BMJ Neurology Open

Carlos II of Spain, 'The Bewitched': cursed by aspartylglucosaminuria?

Andrew Martin,[1] Robert Heard,[2,3] Victor S C Fung [1]

To cite: Martin A, Heard R, Fung VSC. Carlos II of Spain, 'The Bewitched': cursed by aspartylglucosaminuria? *BMJ Neurology Open* 2021;**3**:e000072. doi:10.1136/bmjno-2020-000072

Received 03 May 2021
Accepted 07 July 2021

[1]Movement Disorders Unit, Department of Neurology, Westmead Hospital, Westmead, New South Wales, Australia
[2]Department of Neurology, Gosford Hospital, Gosford, New South Wales, Australia
[3]Westmead Millennium Institute, The University of Sydney, Sydney, New South Wales, Australia

Correspondence to
Dr Victor S C Fung;
victor.fung@sydney.edu.au

ABSTRACT

Carlos II of Spain (1661–1700), last of the Spanish Habsburgs, was known as The 'Bewitched' due to his multiple medical issues and feeble nature. He suffered from a range of ailments extending beyond the well-known Habsburg jaw, including developmental delay, intellectual disability, dysarthria, skeletal deformity, recurrent infections, epilepsy and infertility, among others. The Habsburg dynasty of Spain was characterised by marked inbreeding, and the male line died out with Carlos II. Various diagnoses have been proffered to explain Carlos II's infirmity, though none have been full satisfactory to explain the full breadth of his ailments. As illustrated here, it may be that aspartylglucosaminuria, an autosomal recessively inherited lysosomal storage disorder, can account for both the characteristic facial features and the wide variety of other features exhibited by Carlos II.

INTRODUCTION

Carlos II of Spain (1661–1700), last of the Spanish Habsburg dynasty, was known as El Hechizado (The Bewitched) because of his poor health and feeble nature. He suffered from a range of disorders including developmental delay, intellectual disability, dysarthria, skeletal deformity, recurrent infections, epilepsy and infertility. The Spanish branch of the Habsburg royal family was characterised by marked inbreeding, and the male line died out with Carlos II. Various diagnoses have been proffered to explain Carlos II's infirmity, though none fully explain the breadth of his ailments. As illustrated here, it may be that aspartylglucosaminuria, an autosomal recessively inherited lysosomal storage disorder, can account for the characteristic facial appearance of the Habsburgs, and for the wide variety of other features exhibited by Carlos II.

ASPARTYLGLUCOSAMINURIA

Aspartylglucosaminuria is an autosomal recessively inherited lysosomal disorder of in which glycoasparagines, mostly aspartylglucosamine, are deposited and build up in several different tissues, including the nervous system. Most cases have been described in Finland, where a high carrier rate is prevalent, although mutations are found worldwide.[1 2] Being autosomal recessively inherited, the prevalence is increased in populations with a high degree of consanguinity.

Characteristic clinical features typically include normal birth and early infancy followed, at the age of 2–3, by delayed speech and motor development with intellectual disability.[3] A weak suck in infancy has also been described.[4] A distinctive facial appearance is present, consisting of widely spaced eyes (hypertelorism), puffy eyelids, small ears, full lips, a square and prominent jaw, a cupid bow shape of the upper lip and a short, broad nose. Patients have frequently been described as appearing prematurely aged.[5] In addition, there is frequently relative macrocephaly earlier in development, which may evolve into relative microcephaly, presumably due to retardation of skull growth as the disease progresses[6]

Not infrequently, skin lesions are present. A wide variety of such lesions have been described, including erythema, herpetic-appearing lesions, facial angiofibromas, seborrhoea, gingival overgrowth, buccal oedema and occasionally tumours.[7 8] Fistulas have also been described.[9] Bony abnormalities are often seen, including thick and misshapen ribs, scoliosis and thickened calvaria.[3] Other suggestive features include recurrent pulmonary infections, diarrhoea, hypermobility of connective tissues, hernias, movement disorders and epilepsy.[2] Intellectual disability is typically mild early on, though verbal dysfunction is most prominent, with later progression to severe levels by late adulthood.[4] A range of psychiatric symptoms may be present.

The course is progressive. Most patients die in the fifth decade. Somewhat interestingly, as was the case in Carlos II, patients generally become very apathetic/abulic before death.[2]

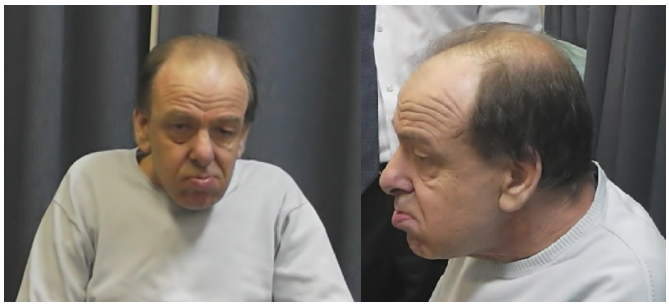

Figure 2 Patient with aspartylglucosaminuria. Note features of a square-shaped face, full, plump lips, puffy eyes, hypertelorism and a short, broad nose with a bulbous tip.

