Test yourself - it's all in the history

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Word count (manuscript): 1795 (excluding Key points)
Figures: 1

Keywords: epilepsy; clinical neurology; neurogenetics

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CLINICAL CASE

Current presentation

The patient is right-handed, in their early fifties, and carries the diagnoses of generalised tonic-clonic seizures, spastic quadriparesis, severe learning disability. Generalised tonic-clonic seizures, the only reported seizure type, occur every few weeks. Current antiseizure drugs include valproate, clonazepam, levetiracetam, and lacosamide. Both the patient's condition and treatment have changed little over the past 11 years for which electronic records are available in clinic. At best, the patient mobilises with aids and communicates through simple gestures with very limited understanding. The patient attends clinic with their elderly mother and two carers.

Would you try to review the syndromic diagnosis or try to establish a cause?

Guidelines advocate classifying an individual's seizure and epilepsy types, the epilepsy syndrome, as well as the underlying aetiology.[1] Reviewing the diagnosis is particularly important when seizures are treatment-resistant.[2]

From this perspective, the patient's history of intellectual disability may be particularly important. Although diagnostic yield is higher in children, even among adults with intellectual disability and epilepsy of unknown cause, broad genetic testing may lead to diagnosis in over a quarter of those first tested.[3]

In fact, in parallel with the patient's clinical care, DNA had been previously collected from them, with appropriate assent, as part of a long-running epilepsy genetics research programme at our centre. The 'epilepsy plus' disease category, defined as epilepsy with concomitant intellectual disability, autism spectrum disorder, structural abnormality, or unexplained cognitive decline, became available through Genomics England (GEL) in the 100,000 Genomes Project.[4] We had the opportunity to submit a large number of samples under this category from patients included in our research programme. In 2017, the patient's sample and current diagnoses were entered for analysis.

To anticipate identification of possible clinically relevant findings, we performed screening for stop gain variants in the *SCN1A* gene region (chr2:165989160-166128013). This process within the GEL research environment identified the variant c.3796G>T:p.Glu1266Ter (NM_001165963) in our patient.

How would you approach this finding?

Variants in *SCN1A*, encoding the alpha subunit of the type 1 voltage-gated sodium channel, are associated with a wide range of epilepsies, which may be inherited or arise *de novo*.[5] A discussion of the clinical relevance of genetic findings should ideally be undertaken within a multidisciplinary team environment, including representation from clinical and laboratory genetics. It is crucial to assess in detail whether the clinical characteristics fit the phenotypes associated with a given gene. Fortunately, we were able to access and review the original paper-based records. The patient was first seen at our centre over 30 years ago. Photocopied original records were available from the age of five years.

Which features would you look out for?

Important features include developmental history and timing of onset of any developmental delay or regression with respect to seizures, seizure types and patterns/triggers, possible seizure precipitants, electrographic and neuroimaging features, other neurological and psychiatric symptoms, other medical conditions or structural abnormalities, and family history.

We subdivide the clinical history by the contemporaneous diagnoses or labels (provided in quotation marks) that were used to describe the epilepsy (Figure 1).

Antecedent history

The patient was born at term via forceps delivery without any perinatal problems. Early development was unremarkable.

"Myoclonic Epilepsy" – age 9 months to 9 years

At age 9 months, over a month after a vaccination, the patient presented with three "minor fits", at least the first of which occurred in the context of fever. The patient was noticed to have myoclonic seizures and commenced treatment with phenytoin. EEGs within the first year of life were normal. Myoclonic seizures did not respond to phenytoin; phenobarbitone was introduced with success. The patient then started having "frank major fits" and sulthiame was added with some initial response. There was an episode of status epilepticus (not further defined) at the age of four years following measles vaccination. Language development had been slow before; around this time, global developmental delay became evident.

At age six years, EEG showed a gross excess of slow activity and the patient began to have episodes of "petit mal". Valproate was introduced; the patient continued to have 2-3 seizures a week on a combination of carbamazepine and valproate, which was maintained for a number of years. The patient attended a special school and had limited verbal communication but could, at best, walk unassisted and ride a pony. At age 11, the patient was said to be a friendly child functioning at the level of a two-year old, who enjoyed ball games and was learning new useful words at school.

"Epilepsy, hyperactivity, mental retardation" – age 10 to 30 years

By age 10, it was noted that the tone in all limbs was increased. At age 16, when first seen in our centre, the patient was having several seizures a week, in the form of "generalised convulsions" preceded by eyelid twitching, as well as brief episodes of confusion with loss of awareness and fumbling movements. It was noted that the patient was "severely retarded", could sometimes show "difficult behaviour"; they might "spend hours drawing or playing records".

