Official Journal of the Irish Medical Organisation

Ir Med J; July/August 2022; Vol 115; No. 7; P635

August 18th, 2022

Tuberous Sclerosis: A Rare Disease with an Orphan Complex

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Abstract

Introduction

In the Republic of Ireland, there are no tuberous sclerosis complex (TSC) specialist clinics.

Methods

A clinical audit was carried out to assess the care received by patients attending two specialist adult epilepsy specialist centres, measuring their care against the UK guidelines.

Results

Although many baseline investigations are carried out, only one-third of patients had diagnostic genetic testing results available. Neuropsychiatry is largely neglected, and the completion of neuropsychiatric assessments checklists is inadequate. Discussions concerning SUDEP are not happening and access to treatment is limited. Reporting of radiological findings in TSC is inconsistent and the number of adults with TSC accessing specialist epilepsy services appear to be low.

Discussion

TSC care in the Republic of Ireland is fragmented, difficult to navigate and wasteful of resources due to the complex nature of the disease and no formal clinical setting to manage it. The service gaps echo the demand for an improved care system including consistent radiological reporting of TSC pathology. The absence of a specialist TSC clinic compounds the complexity of navigating care for individuals with TSC, families and healthcare professionals. Extending this audit nationally will give a more complete picture and highlight the resources required to bring care of these patients in line with recommended guidelines.

Introduction

Tuberous Sclerosis Complex (TSC) is a rare, multi-system autosomal dominant genetic disease with variable penetration caused by mutations in *TSC1* or *TSC2.* TSC causes non-cancerous (benign) tumours to grow in the brain and on other vital organs, including the kidneys, lungs, and heart. Eighty-five percent of patients have epilepsy which along with TSC- Associated Neuropsychiatric Disorders, intellectual disability, dermatological and renal manifestations, are amongst the most common abnormalities.[1] Many individuals display signs of the disease by the age of one; however, clinical features can be subtle, taking years to develop and they may change throughout an individual's lifetime. Therefore, TSC can go unrecognised, undiagnosed, and untreated for years.[2] Consensus guidelines for the diagnosis, surveillance, and management of TSC were published in 1997, 1998, 2013, and were most recently updated in 2021[3] in the United States and in 2018 in the United Kingdom (UK).[4]

TSC clinics have existed for many years worldwide. The TSC clinic in Bath is the oldest and largest TSC clinic in the UK and was founded by Professor John Osborne in the early 1990s. St George's TSC clinic, London, has been running since 1993 and has been at the forefront of research into treating the condition. At present here are over 16 specialist TSC clinics in the UK now and over 25 in the United States. The **T**uber**O**us **SC**lerosis registry to increase disease **A**wareness (TOSCA) recruited 2093 patients from 170 specialist centres in 31 countries[5]. The birth incidence of TSC is 1-5800,[6] and it is estimated that there are 600-800 people with TSC in the Republic of Ireland (ROI). However, there are no specialist multidisciplinary TSC clinics in the ROI, and so patients and families are currently invisible and unaccounted for in the Irish health system.

In this study, we audited the care of patients with TSC in two large specialist adult epilepsy clinics in Dublin, compared to the care that is recommended by UK consensus guidelines.[4] The audit aimed to identify gaps in care to harness data to plan improvements in care, to foster an inter-disciplinary network of care for each patient, and to improve communication and ease of healthcare navigation.

Methods

Patients were identified using the Epilepsy Electronic Patient Record, a national digital point-of-care clinical record that crosses geographic and institutional boundaries.[7] Extensive phenotypic information is stored in the record. For data that was not digitally recorded a chart review was performed. The UK guidelines were used to create a clinical audit tool to collect information on each patient. The data was stored pseudonymously on an Excel worksheet stored on a password-protected partition in the digital records of the Department of Neurology in St James's Hospital, Dublin.

A data privacy impact assessment (DPIA) was conducted in advance of the audit and was subject to the rules governing clinical audit at each site. A data sharing agreement covered the amalgamation of the data for analysis. Results are presented in graphic and tabular form. The audit included 46 questions under the following headings: patient characteristics, genetics, central nervous system, kidney, lung, heart, eyes, skin, liver and pancreas, and access.

Results

TSC patients (*n* = 41) attending two large adult epilepsy services in Dublin were included. The mean age of patients was 39 years (19-73 years). There were 27 male and 14 female patients. Only 14 (31%) of patients had records of genetic testing and no patients had documented Tuberous Associated Neuropsychiatric disorders (TAND) assessments. There was no recorded evidence that sudden unexpected death in epilepsy (SUDEP) was ever discussed.

