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

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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, dystarthritis, 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 fully 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 development delay, intellectual disability, dystarthritis, 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 have been fully satisfactory to explain the 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.

ASPARTYLGLUCOSAMINURIA
Aspartylglucosaminuria is an autosomal recessively inherited lysosomal disorder of which glycoasparagines, mostly aspar-tylglicosamine, 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 progresses6 7

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.8 Fistulas have also been described.9 Bony abnormalities are often seen, including thick and misshapen ribs, scoliosis and thickened calvaria.9 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.6 9 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
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. The Spanish branch, of which Carlos II was the last, in particular, had a very high degree of consanguinity. This would, of course, significantly increase the risk of recessively inherited diseases such as aspartylglucosaminuria, in contrast, may account for many, if not all, of the features demonstrated by Carlos II. Further, features of diarrhoea, skeletal changes and seizures would be unusual. Similarly, hypotuitarism 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, may account for further elements of his phenotype. The recent hypothesis of hydrocephalus, 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. The Spanish branch, of which Carlos II was the last, in particular, had a very high degree of consanguinity. 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. 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, and small ears seen in Carlos II. Further, features of diarrhoea, skeletal changes and seizures would be unusual. Similarly, hypotuitarism 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, may account for further elements of his phenotype. The recent hypothesis of hydrocephalus, 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.

Prior hypotheses have included such disorders as hypotuitarism combined with renal tubular acidosis, fragile X syndrome, Klünefelter syndrome, hydrocephalus and male XX hermaphroditism associated with a fragile X syndrome. 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, hypotuitarism 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, may account for further elements of his phenotype. The recent hypothesis of hydrocephalus, 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.

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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.

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REFERENCES

17 Hodge GP. A medical history of the Spanish Habsburgs, as traced in portraits. JAMA 1977;238:1169–74.