CARLOS II, THE BEWITCHED

Carlos II was a sick and frail monarch, and the tragic end product of years of disastrous inbreeding. Ascending the throne at the age 4, he ruled over the Spanish Empire ineffectually for 35 years. His death in 1700 without an heir threw Europe into the convulsive and disastrous War of the Spanish Succession. Its end result was to weaken both Spain and France, allowing the rise of the English.[10]

Carlos II exhibited many features described in aspartylglucosaminuria. Contemporary sources record that he was 'big-headed' and a 'weak breast-fed baby'. The bones of his cranium had not fused at the age of three, and he was unable to walk until well after the age of 6.[11] Carlos II was unable to speak until the age of four, and thereafter acquired little language.[11 12] He also had prominent dysarthria, with his tongue being described as *'trabado* [locked], with such a fumbling in his speech'.[11] In addition, he was described as showing little interest in his surroundings. He had severe intellectual disability, and was most commonly described as 'mentally retarded'.[13] He had prominent psychiatric disturbance, and was melancholic, and excessively superstitious.[13]

He also suffered from chronic and episodic diarrhoea. Late in life, he developed seizures.[12] He had frequent pulmonary infections from a young age, and at autopsy his lungs were said to be 'corroded'.[13] He was also described as being generally 'swollen', suggestive of oedema.[12] Somewhat interesting, too, is the description of cutaneous lesions, with mentions of a 'herpetic rash on both cheeks', and a discharging wound that 'oozes underneath the right ear', which may represent an abscess or fistula.[11] Of later monumental historical significance is his well-known sterility.[11] The autopsy is also reported to have demonstrated a heart the size of a peppercorn, intestines rotten and gangrenous, a single testicle 'black as coal' and 'a head full of water'.[12]

Figure 1 Left: Carlos II of Spain, Juan Carreño de Miranda (Wikipedia, public domain). Middle: Carlos II of Spain, Anonymous (Wikipedia, public domain). Right: Phillip IV of Spain, Velazquez (Wikipedia, public domain). Note the classic, though less prominent, Habsburg jaw and other similar facial features to Carlos II.

Most characteristic, however, is the distinctive facial appearance, well documented in multiple portraits. There is the strong, square jaw (the famous 'Habsburg jaw'), a large tongue, plump, round lips, a cupid bow upper lip, a flat, broad nose and large forehead, all reminiscent of the typical findings of aspartylglucosaminuria (figures 1 and 2). He is also frequently described to have severe difficulty eating, with near continuous drooling.

Prior hypotheses have included such disorders as hypopituitarism combined with renal tubular acidosis,[13] fragile X syndrome, Klinefelter syndrome, hydrocephalus and male XX hermaphroditism associated with a fragile X syndrome.[12] Each of these, however, fails to account for all the features of Carlos II's illness. For example, while the facial features of fragile X syndrome are similar, this condition lacks the classic features of full lips, broad and prominent jaw, and small ears seen in Carlos II. Further, features of diarrhoea, skeletal changes and seizures would be unusual. Similarly, hypopituitarism also does not account for the macrocephaly, the facial features or other systemic aspects of his disorder. The addition of renal tubular acidosis, as proposed by Alvarez *et al*,[13] may account for further elements of his phenotype. The recent hypothesis of hydrocephalus,[12] again, is an incomplete explanation. The diagnosis of aspartylglucosaminuria, in contrast, may account for many, if not all, of the features demonstrated by Carlos II.

Well documented is the extensive history of consanguinity and inbreeding in the Habsburg dynasty, resulting in an adverse effect on survival with some 29.4% of Habsburg children dying before age 1, and 50% before age 10.[13 14] The Spanish branch, of which Carlos II was the last, in particular, had a very high degree of consanguinity.[13] This would, of course, significantly increase the risk of recessively inherited diseases such as aspartylglucosaminuria.

The Habsburg jaw may be actually due to maxillary regression rather than mandibular prognathism.[15] A firm aetiology has not yet been identified. Hypotheses previously put forward to explain the Habsburg jaw do not account for the wide variety of other neurological abnormalities seen in Carlos II and other members of the family. Multiple members of the family had a prominent jaw without other deficits. It may be that heterozygotes of the aspartylglucosaminuria gene can express a partial phenotype.[5] This could account for variable neurological manifestations in members of the family who possess the Habsburg jaw. The extensive inbreeding, or 'pseudodominance' (in which a single recessively inherited gene is still expressed), may thus account for the appearance of the jaw in what may otherwise appear as an autosomal

dominant trait. While Carlos II did not appear to have prognathism, a distinctive feature of aspartylglucosaminuria, various other dental malocclusions may also occur.[16]

It may also be wondered why other members in the family have not suffered a similar disorder. It may be, in fact, that many have been affected with such a disorder. As mentioned above, the Habsburgs were a generally sickly group, with a high mortality rate.