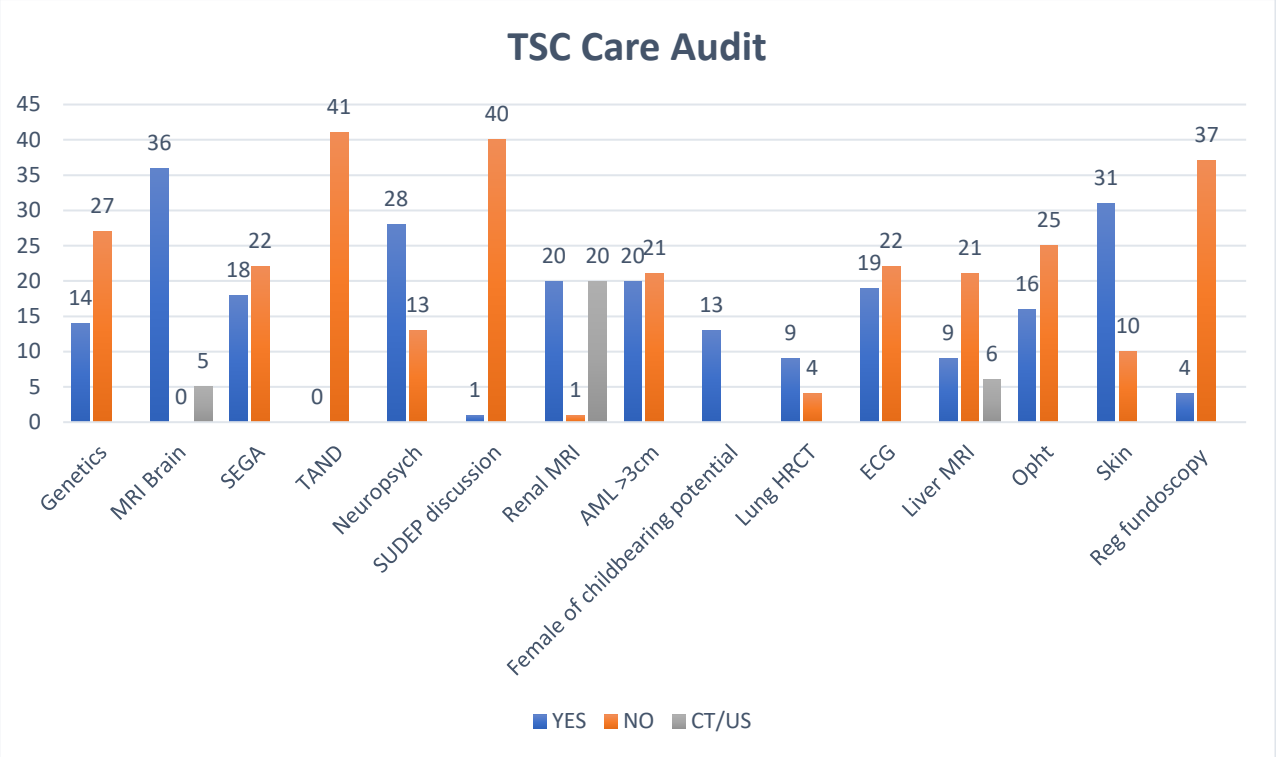
Figure 1 summarises the access to recommended tests in the two clinics. Baseline magnetic resonance imaging (MRI) of brain was performed in 88% of patients, while computed tomography (CT) of brain was used for the remaining 12% of patients. Subependymal giant cell astrocytomas (SEGA's) were identified in 43% of patients. Almost half of patients had angiomyolipoma (AML) bigger than 3cm in size. Interpretation of radiological investigation reports was often difficult and frequently required a specialist consultant to review the scans of patients where the reporting was ambiguous.

Nineteen patients had an electrocardiogram (ECG) at baseline, and only 13 had a documented ophthalmology review, with fewer patients having regular fundoscopy. Thirty-one patients had a dermatology review at baseline, but no patients had ongoing dermatology review as recommended by the UK consensus guidelines. Approximately half the patients had liver/pancreas imaging.

All women of childbearing age were screened for lymphangioleiomyomatosis (LAM) in one centre, but there was no evidence of ongoing surveillance. In the other centre, five of nine female patients of childbearing age had been screened for LAM.

