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LETTER TO THE EDITOR

Reply: Attenuated variants of Lesch–Nyhan disease: the case of King James VI/I

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Sir, In the 13th century, Jacobus de Voragine described how God punished the murders of St Thomas. The perpetrators were inflicted with a terrible syndrome that included self-injurious behaviour, compulsive–aggressive acts, intellectual deficiency, gout and renal failure. This syndrome is so highly characteristic of Lesch–Nyhan disease that Beck speculated Jacobus must have had first-hand experience with a patient with the disease (Beck, 1991).

Now P. Garrard *et al.* (2010) recall the medical disorder of King James VI/I. As a child, there was evidence of motor and speech delay with awkward coordination that persisted without worsening throughout adulthood. His condition has been compared to cerebral palsy, with prominent writhing movements in addition to spasticity. As an adult, however, he also suffered recurrent attacks of severe joint pain, suspicious of gout. There were also symptoms suggestive of urological problems such as dysuria, haematuria, sandy urine and renal colic. At autopsy, there was evidence for chronic nephropathy and urinary stones. Taken together, these features are highly suspicious for an attenuated variant form of Lesch–Nyhan disease (Jinnah *et al.*, 2010), where self-injurious behaviour may be absent and cognitive impairment subtle. Few other disorders combine a non-progressive motor disorder with gout and kidney stones.

Additional evidence may also support this proposal. Although King James VI/I was reported to be cognitively normal or even gifted, and he did not exhibit self-injurious behaviour characteristic of classic Lesch–Nyhan disease, he did have a reputation for bad behaviour (Beasley, 1995). He was constantly 'restless', and prone to unexpected aggression or moodiness. He preferred a good hunt on his horse over tending to important political matters, and he was known for urinating from atop his horse without dismounting. He was described as having a roving gaze that often embarrassed visitors, as well as other 'dirty' behaviours. His indiscrete sexual behaviour received plenty of attention, with documented partners of both sexes.

His behaviour was sometimes ascribed to a weak constitution or poor nursing. But could it also be part of his medical syndrome? Was his 'restlessness' a form of attention-deficit hyperactivity disorder, which is nearly universal in Lesch–Nyhan disease and common in its variants (Nyhan, 1976; Schretlen *et al.*, 2001, 2005; Jinnah *et al.*, 2006)? Was his behaviour sufficiently characteristic to raise suspicion for a disinhibited frontal lobe syndrome, which is also characteristic of Lesch–Nyhan disease and its variants? And the roving eye movements? Could this be the saccadic distractibility that has also been documented in this disorder (Jinnah *et al.*, 2001)? Perhaps his troublesome behaviour was more the result of a genetically determined behavioural phenotype than bad nursing.

Of course, it is important to avoid reading too much into history. While there is intriguing evidence supporting the idea that King James VI/I had an attenuated form of Lesch–Nyhan disease, as scientists we must also look for evidence that he did not. In particular, King James VI/I reportedly had a son who had some type of disability. It is hard to explain how he could have passed his disorder to his son, in view of the known X-linked recessive pattern of inheritance of Lesch–Nyhan disease and its variants (Jinnah *et al.*, 2000), unless we also begin to question lineages.

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