Various psychiatric and neurological disorders have been described in multiple members, ranging from psychosis, to frequent epilepsy and difficulty walking (suggesting ataxia), and, of course, the distinctive facial features.[11 17] As previously discussed, heterozygote carriers of the aspartylglucosaminuria gene may demonstrate variable penetrance, accounting for the different in phenotype across different members of the family.[5]

The origin of the Habsburg dynasty is generally traced to Guntram the Rich (c. 920), who lived in the Upper Rhine area.[10] The Spanish line is now extinct, limiting the ability to evaluate modern descendants. The extant Austrian line of the family was less marked by consanguinity, again limiting the ability to generalise to Carlos II's illness. The highest prevalence of aspartylglucosaminuria is in Finland, with a carrier rate of 1 in 30.[2] It is possible, though difficult to prove, that his genetic mutation originated from northern Europe. Sporadic de novo mutation is an alternative explanation.

The historical and physical features exhibited by Carlos II are suggestive of aspartylglucosaminuria. While we can never know for certain the diagnosis, his case serves to raise attention to this rare but distinctive disorder.

Contributors AM: manuscript design, collection of data, writing first draft and final version of the manuscript. RH and VSCF: review of final version of the manuscript.

Funding VSCF receives a salary from NSW Health, has received unrestricted research grants from the Michael J Fox Foundation, Abbvie and Merz, is on Advisory Boards and/or has received travel grants from Abbvie, Allergan, Cavion, Ipsen, Merz, Praxis, Seqirus, Stada, Teva and UCB, and receives royalties from Health Press.

Competing interests None declared.

Patient consent for publication Parental/guardian consent obtained.

Ethics approval The authors confirm that the approval of an institutional review board was not required for this work. The patient has provided written consent, which can be obtained on request by the editor. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Provenance and peer review Not commissioned; internally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as online supplemental information.

ORCID iD

Victor S C Fung http://orcid.org/0000-0002-9198-7511

REFERENCES

1 Valkonen S, Hietala M, Savontaus ML, *et al*. Origin of Finnish mutations causing aspartylglucosaminuria. *Hereditas* 1999;131:191–5.
2 Arvio M, Mononen I. Aspartylglycosaminuria: a review. *Orphanet J Rare Dis* 2016;11:162.
3 Aronson NN. Aspartylglycosaminuria: biochemistry and molecular biology. *Biochim Biophys Acta* 1999;1455:139–54.
4 Arvio M, Autio S, Louhiala P. Early clinical symptoms and incidence of aspartylglucosaminuria in Finland. *Acta Paediatr* 1993;82:587–9.
5 Arvio MA, Peippo MM, Arvio PJ, *et al*. Dysmorphic facial features in aspartylglucosaminuria patients and carriers. *Clin Dysmorphol* 2004;13:11–15.
6 Arvio M, Arvio P, Hurmerinta K, *et al*. Reduction in head size in patients with aspartylglucosaminuria. *Acta Neurol Scand* 2005;112:335–7.
7 Arvio P, Arvio M, Kero M, *et al*. Overgrowth of oral mucosa and facial skin, a novel feature of aspartylglucosaminuria. *J Med Genet* 1999;36:398–404.
8 Arvio P, Arvio M, Wolf J, *et al*. Impaired oral health in patients with aspartylglucosaminuria. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1998;86:562–8.
9 Arvio P, Arvio M. Progressive nature of aspartylglucosaminuria. *Acta Paediatr* 2002;91:255–7.
10 Encyclopedia Britannica, Inc. The New Encyclopedia Britannica. In: *The house of Habsburg. Macropaedia*. 15th edn. Chicago: Encyclopedia Britannica, 2007.
11 Nada J. *Carlos the bewitched*. London: Jonathan Cape Ltd, 1962.
12 Turliuc MD, Cucu AI, Perciaccante A, *et al*. Hydrocephalus of King Charles II of Spain, the Bewitched King. *Eur Neurol* 2019;81:76–8.
13 Alvarez G, Ceballos FC, Quinteiro C. The role of inbreeding in the extinction of a European Royal Dynasty. *PLoS One* 2009;4:e5174.
14 Khan R. Inbreeding & the downfall of the Spanish Hapsburgs. Available: http://blogs.discovermagazine.com/gnxp/2009/04/inbreeding-the-downfall-of-the-spanish-hapsburgs/#.XVDU4XnsmUk [Accessed 11 Oct 2019].
15 Peacock ZS, Klein KP, Mulliken JB, *et al*. The Habsburg Jaw-re-examined. *Am J Med Genet A* 2014;164A:2263–9.
16 Arvio P, Arvio M, Pirinen S. Characteristic dental arches and occlusion in patients with aspartylglucosaminuria. *J Craniofac Genet Dev Biol* 1997;17:133–40.
17 Hodge GP. A medical history of the Spanish Habsburgs. as traced in portraits. *JAMA* 1977;238:1169–74.