribution of severity [11]. The findings from this study of autism, genetic conditions, ADHD and psychosis are all likely a significant underestimate.

A systematic review identified prevalence of autism in people with epilepsy as 9.0 % when including all population types. When excluding syndromic epilepsy or developmental delay prevalence was 11.2 % [12]. The prevalence of 4 % of autism in the study cohort appears a significant under-representation. The lack of autism diagnosis could impair quality of life and meaningful engagement in addition to leading to increased adverse outcomes to the epilepsy. [13].

Epilepsy is strongly associated with genetic variation including complex single gene disorders with a very high prevalence of epilepsy. [14] Beyond this, most epilepsies will be contributed to by genetic factors whether it be polygenic risk alleles or multifactorial. The participants included in this cohort with a genetic diagnosis (4 %) will be a significant underrepresentation of the true presence of genetic etiologies. This may affect access to certain specialist treatments and newer ASMs. [15] Historically genetic testing has not been part of routine practice in this service.

The prevalence of ADHD in adults with epilepsy is suggested to be around 20 %. [16]. There appears to be a lack of comorbid diagnosis as only one person was diagnosed in this cohort.

The prevalence of psychosis in people with epilepsy is estimated at 6 to 7 %. [17] There is an under-representation in the study population with one person diagnosed. However, 19 % were prescribed antipsychotics. The rationale for this is unclear. It is recognised that one in three people with epilepsy have a psychiatric disorder [18]. Therefore, 29 % being on other CNS acting medication is consistent with this.

4.2. SUDEP and seizure associated risk factors

There were no deaths due to SUDEP or any other direct epilepsy related cause in epilepsy population in the study years (2018—2021).

Tonic-clonic seizures are the biggest risk factor for SUDEP. [19] In this cohort while two in three participants had a diagnosis of generalised seizures less than a quarter (22 %) had a generalised seizure in the previous 12 months, with most (19 %) reporting only one in the previous year. This coincides with the high levels of concordance (92 %) and being managed with one ASM, all of which are positive factors identified in reducing SUDEP risk. [19].

In this cohort, most participants had no epilepsy care plan (56; 82 %). Almost no-one had nocturnal surveillance in place (64; 94 %), and

Table 5
Risk related information.

Variable	n	Category	Number (percentage)
Status epilepticus	68	No	64 (94 %)
(in last 5 years)		Yes	4 (6 %)
Nocturnal seizures reported	68	No	65 (96 %)
		Yes	3 (4 %)
Surveillance reported	68	No	64 (94 %)
		Yes	4 (6 %)
Emergency admission in	68	No	50 (74 %)
last 5 years	68	Yes	18 (26 %)
Epilepsy care plan	68	No	56 (82 %)
		Yes	12 (18 %)
SUDEP discussion	68	No	68 (100 %)
		Yes	0 (0 %)

none had received any discussion around SUDEP and risk management. At least 4 % were known to have nocturnal seizures. Nocturnal surveillance and communication of person centred risk has been shown to reduce risk of SUDEP [9,10,19–21] These findings likely reflect service provision and may help direct where intervention is most needed. More than one in four required attendances at the emergency department in the last five years. The circumstance around emergency contact needs better understanding. Brief review of these presentations suggest they are almost exclusively for single breakthrough seizures, due to (1) the absence of support from an epilepsy nurse, (2) the reluctance of local general practitioners to carry the responsibility of managing these patients in the community, and (3) a deeply ingrained cultural habit of having anyone with a seizure'checked out' by emergency department doctors in hospital, regardless of how minor the seizure is or how quick the recovery. This is despite repeated discussions on this subject by the neurologist in outpatient clinics. There are a very few cases of emergency presentations with recurring seizures or status epilepticus. These recurrent cases are all in patients without ID and all secondary to alcohol excess or recreational drug use.

Malta has around 4000 people with epilepsy. Gozo with 7 % of the population of Malta would be estimated to have approximately 280 people with epilepsy. However, only 68 were open to the neurology services (approximately 25 %). This suggests that other social factors are influencing engagement. There are recent anecdotal reports of epilepsy being viewed as "demonic possession", with association with mental illness and intellectual disability due to general ignorance to the condition. [22,23] A small study in Malta identified that perceived stigma in epilepsy is linked to the individual's level of anxiety and higher seizure frequency was associated with a higher stigma score. [24] Another linked area is religion. Over 90 % of Maltese identify themselves as Catholics. [25] Ignorance and stigma influenced by religion could be a factor. [26,27] It is considered challenging addressing stigma as patients do not usually discuss stigma directly, although this may be inferred from the use by carers and parents of local colloquialisms like '*miskin*' (poor thing), '*jahasra*' (what a shame) when talking about the patient, often in their presence.

