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Review

Adrenocortical carcinoma in a 17th-century girl

Tobias Else[a], Richard J. Auchus[a], Walter L. Miller[b,*]

[a] Department of Medicine, University of Michigan (TE, RJA), United States
[b] Department of Pediatrics and The Center for Reproductive Sciences, University of California, San Francisco, CA 94143-0556 (WLM), United States

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ABSTRACT

Adrenocortical carcinoma (ACC) is a rare, often fatal disease, that may be seen sporadically or with hereditary predisposition syndromes. Patients with ACC are usually girls under the age of seven who present signs of excess production of adrenal glucocorticoids and androgens, with the diagnosis being confirmed by imaging. Here we reproduce and examine what we believe to be the first autopsy case report of a child with ACC, reported by Dr. Henry Sampson in *Philosophical Transactions*, published by The Royal Society of London in 1697. The paper describes the autopsy of a girl with severe virilization and profound signs of Cushing syndrome who died at age six, strongly suggesting ACC. She apparently had extensive pulmonary metastases, and may have had liver involvement. The report indicates her disease arose from her left kidney and there is no indication of an adrenal origin, perhaps because the adrenal gland was not generally known as a separate organ at that time. This classic example of an early case report is particularly instructive in the context of medical knowledge and understanding in the 17th century compared to current knowledge.

Contents

1. Introduction

The adrenal is a small, anatomically obscure organ. Ancient medical observers such as Galen of Pergamon (130–200CE) failed to recognize the adrenal gland, which was first described as an identifiable structure in 1563 by Bartolomeo Eustachio in his anatomical tretise 'Opuscula Anatomica' [1]. However the beautifully detailed anatomic engravings by Pier Matteo Pini that were to accompany Eustachio's text were not published at that time, but were sequestered in the Papal Library until 1714, when the Vatican finally permitted their publication by GM Lancisi as 'Tabulae Anatomicae'. The adrenal remained no more than an anatomical curiosity until Thomas Addison described the clinical consequences of adrenal insufficiency in work published in 1849 and 1855, and Charles-Edouard Brown-Sequard demonstrated that adrenalectomy (but not a sham operation) was lethal to dogs in 1856 [1]. Thus clinial descriptions of adrenal disease before the mid-19th century are rare and veiled; for example, it is clear that Luigi De Crecchio described non-salt-wasting, virilizing congenital adrenal hyperplasia in 1865, but failed to appreciate the role of the autopsied patient's massively enlarged adrenals [2].

Adrenocortical carcinoma (ACC) is a rare, often fatal disease; pediatric cases are usually seen in girls under the age of seven.

* Corresponding author at: Center for Reproductive Sciences, Room HSE-1634, University of California, San Francisco, San Francisco, CA 94143-0556, United States.
E-mail address: wlmlab@ucsf.edu (W.L. Miller).

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Early reports of ACC are of interest as they illustrate the development of knowledge of the adrenal cortex and of the actions of its various secretions. A mid-20th century review of Cushing syndrome applied the eponym Cooke-Apert-Gallais syndrome to malignant adrenal tumors associated with adiposity and virilism [3]. Cooke's report [4] in 1811 preceeded those of Apert [5] and Gallais [6] by a century, and is widely regarded as the first description of both adiposity and virilization associated with an adrenal tumor. Fox [7] reported a similar case in 1885, mentioning five other cases, and in 1905, Bulloch & Sequira reviewed the pathology literature on ACC, compiling 12 cases [8], including that of Adams [9]. These authors notably also reviewed early cases of congenital adrenal hyperplasia, clearly noting that the adrenal could profoundly influence the sexual phenotype. However, in reviewing the history of hyperandrogenic disorders in women, Azziz [10] pointed to a much earlier case of probable ACC, which had not been noted in earlier reviews, that includes a clear description of combined glucocorticoid excess and hyperandrogenism. That case [11], reported by Henry Sampson in 1697, is discussed here in detail.

In 1697 Henry Sampson, Fellow of the Royal College of Physicians, London, published a brief report entitled "A relation of one Hannah Taylor, a very extraordinary child of about six years of age, who in face, etc. was as large as a full grown woman; and of what appeared on the dissection of her body" [11]. Dr. Sampson (ca. 1629–1700), received his BA from Pembroke Hall, Cambridge in 1650, and was an unordained nonconformist (i.e. not Anglican) minister before pursuing medicine. He studied at the Univerity of Padua and at the University of Leyden, from which he received his MD in 1668, and became an honorary fellow of the Royal College of Physicians in 1680 [12]. He published several reports in the *Philosophical Transactions*; the one under consideration is readily found at http://rstl.royalsocietypublishing.org/content/19/215-235.toc, and is reiterated here, with commentary in the following section.