In their early 20s, the patient underwent inpatient investigations at our centre. The patient was reported to have "complex partial seizures" involving head deviation to the left, limb stiffening, and whole-body tremor lasting for 1 minute. These might progress to "generalised tonic clonic seizures".

In the following years, the patient's condition deteriorated and they became less active. Valproate was reduced; this was associated with reduced drowsiness but a recurrence of brief "absences" and exacerbation of "myoclonic seizures" and "generalised tonic-clonic seizures".

Lamotrigine and gabapentin were trialled, but were both associated with increased frequency of myoclonic and generalised-tonic-clonic seizures. At age 26 the patient was admitted to hospital for myoclonic status; this resolved with reinstatement of valproate and introduction of clonazepam.

At age 28, carbamazepine was withdrawn; this was associated with improvement in myoclonic seizures.

"Spastic quadriparesis, cognitive impairment, epilepsy" – age 31 to 33 years

Following the institution of combination therapy with valproate, clonazepam, and topiramate, the pattern of seizures stabilised with a few "generalised tonic-clonic" seizures a year. EEG continued to show encephalopathy. At age 33, the patient was experiencing daily "absences".

"Generalised tonic-clonic seizures, spastic quadriparesis, severe learning disability" – age 34 years onwards

Several further changes to antiseizure treatment were attempted. Despite initial improvement, remission was never sustained. A number of side effects related to mobility, sleep, and behaviour were suspected. Around age 40, the patient started to "bend forwards whilst walking", and subsequently started needing a wheelchair. To date, the patient has tried 19 antiseizure medications.

Which features are in keeping with the genetic finding?

The patient presented with febrile seizures within the first year of life; seizures were later also triggered by vaccination. Development became delayed only after seizure onset. Seizure types included myoclonic jerks. Seizure control deteriorated on sodium channel blockers. All these are features of Dravet syndrome, an epileptic and developmental encephalopathy.[6] Most cases are associated with *de novo* mutations in *SCN1A*.[5–7] Among heterozygous pathogenic variants in *SCN1A*, truncating variants, such as that in our patient, are expected to lead to loss of protein function (haploinsufficiency), and such variants are distributed across the gene.[7]

Importantly, subsequent multidisciplinary review did not identify variants in other genes associated with similar conditions, such as *PCDH19* (in females), *GABRG2* and *SCN2A*.[8] Ideally, we would confirm that the variant has arisen *de novo* in the patient. This was not possible; however, the existing evidence was sufficient to formally classify this variant as pathogenic.[9]

DISCUSSION

Dravet syndrome was first described in 1978 as severe myoclonic epilepsy of infancy.[6] By the time Dravet syndrome became a widely recognised clinical entity among paediatric neurologists in this country, the patient was already in adult services. The diagnoses and seizure classification the patient carried over the years varied, reflecting changing terminology as well as the evolution of the presentation; myoclonus can become a less prominent feature with age in Dravet syndrome.[10] By the time of wide recognition of the condition amongst adult neurologists, and subsequent identification of *SCN1A* mutations as the genetic cause for the syndrome, the original notes of our patient, revealing the salient features, were confined to the archives.

Diagnostic genetic testing must be informed by clinical phenotype; this is increasingly possible with accumulating data on genetic epilepsy syndromes and is best undertaken early in the disease course. In retrospect, the genetic diagnosis could have been achievable through single gene testing for *SCN1A*, or clinical panels which incorporate this gene. However, in adults, access to genetic testing on a clinical basis remains variable. We hope that through providing England-specific large-scale data for estimating the diagnostic yield of testing adults in the "epilepsy plus" category, the results from the 100,000 genomes project will help determine guidelines for genetic testing in such a scenario.

