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Historical Note

When genotype prevails: sexual female-to-male transformation in Classical Antiquity, recorded by Gaius Plinius Secundus and Phlegon

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ABSTRACT

Cases of sexual reassignment in classical antiquity, namely a female-to-male gender change occurring after childhood, are described in the literature. Textual evidence concerning these cases of androgynism and their symbolism as well as a comprehensive scholar analysis is provided in the present study. Medical interpretation of these cases covers the entire spectrum of differential diagnosis of heterosexual puberty in pseudohermaphrodites characterized by genital ambiguity.

Key words: Androgynism, 5α reductase deficiency, Heterosexual puberty, Plinius, 17βHSD deficiency

FEMALE-TO-MALE SEXUAL TRANSFORMATION IN CLASSICAL ANTIQUITY

Cases of sexual reassignment, i.e. a female-to-male gender change occurring around or after puberty, are recounted in the literature of classical antiquity. Apart from mythological stories, such as the myth of Poseidon and Caenis and Ovid's "Metamorphoses", actual cases are described by famous ancient scholars who reported female-to-male transformation as a reality and not as an imaginary tale.

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Textual evidence concerning cases of sexual reassignment and their symbolism as well as a comprehensive scholar analysis are provided by at least two major Greek and Roman writers, namely Pliny the Elder and Phlegon.

Gaius Plinius Secundus, better known as Pliny the Elder (Πλίνιος ο Πρεσβύτερος), was a Roman naturalist, natural philosopher and author who lived between 23 AD and 79 AD. Pliny's "Historia Naturalis" is one of the largest encyclopaedic works dating back to the Roman Era: it purports to cover the entire field of ancient knowledge, based on the best authorities available to the author, and includes the advances in technology and understanding of natural phenomena of the time. It encompasses the fields of astronomy, botany, geology, zoology, and mineralogy as well as the exploitation of those resources.

Four cases of real, and not imaginary, female-to-male transformation were reported by Plinius in "Historia Naturalis" (VII §34) ("ex feminis mutari in maris non est fabulosum"):

"Women-to-men transformation is no fabled event. We discovered in the Annals that under the consulship of P. Licinius Crassus and C. Cassius Longinus, a Casinum girl, still under the authority of the father, became a boy and was deported to a desert island. Licinius Mucianus reported having personally known someone in Argos called Arescon, whose name previously was Arescousa and who had been married. Soon after a beard and all characteristics of masculinity had arisen, he married a woman. This writer witnessed the same case concerning a boy from Smyrna. I myself encountered in Africa a citizen of Thysdrus who was transformed to a man on her wedding day (the man was still alive when I was writing this account)".[1]

The first case comes from Rome, the second from Argos in the Peloponnese, the third from Smyrna in Asia Minor and the fourth from Thysdrus in North Africa, constituting therefore representative cases from all around the Mediterranean. All four narratives refer to cases of transformations from female to male sex occurring around puberty.

Phlegon of Tralles (Φλέγων) was a Greek writer and freedman of the emperor Hadrian, a great thinker and researcher, who lived in the 2nd century AD. His opus magnum was the *Olympiads*, a historical chronograph in sixteen books covering the period from the 1st to the 229th Olympiad (776 BC to AD 137). Phlegon reports three cases of female-to-male transformation, attested in a way similar to those described by Pliny and, in fact, constituting a chronological sequel to them. They are, citing the author's words, as follows:

"Also in Mevania, a city in Italy, at a villa of the Empress Agrippina, there appeared a hermaphrodite in the archonship of Dionysodorus in Athens and the consulship in Rome of Decimus Iunius Silanus Torquatus and Cointus Aterius Antoninus. A virgin by the name of Philotis, of Smyrnaean descent, of the proper age for marriage and betrothed to a man by her parents, became a man, male pudenda having been shown forth.

And another such hermaphrodite appeared in Epidaurus during that time, a child of poor parents, who was called Symferousa before, and when she became a man he was called Symferon, and lived as a gardener.

And also in Laodicea of Syria a woman, by the name of Aetete, still in wedlock with a man, changed (sexual) form and, becoming a man, was renamed Aetetos, in the archonship in Athens of Macrinus, and the consulship in Rome of Lucius Aemylius Ailianus and <...> Veter. This one I myself have inspected."[6]

The first case comes from Mevania, a city of Umbria, in Italy, concerning a female originating from Smyrna, Asia Minor, the second from Epidaurus, the Peloponnese, and the third from Laodicea of Syria, a personal testimony of Phlegon himself. Similarly to the Plinian accounts, these cases come from Greece, Asia Minor and the Middle East. All three cases refer to transformations from female to male sex occurring during or soon after puberty.

MEDICAL INTERPRETATION

Gaius Plinius Secundus (Pliny the Elder) and Phlegon described cases of sexual reassignment, namely a female-to-male gender role change occurring after childhood and consisting of a female-to-male phenotypic transition. All cases were raised as females during childhood and changed to males in puberty.

Puberty is characterized by a pronounced increase in sex steroids produced by the gonads. Heterosexual puberty is due to an increase in serum androgen levels without evidence of a simultaneous increase in estrogens, leading to development of male secondary characteristics without breast development.