One centre had access to a nurse specialist with an interest in TSC. Everolimus, a precision medication that modifies the disease biology in TSC, is not reimbursed in Ireland for epilepsy despite a phase three placebo-controlled study supporting its effectiveness[8], however, it is available for skin and renal manifestations and is prescribed in non-TSC specialist clinics for these abnormalities.

Figure 1: Comparing Investigations of TSC patients in two large epilepsy specialist clinics in Dublin to that recommended by UK consensus guidelines.



MRI: magnetic resonance imaging, SEGA: subependymal giant cell astrocytoma, TAND: tuberous associated neuropsychiatric disorders, Neuropsych: neuropsychology, SUDEP: sudden unexpected death in epilepsy, AML: angiomyolipoma, HR CT: high resolution computerised tomography, ECG: electrocardiography, Opthal: ophthalmology, Reg: regular, CT: computerised tomography, US: ultrasound.

Discussion

The results of this audit shows that many identified patients who exhibit numerous TSC manifestations face a lack of coordinated disease management. Although many baseline investigations are carried out, most patients have no formal disease surveillance plan. While a clinical diagnosis can be reliably made using consensus criteria, the fact that only one-third have genetic testing done demonstrates a failure to appreciate the importance of genetic classification in prognosis (TSC2 genotype implies more severe phenotype[9] and TSC-PKD1 genotype implies significant renal pathology[10]. The national UK guidelines recommends genetic diagnosis for all patients with suspected TSC. While epilepsy is managed well in these cohorts, many patients have other neurological manifestations including neuropsychiatry symptoms, and completion of neuropsychiatric assessments checklists is lacking.

Access to treatments is limited despite the proven efficacy of the precision therapy. Multidisciplinary care relies on cumbersome interservice referral rather than having a patient-centred one-stop clinic. Assessing surveillance imaging was outside the scope of the audit but based on anecdotal evidence suggests this can be haphazard and long waitlists exist.

An important finding of this audit was variability in the reporting of radiological findings. Imaging has a fundamental role in the diagnosis, surveillance, and management of TSC. There is a need for consistent reporting of TSC radiological features in order to avoid delayed or incorrect diagnosis.[11]

This project highlights the gaps in care for TSC patients in two large epilepsy services in Dublin, Ireland. The authors acknowledge that this audit has been undertaken in two epilepsy centres, and it is possible that TSC patients are accessing care from other disciplines in other hospitals. However, this observation emphasises that TSC is fragmented and lacks coordination. And while the UK consensus guidelines do not necessarily recommend which discipline should undertake specific screening, for example, skin examination or fundoscopy, without a coordinated approach to care, such screening is at risk of being neglected or thought of as being carried out by someone else.

Another cause for concern is the low number of TSC patients identified by our audit. The Dublin Mid Leinster (DML) and Royal College of Surgeons Ireland (RCSI) hospital groups provide care for 1,600,000 people,[12,13] and that the prevalence of TSC is one in 6,000 people, TSC patients in our clinics appears to be under-represented. Based on the frequency of epilepsy in TSC (85%) and allowing for a 25% distribution in paediatric clinics, we estimate that 170 patients with TSC should be attending these our clinics for epilepsy care. In a recent report assessing presentations of people with an intellectual disability to Irish hospitals, TSC was the fifth most common condition presenting to the acute services.[14] Our audit highlights that many of the patients with TSC do not appear to be linking back to specialist care, in this case, an adult epilepsy specialist service.

TSC care in the ROI is fragmented, difficult to navigate and wasteful of resources due to the complex nature of this disease and the lack of a formal clinical setting to manage it. The absence of a specialist TSC clinic compounds the complexity of navigating care for individuals with TSC, families and healthcare professionals. The National Rare Diseases Office are developing rare disease care pathways, including one for TSC, but as yet no resources have been allocated.[15]

We are in the process of extending this audit to all epilepsy centres in the ROI including paediatric services, with the aim to establish a national picture of care gaps and an individual care network for each patient. Extending the audit to relevant disciplines outside the epilepsy services would reduce selection bias and feasibility is being explored. A research group has been established, and a PhD project has been initiated with funding from The SFI research centre FutureNeuro (www.FutureNeuro.ie) to further investigate TSC care in Ireland and explore the barriers and facilitators to a multidisciplinary care clinic.

Declaration of Conflicts of Interest:
I have no conflicts of interest relating to this article.

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