The diagnosis of Dravet syndrome helps explain our patient's pattern of response to antiseizure drugs; valproate is among the first-line treatments for Dravet syndrome, whereas sodium-channel blocking drugs may exacerbate seizures and should generally be avoided.[12] It is plausible that optimal medication early in the disease course may lead to the greatest gains [13] – or reduction of developmental delay or losses. Experience from our centre supports the idea that in adults, too, medication changes informed by diagnosis (e.g carbamazepine withdrawal), may lead to improvement in seizure control and cognitive function.[10]

Our case is very probably not unusual: we do not know how many undiagnosed genetic epilepsies are in our adult clinics. It is important to at least consider whether an individual might have a genetic epilepsy, particularly when no specific clinical syndromic diagnosis has been made, and when there are multiple features suggestive of an underlying molecular genetic diagnosis, such as a clinical genetic diagnosis, an epileptic and/or developmental encephalopathy (D/EE), or other intellectual disability or decline, autism spectrum disorder, dysmorphism, or treatment resistance. Detailed guidance on reviewing epilepsy cause has also been published recently in this journal.[16]

Reviewing the diagnosis and seeking a cause of epilepsy is particularly important in the case of newly-referred patients, including at transition to adult services, and when the patient meets criteria for drug-resistant epilepsy. Ideally the search for a missing syndromic diagnosis or cause should be repeated e.g. 5-yearly for those who remain resistant to treatment. Dravet syndrome is a clinical diagnosis that can be made when the early history is known. Our case illustrates how such a diagnosis may be missed with typical pressures in clinics, and sometimes will emerge following broad genetic testing.

CONCLUSION

Due to increasing knowledge of the genetics of epilepsy, definitive genetic diagnoses in adults with early-onset epilepsies are increasingly possible. Clinicians must be attentive in reviewing patients' histories to both recognise the opportunity to review the diagnosis and to assess phenotypic compatibility with any genetic findings. Particularly for the latter, original records, which are becoming a rarity, are often invaluable.

Key points

1. Advances in epilepsy genetics present the opportunity to make definitive diagnoses. The key is to consider doing the test.

2. In contrast to newly-presenting children, making a genetic diagnosis in adulthood may be challenging due to critical details being "hidden" or lost. Original records, and parental accounts, where available, are an invaluable source of information.

3. The absence of full details from the early history may compromise targeted candidate gene testing; this group, in particular, may benefit from whole exome or whole genome sequencing.

4. The diagnosis of Dravet syndrome has implications for antiseizure treatment, even into (late) adulthood.

Competing interests

SMS reports representing the Association of British Neurologists and The Royal College of Physicians (London) at the MHRA Valproate Stakeholders Network, is a member of the scientific advisory board of Dravet Syndrome UK, patron of AHC UK, and has received honoraria or grant funding from UCB, Eisai, Vitaflo and Nutricia. SB has received honoraria from UCB. KS and HMC declare no potential competing interests. FRG is a committee member of the MHRA Neurology, Pain and Psychiatry Expert Advisory Group and MHRA Sodium Valproate Expert Working Group, and council member of ILAE British branch and has received honoraria from LivaNova.

Acknowledgements

This research was made possible through access to the data and findings generated by the 100,000 Genomes Project. The 100,000 Genomes Project is managed by Genomics England Limited (a wholly owned company of the Department of Health and Social Care). The 100,000 Genomes Project is funded by the National Institute for Health Research and NHS England. The Wellcome Trust, Cancer Research UK and the Medical Research Council have also funded research infrastructure. The 100,000 Genomes Project uses data provided by patients and collected by the National Health Service as part of their care and support.

Contributors

KS: drafting of the report; HMC: genetic analysis; Genomics England Research Consortium: generation of genomic data; SB, FRG, SMS: critical review of the report.

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Funding

KS is supported by a Wellcome Trust Strategic Award (WT104033AIA). HMC, SB and SMS are supported by the Epilepsy Society. SB is supported by the Muir Maxwell Trust. Part of this work was undertaken at University College London Hospitals, which received a proportion of funding from the NIHR Biomedical Research Centres funding scheme.

Ethical approval information

The study was approved by the National Research Ethics Service Committee London - Camden and Islington (11/LO/2016).

Data sharing statement

Data are available to bona fide researchers upon reasonable request and subject to Data Protection, ethics approval and Genome England Ltd requirements.

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Figure legend

Figure 1. Timeline of diagnoses, treatments, clinical course and investigations. Abbreviations: ACZ – acetazolamide; CBZ – carbamazepine; CNZ – clonazepam; CPS – complex partial seizure; ESM – ethosuximide; GBP – gabapentin; GTCS – generalised tonic-clonic seizures; LCM – lacosamide; LD – learning disability; LEV – levetiracetam; LTG – lamotrigine; PHB – phenobarbital; PHT – phenytoin; PER – perampanel; SE – status epilepticus; STM – sulthiame; TPM – topiramate; VPA – valproate; ZON – zonisamide