Male phenotype is denoted by the development of male secondary sexual characteristics (beard, etc). We can assume, therefore, that Gaius Plinius Secundus and Phlegon described cases of Disorders of Sexual Differentiation (DSD) among persons who, although raised as females during childhood, subsequently presented signs of virilization, leading to heterosexual puberty and gender reassignment from females to males.

Virilizing tumors of the adrenals or ovaries should be excluded in the aforementioned cases as they are

usually lethal if untreated due to their malignant origin. Gaius Plinius Secundus described cases of individuals who lived a long life after the female-to-male transition (one was still alive years after the event; the other was married to a woman years after, etc.).

Heterosexual puberty has never been reported in true hermaphrodites, in female pseudohermaphrodites, in complete (Swyer syndrome) and gonadal dysgenesis or in the "androgen insensitivity syndrome" (AIS).[3] Therefore, despite their manifestation of external genitalia ambiguity and breast development, none of the above entities appear to offer a likely diagnosis due to absence of heterosexual puberty.

46XY DSD (male pseudohermaphroditism) is the most likely diagnosis in cases of female-to-male transition, with the defect being hidden among the disorders affecting androgen synthesis. Among all enzyme deficiencies in the steroidogenic pathways, only 17β hydroxysteroid dehydrogenase (HSD17B3) or 5α-reductase type 2 deficiencies lead to similar clinical phenotypes characterized by ambiguous genitalia and heterosexual puberty with signs of spontaneous virilization, namely changes in voice, in musculature, in facial and body hair as well as in the appearance of scrotum and phallus. HSD17B3 is the enzyme converting androstenedione to testosterone, while 5α-reductase type 2 converts testosterone to dihhydrotestosterone (DHT), the most potent androgen.[3] Differential diagnosis between 5α-reductase type 2 and HSD17B3 deficiencies depends on clinical phenotype given that it provides evidence about the degree of gender reversal, which could be analyzed in two components: the degree of prepubertal external genitalial ambiguity (towards the female phenotype) and the degree of post-pubertal masculinization.

Since DHT is the major determinant of male external genitalia formation, striking ambiguities in external genitalia might be due to defects in DHT production rather than to inadequate testosterone biosynthesis. Unlike 5α-reductase type 2 deficiency, HSD17B3 deficiency is characterised by only a slight decrease in DHT levels thanks to intact 5α-reductase activity.

Moreover, the post-pubertal degree of virilization is higher in cases of 5α-reductase type 2 deficiencies than in cases of HSD17B3 deficiency.

Heterosexual puberty in cases of HSD17B3 deficiency is due to isoenzyme HSD17B5. Although HSD17B3 converts androstenedione to testosterone in the testes, HSD17B5 is responsible for extragonadal production of testosterone in peripheral tissues, such as placenta, prostate, adrenals and liver, while it slightly contributes to testosterone levels produced by the testes.[4] Furthermore, there is an age-dependent regulatory transcription mechanism of HSD17B3 and HSD17B5 isoenzymes, with the former increasing and the latter decreasing with age.[5]

Heterosexual puberty in cases of 5α-reductase type 2 deficiency is due to isoenzyme 5α-reductase type 1 as well as to the virilizing effect of the elevated pubertal testosterone levels. Unlike 5α-reductase type 2, type 1 is not expressed in the intrauterine period, therefore contributing to postnatal sexual differentiation but not to a fetal one.[6] Additionally, in contrast to 5α-reductase type 2, the production of which decreases with aging, type 1 is expressed invariably throughout life, thus compensating for 5α-reductase type 2 deficiency. Therefore, the post-pubertal virilizing effect in cases of 5α-reductase type 2 deficiency is much more pronounced as compared to cases of HSD17B3 deficiency.

In conclusion, all the available evidence points to the gender role changes described by Gaius Plinius Secundus and Phlegon having been cases of 46XY DSD - male pseudohermaphroditism with heterosexual puberty. The most likely diagnosis for these historical descriptions is 5α-reductase type 2 or HSD17B3 deficiency, the former leading to more striking and gender reversal. Since all these individuals were raised as girls throughout the long period of childhood, the immense social impact of their transformation did not take place until during or after puberty, when gonadal production of testosterone transformed them into adult males, this leading to the dramatic change of their social status. In these individuals, the genotype, namely the 46XY male phenotype, finally prevailed.

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REFERENCES

1. Pliny the Elder, Historia Naturalis VII 36, Collection des Universités de France.
2. Keller O, 1877 Rerum naturalium scriptores graeci minores. Publisher: In aedibus B.G. Teubneri.
3. Kousta E, Papathanasiou A, Skordis N, 2010 Sex determination and disorders of sex development according to the revised nomenclature and classification in 46,XX individuals. Hormones (Athens) 3: 218-131.
4. George MM, New MI, Ten S, Sultan C, Bhangoo A, 2010 The clinical and molecular heterogeneity of 17βHSD-3 enzyme deficiency. Horm Res Paediatr 74: 229-240.
5. Hoppe U, Holterhus PM, Wunsch L, et al, 2006 Tissue-specific transcription profiles of sex steroid biosynthesis enzymes and the androgen receptor. J Mol Med 84: 651-659.
6. Thiele S, Hoppe U, Holterhus PM, Hiort O, 2005 Isoenzyme type 1 of 5alpha-reductase is abundantly transcribed in normal human genital skin fibroblasts and may play an important role in masculinization of 5alpha-reductase type 2 deficient males. Eur J Endocrinol 152: 875-880.