



Multiple sclerosis or neuromyelitis optica? Re-evaluating an 18th-century illness using 21st-century software

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Reviewer

Alexander Silvester

Summary

In this paper we report the application of an extensive database of symptoms, signs, laboratory findings and illnesses, to the diagnosis of an historical figure. The medical diagnosis of Augustus d'Este (1794–1848) – widely held to be the first documented case of multiple sclerosis – is reviewed, using the detailed symptom diary, which he kept over many years, as clinical data. Some of the reported features prompted the competing claim that d'Este suffered from acute porphyria, which in turn was used in support of the hypothesis that his grandfather, King George III, also suffered from the disease. We find that multiple sclerosis is statistically the most likely diagnosis, with neuromyelitis optica a strong alternative possibility. The database did not support a diagnosis of any of the acute porphyrias.

Introduction

Clinical decision-making relies on observation and pattern recognition by human experts, yet diagnosis has largely changed from a consulting room art into a laboratory science. Until recently medical historians have remained unaffected by this technological revolution, but the advent of computerized databases linking clinical and laboratory information may in time be able to lend to retrospective diagnosis some of the scientific rigour from which modern medicine has benefited.

Garrard *et al.*¹ recently interrogated the powerful neurological diagnostic database SimulConsult[®] (see <http://www.SimulConsult.com>)² using clinical records made by Sir Theodore Mayerne, the personal physician to King James VI/I (1566–1625). Macalpine and Hunter³ had suggested that James's lifelong physical and mental symptoms were features of variegated porphyria, using this idea to support their theory

that his great-great-great-great-grandson King George III (1738–1820) suffered from the same condition. Instead of porphyria, however, the database raised the unexpected possibility that King James's clinical features were compatible with the attenuated variant of Lesch-Nyhan syndrome described by Jinnah *et al.*⁴

In this paper, we examine the symptoms of another celebrated neurological patient from the same Royal lineage, using identical methodology. Augustus d'Este, whose recurrent neurological signs and symptoms are generally believed to represent the earliest known description of multiple sclerosis (MS),^{5,6} was a grandson of George III. His well-documented illness attracted the porphyria-seeking attention of Macalpine and Hunter, who sought to capitalize on features that they considered 'atypical' for MS.⁷ Our interest in d'Este has other motivations. First, the detailed symptom descriptions in d'Este's diaries make him an ideal subject for the clinical database approach. Second, in view of its broad clinical

spectrum, the antibody-mediated autoimmune disease neuromyelitis optica (Devic's syndrome/NMO)⁸ could be realistically considered as an alternative diagnosis. Finally, the principal competing diagnostic claim (acute porphyria)⁷ is long overdue for rigorous examination.

Augustus d'Este's neurological illness

George III had nine sons, of whom the sixth, Prince Augustus Frederick (1773–1843), spent much of his early life in continental Europe.⁹ Aged 20, he met Lady Augusta Murray, whom he married in Rome in 1793. Two years later the marriage was annulled under the 1772 Royal Marriages Act, leaving their two children, Augustus Frederick (born 1794) and Augusta Emma (1801) effectively illegitimate. The Prince remained affectionate towards his only son, and perpetuated the family connection by encouraging him to take the name d'Este, which carried Royal connections, albeit without property or status.

In his late 20s, while serving in the British Army, d'Este began writing a diary, in which he described a relapsing medical condition that was later identified as 'the first account of disseminated sclerosis'.¹⁰ Symptoms began with visual disturbance: d'Este notes transient reading and writing difficulties in December 1822 followed by full recovery after a few weeks. Similar episodes, some associated with pain adjacent to the affected eye, are recorded in 1825, January 1826 and June 1827. A longer and more troublesome episode in October 1827 is described as producing a 'confusion of sight ... to the extent of my seeing all objects double. Each eye had its separate vision.'

Ocular symptoms eventually abated, but before long walking difficulties began to emerge. D'Este writes: 'Every day I found gradually ... my strength leaving me: I could clearly perceive each succeeding day that I went up and down the staircase with greater difficulty.' By 4 December, he was unable to walk or stand without assistance, and was aware of '... numbness about the end of the back-bone and the perineum'. This state of profound paraplegia continued for three weeks before beginning to improve.