The majority of subjects appear to have well controlled epilepsy while taking low numbers of ASMs. This could be explained largely due to the actions taken by the newly established neurology service which was first introduced in Gozo in 11/2018 with the author (AP) as it's first neurologist who had sub-specialised as an epileptologist in the UK. He inherited people with epilepsy previously cared for by non-neurologists. The main issues he encountered were overtreated patients and outdated treatment.

This included patients who only ever had few seizures, or who have not had seizures for over five years, but would often be on two or three medications, usually a combination of phenytoin / valproate / carbamazepine and occasionally phenobarbitone.

Therefore, most patients who had well controlled epilepsy have been going through a slow but consistent process of therapeutic optimisation and modernisation since the service was set up approximately four years ago, in order to minimise treatment burden and long-term side effects.

There are undoubtedly Gozo-based patients who, due to preference or seizure severity, had been referred to colleagues in Malta for specialised neurology input previous to the commencement of the new service and who have elected to continue being followed up in Malta even after the local neurology service was set up. There are also several patients, often with intellectual disabilities, cared for by parents or siblings, who have epilepsy but do not attend hospital because of transport difficulties, perceived stigma, good seizure control making visits unnecessary in their view, or on the other hand the impression that nothing can help their situation. Unfortunately, the unavailability of epilepsy outreach nurses locally makes it extremely difficult for the hospital-based neurology services to follow them up presently.

4.3. Action to improve services for epilepsy care

The Maltese National Health Service (NHS) is modelled on the United Kingdom NHS in that it is a single payer system free at point of care that is funded by government via national health insurance and taxation. With no Maltese equivalent, practice is often modelled on NICE and other National guidelines. There are a number of steps towards improving patient safety:

1. Increase the availability of epilepsy specialist nurses, hospital based but with community outreach roles for education and support.
2. Resources to create epilepsy care plans for each individual patient that can be provided to carers, respite and day centres, chaperones.
3. Investment in education and engagement of the public on epilepsy.

4.4. Limitations

This is a retrospective review of a clinical caseload and reliant upon the information recorded in clinical records. This investigation is descriptive in nature with no control for comparison. The findings represent association and not demonstrate causality.

5. Conclusion

Malta is a high-income country with a public funded health system and a small population. The clinical factors reviewed identify areas of risk where there is opportunity for intervention. This includes a focus on those attending the emergency department, and those with higher seizure burden with tonic-clonic seizures. Wider aspects of epilepsy management include the role of the clinician and team to ensure everyone is counselled on SUDEP risk in accordance with international guidance.

There should be specific focus on those prescribed antipsychotic medication, the rational and monitoring. This is a known risk factor for premature mortality. [7] Genetic testing is now commonplace in complex epilepsy populations. People may not have access to certain new treatments without a clear diagnosis. With the move towards personalized medicine, one should not discard the potential for technological interventions in the gathering of data in the home environment – especially in the context of night-time surveillance.

It is important to understand why over 75 % of the expected population with epilepsy on Gozo are not engaged with local neurology services especially as health care is free for them. It could be that there are strong links to stigma, which in itself is fostered by religious and societal values. These aspects need to be further researched. With diffuse integration of smartphones across the population, data gathering through questionnaires, and even unobtrusive monitoring capabilities can be introduced. This would help inform the epilepsy care team and provide insights to engage people with epilepsy better.

6. Data statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

7. Ethics Statement

We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Author contributions

All authors satisfy the ICMJE guidance by substantially contributing to the design, analysis and interpretation of the work, drafting of the manuscript, final approval of the manuscript and all agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work is appropriately investigated and resolved.

CRediT authorship contribution statement

Adrian Pace: Writing – original draft, Visualization, Validation, Project administration, Methodology, Data curation, Conceptualization. **Lance Watkins:** Writing – review & editing, Writing – original draft, Visualization, Validation. **Daniel Fiott:** Visualization, Validation, Data curation, Writing – original draft, Writing – review & editing. **Paul Bassett:** Conceptualization, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Richard Laugharne:** Project administration, Resources, Validation, Visualization, Writing – review & editing. **Christopher James:** Supervision, Visualization, Writing – review & editing. **Rohit Shankar:** Conceptualization, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing.

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2024.109795.

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