2. Results

2.1. Sampson's report

Hannah Taylor was born in *Crouched Fryars* June 12, 1682. [**comment A**] She was till three Years old very sickly, lean and not able to go alone; but about *Bartholomewtide* [**B**], 1685 she began to grow strong and fat, which increased till the time of her Death: She was also a very foreward Child of Understanding, had her *Pubes* grown thick and long, as also Hair under her Arm-pits and a Downeyness upon her Chin, unusual with those of her Sex, except in some aged Persons. [**C**]

About half a Year before she dyed she began to complain of Pains, especially on her left side, and voided Gravel often by Urine, and with pain. Her Breath was straight [**D**], as is usual to fat People, especially when she went up a pair of Stairs: Yet on that very Evening before she dyed she walked abroad, was merry and lively, went to Bed, and slept as at other times; but after Midnight she awakened, cried out of a great pain in her side, and said, Mother, I want Breath, I shall dye; and in less than a quarter of an hour was quite dead. [**E**]

The Measures and Weight of her Body were as followeth. Round the Breast a Yard and 2 Inches, over the Hips at the Navel 1 Yard 5 Inches, over the Stomach a Yard, her height 1 Yard wanting an Inch, round the Thigh 1 Foot 9 Inches, Calf of the Leg 13 Inches, upper part of the Arm 14 Inches, the Wrist 7 inches, her weight 95 lb. [**F**] She had a Face as big and broad as any fat grown Woman of 20 Years [**G**]. Her Chin and Breast were so thick laid with fat, that she was forced to hold up her Head (or rather throw it backward) as she walked. These Measures were all taken before the Dissection. The thickness of the Fat upon the Muscles of the *Abdomen* was 2 inches, and not much less upon the *Sternum*: After the Fat was removed (which was as much as is usually in most fat and grown Persons) the *Abdomen* was very protuberant and round, and yet the Fat contained therein not extraordinary much, neither on the *Omentum* or Mesentery: yet it was more than is usual in well fed Persons, and so much, that with the bigness of the other Internal Parts (which were all of the largest size) it made her have so big and protuberant a Belly [**H**]. The Guts were all inflamed and thick, the Liver large, the left Kidney (where was the seat of her Misery) exceeding large, and double the bigness of that on the right side; upon the Dissection whereof there issued out a vast quantity of Blood, both from all the Vessels of it, and out of its *Pelvis*; and after several times Spunging of it, yet it came flowing in from the emulgent Artery: a certain Argument of a great Plentitude in the descending Trunk, which caused the Inflammation of the Mesentery and the *Nephritis* in the Kidney [**I**]: Here was also some small Gravel, which possibly had choaked up the *Ureter*, though that was not examined; but because there was no Blood in the Bladder I justly make this Conjecture. The Uterine Parts had nothing bigger, or more remarkable than in others her Age. The Testicles were large but smooth and white, without Protuberances or shew of Eggs [**J**]. The Bladder had a Purulent Matter in it [**K**]. When the Breast was denuded of its Fat, it shewed no bigger than of another Child of her Age [**L**]. The [pleural] Cavity was totally filled with the Lungs and Heart. The Heart was well and had very strong Fibres and no *Polypus* [thrombosis]. But the Lungs, besides that they were extended to fill up the whole Cavity, were annexed strongly to several parts of the *Pleura*, and had several Protuberances as big as Nutmegs filled with a Pulp like an *Atheroma*, and were in divers places rotten and corrupted [**M**]. *Quaere*, Why one with so bad Lungs was so Fat? Why had she not rather a Consumption? [**N**]

The evident cause of Death lay in the Inflammation of the lower Parts, but the suddenness thereof must be from some impression which that Inflammation made upon the Original of the Nerves moving to the *Diaphragm*,*Bronchia* and other Parts of Respiration, for her great and only Complaint was want of Breath [**O**]. Besides her very Face and Head were miserably coloured with redness of stagnant Blood. [**P**] The Head was not opened.

2.2. Comments on Sampson's report

A. There is a Crouched Friars Residential Home for the elderly and infirm at 103–107 Crouch Street, Colchester CO3 3HA, United Kingdom. The term 'crouched fryars' derives from *Fratres Cruciferi,* a Roman Catholic order that came to Colchester, England in 1245 [13].

B.'Bartholomewtide' is the festival of St. Bartholomew; August 24.

C. This is a clear description of hyperandrogenism, with increased muscle mass, pubic and axillary hair and early facial hair. Becoming 'fat' as described later, suggests increased glucocorticoid secretion. Hyperandrogenism plus hypercortisolemia in 3 year old female strongly suggests ACC. In children under 7 yo, Cushing syndrome is usually of adrenal, not pituitary origin [14], and ACC is an especially common cause. In general surveys that exclude syndromic causes of ACC, pediatric ACC is about 3 times more common in girls [15,16], but in a large study of a Southern Brazilian genetic isolate of ACC caused by *TP53* mutations the female predomonance was only 1.7:1 in patients less than 4 years old [17].

D. The term 'straight breath' indicates orthopnea; from Greek ορθοσ (orthos, 'straight') and πνοια (pnoia, 'breath'). Breathing is easier when sitting or standing up straight.