By June the following year he was able to take long walks in the Alps, despite reduced agility

and severe perineal pain. In October 1828 he notes an episode of acute urinary retention requiring catheterization, and in January 1829 transient faecal incontinence. In 1830 he experienced erectile impotence, noting '... in my acts of connection a deficiency of wholesome vigour'.

Over the course of the following decade d'Este underwent leeching, electrical stimulation, herbal remedies, spa baths and exercise, without benefit. In June 1843 he reported the need for a stick to maintain balance while standing or walking, and numbness in the backs of his legs. In September of the same year there was an episode of dizziness accompanied by 'total abruption of strength in my limbs'.

In January 1844 d'Este noted a further abrupt deterioration in what remained of his lower limb strength. There was a slow and partial recovery over the following two years, but he was able to stand for only a few minutes at a time, and troubled by 'sharp spasmodic pains in my feet and legs' (Firth, 1948, p. 48). He noted upper limb functional impairment for the first time, and a review of his script reveals non-specific deterioration of his handwriting. Distressing bladder sensations and progressive lower limb weakness characterised the last two years of his life. Augustus d'Este died in December 1848, aged 53. No postmortem examination was carried out.

Database analysis of the illness

SimulConsult[®] is an online application that compares an individual patient's clinical findings with those of some 2300 genetic, neurological and metabolic disorders.² The stored information is regularly updated by clinicians with reference to published literature. Newly-recognized diseases and their clinical correlates can also be added to the database, ensuring that its 'knowledge' accurately reflects current clinico-pathological understanding.

To interrogate the database, the patient's age, gender, and the presence or absence of a family history is input. When family history is present, SimulConsult[®] requests more detailed information including parental consanguinity. One or more clinical or laboratory features can then be input, including symptoms and signs referable to the major organ systems, age at

onset, and approximate duration. Temporal modifiers (abrupt, subacute, chronic) can also be input.

Once all the available clinical information has been input, SimulConsult® produces a weighted

differential diagnosis that includes both inherited and acquired neurological disorders, listed in descending order of probability. The relative probabilities may optionally reflect their incidence, which results in an inflation of the relative likelihood of more common conditions. If incidence is not taken into account, the likelihoods will simply reflect the closeness with which the input features match those of each candidate condition. For the purposes of the current simulation, the incidence of MS was set at 1500/million, and that of NMO at 90/million (M Segal, personal communication).

To determine the range of conditions that might be compatible with Augustus d'Este's history, the following data were provided as input to the programme:

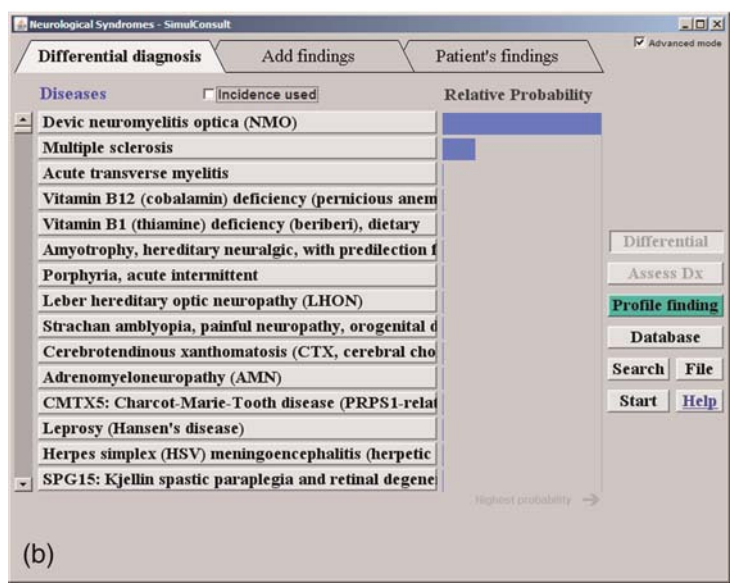
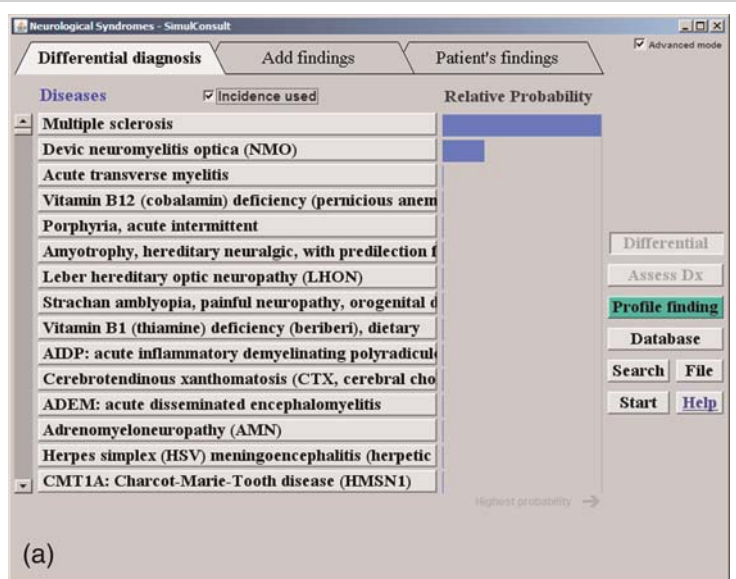
- (1) 53-year-old man with no known family history of similar illness;
- (2) Urinary retention; visual impairment; eye pain with eye movement; gait disturbance, clumsy, shuffling or unsteady; and hypoalgesia; lower body predominance to findings; onset at around 25 years;
- (3) Erectile impotence with onset at around 40 years of age;
- (4) Abnormalities of speech, tremors of limbs, trunk or head, and ataxia were input as being absent;
- (5) Emergence of symptoms over days (acute, abrupt); recurrent exacerbations.

The output screens (truncated after 15 diseases) in the two modes are reproduced in Figure 1. Both confirm the expected similarity of the illness to MS, as well as an overlap with NMO that surpasses MS when disease incidence is ignored. Acute intermittent porphyria is mentioned among a list of considerably less likely, mostly rare, diagnoses.

Discussion

Using the example of a historical figure for whom a large volume of clinical information is available, we have shown how a comprehensive database of clinical and laboratory information can be used to make credible, evidence-based conjectures about the nature of medical illnesses from the remote

Figure 1
Differential diagnosis in Augustus d'Este according to a database (SimulConsult®) of clinical features and their occurrence in genetic and acquired neurological disease. a. The relative probabilities of the first 15 conditions retrieved when disease incidence was taken into consideration; b. the programme's output when incidence is ignored



past. It would be an exaggeration to describe the software as an 'authority'; its main role at present is to assist the clinician by placing before him an exhaustive list of diagnostic possibilities. Ongoing refinement of the data by individual disease experts will, however, eventually turn it into a reliable and up-to-date readout of current knowledge.

Equally importantly, we have provided unbiased, independent evidence against the popular notion that d'Este's symptoms were compatible with the neurological features one of the acute porphyrias. Arguing, as Röhl and colleagues have done, from the well-known recurrent psychiatric symptoms of d'Este's grandfather (King George III), and the asthmatic attacks suffered by his father, that acute porphyria passed through subsequent generations, can now be regarded as equally fanciful.¹¹ A recent re-evaluation of King George III's illness shows that the case for porphyria was based on highly selective reporting of the historical records.^{12,13} It is clear that the King's mental illness meets modern criteria for bipolar disorder with three episodes of acute mania. A fourth episode was followed by chronic mania and later by apparent dementia.^{14,15}

Retrospective diagnosis of historical figures is controversial. Some historians have argued that disease is a social construct and not amenable to such consideration. Medical historians, on the other hand, consider metabolic and immunological disorders such as those discussed in the present paper to be enduring entities that are relevant to the understanding of historical figures. These two views are discussed by Beveridge.¹⁶ The present paper uses a novel approach the retrospective diagnosis and no opinions are expressed on the possible consequences of the diagnoses considered on the behaviour of d'Este.

In summary, although the question of whether d'Este's diagnosis was MS or NMO is unlikely ever to be fully resolved, our approach has illustrated how previously overlooked possibilities can be brought to the attention of the historian as well as the clinician. More importantly, our

results clearly expose the idea that d'Este's neurological illness was caused by acute porphyria as at best redundant, and at worst a clumsy attempt at forcing the evidence to fit the theory.

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