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A unique case of iatrogenic hebephiliac behavior emerging late in life in a patient with Gordon Holmes Syndrome

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ABSTRACT

Background: Pedophilic or hebephiliac behavior is defined iatrogenic when emerging for the first time as a side effect of medications. To date, pedophilic or hebephiliac behavior emerging after testosterone replacement therapy (TRT) has never been described.
Case presentation: a patient diagnosed with Gordon-Holmes syndrome (GHS), a genetic condition characterized by cerebellar ataxia and hypogonadotropic hypogonadism (HH), at the age of 55 developed hebephiliac attitudes after starting TRT. A multidisciplinary approach integrating psychiatric evaluation, general (IQ) and specific (social cognition) neuropsychological assessment, and structural brain MRI was important to characterize the patient's clinical and functional profile.
Discussion: We discuss how the co-occurrence of HH, requiring hormone replacement therapy, combined with the patient's borderline IQ explains the sexual offenses against pre-adolescents in light of the Insufficient but Non-Redundant Parts of Unnecessary but Sufficient Conditions (INUS) model of causation. In other words, both the administration of TRT and the borderline IQ are configured as INUS causes for understanding the illegal behavior.

Introduction

It is widely known that psychiatric symptoms can emerge as a consequence of neurological conditions or as effects of a substance assumption. Indeed, almost all psychiatric conditions in the DSM-5-TR include the diagnostic criteria "*the symptoms are not attributable to the physiological effects of a substance or another medical conditions*". This is not true for paraphilic disorders, including pedophilia and hebefilia. Understanding when paedophilic or hebephiliac behaviour emerges as a consequence of an underlying medical condition is challenging (Scarpazza et al. 2023).

Besides idiopathic pedophilia, additional forms of pedophilic or hebephiliac behavior, resulting in sexual abuse of children or adolescents, may emerge *ex novo* (i.e., for the first time) later in adult life as a consequence of brain insult (Sartori et al., 2016; Scarpazza, Finos et al. 2021a, 2021b, 2023; Camperio Ciani et al. 2019; Scarpazza et al., 2018; Gilbert and Focquaert, 2015; Joyal, 2023; Lopes et al., 2020) or as an adverse event of the excessive assumption of neurostimulant drugs, such as in patients treated for Parkinson's disease (e.g. Solla et al. 2006; Mendez & Shapira, 2011 case 5). The etiology of hebephiliac behavior is neurological in the first case and iatrogenic in the second one.

To date, hebephiliac behavior has never been described to emerge *ex novo* following testosterone replacement treatment (TRT).

Although hebephilia is not characterized by increased levels of testosterone, reduction of plasma testosterone levels by antiandrogens or gonadotropin-releasing hormone (GnRH) agonists has been shown to be effective in controlling sexual fantasy, sexual urges, and sexual behavior in these individuals (Landgren et al. 2020). This suggests that abnormally lower testosterone levels may exert a protective effect toward the acting out of hebephiliac tendencies in individuals with previously normal levels of testosterone.

Here, we report a case of hebephiliac behavior that emerged after testosterone replacement therapy in a patient with Gordon Holmes Syndrome (GHS). GHS (OMIM #212,840), formerly known as Cerebellar Ataxia and Hypogonadotropic Hypogonadism (HH) syndrome with low plasma testosterone levels, is a rare genetic condition with

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autosomal recessive inheritance (Seminara et al. 2002). Cerebellar atrophy initially manifests itself with speech dysarthria, whereas ataxia usually appears between the first and the fourth decade of life, often leading to difficulties in daily living activities and, eventually, the need for wheelchair assistance. Hypogonadism is associated with a spectrum of symptoms in affected individuals, with variable levels of delay in the development of typical signs of puberty, ranging from subtle abnormalities in pubertal changes to complete absence of sexual development; nonetheless, most patients inevitably develop other problems with the reproductive system later in life. Hypogonadism is typically diagnosed during puberty and treated with GnRH stimulation or TRT to improve sexual function but also to support overall maturation, including brain development. Additionally, some affected individuals also present with neuropsychological issues, including memory problems, developmental delay with intellectual disability, or even cognitive decline with dementia. A few genes have been related to the condition so far, including PNPLA6, often associated with white matter abnormalities. A total of 40 cases have been reported to date in the international scientific literature (Locci et al., 2021).

Case description

Here we describe the case of male patient who was diagnosed with GHS only later in life, when he was already 55 years old and started displaying hebephiliac attitudes after TRT implementation. The patient and his parents provided a written informed consent to the scientific reporting of his case. The clinical description of this case has been reported previously (Locci et al., 2021). The patient was prosecuted for enacting sexually and socially inappropriate behaviors towards teenagers, including pre-adolescents and adolescents, luring on social media, texting and video sharing with sexual content, and insidious genital palpations.

The patient was the only child born to non-consanguineous parents. He never met his biological father, and until the age of 14 years, he lived with his mother alone, then with the new partner of his mother, whom the patient considers his true father. The patient's family possesses a low socio-economic and educational background, which appears to have contributed to overlooking the physical, psychological, and relational dysfunctional features that the patient began to manifest early in adolescence. Developmental history revealed delayed psychomotor milestones, including mild gross-motor problems, slight language delay, and inadequate acquisition of personal and social autonomy. Development of primary sexual characteristics was also delayed with the occurrence of micro-orchidism and micro-penia, while secondary features, including facial and pubic hair and changes in vocal timbre, failed to develop. He interrupted his studies after graduating from Junior High School with the lowest score. Then, he started working and tried multiple unsuccessful job experiences. Later, he remained unemployed for more than ten years due to the onset and progressive worsening of motor and functional impairments caused by the GHS-related cerebellar ataxia, being finally certified with 50% legal disability.

The patient has always lived with his parents, who provided him with financial support and full accommodation care. In the last two decades, he has been spending most of his time on occasional housekeeping, watching television, and engaging mainly in fishing practice as his only and prevalent hobby during the weekends. His personal and social attainments and affective and socio-relational attitudes remained inadequate.

After the onset of balance and coordination difficulties, in his early 50 s, the patient finally underwent neuroradiological assessment through brain magnetic resonance imaging (MRI) that revealed "*cerebellar atrophy mainly affecting the superior vermis and T2/FLAIR-hyperintensities in the periventricular white matter*" (see Fig. 1). Further clinical investigations confirmed the presence of HH signs and symptoms along with decreased serum levels of FSH, LH, and testosterone, as well as borderline intellectual functioning with a full-scale intelligence quotient (FSIQ) of 77. Subsequent genetic analyses revealed two compound heterozygous missense mutations in *PNPLA6* gene which have been related to GHS (Locci et al., 2021). The patient was eventually diagnosed with GHS at 55 years of age. Thus, to treat the symptoms associated with the HH, the patient underwent TRT intramuscularly (1000 mg once every 12 weeks), with evidence of improvements in the endocrine-related condition, including growth of hair, beard, and pubic hair, and a lowered vocal timbre. Shortly afterwards, he started exhibiting noticeable behavioral changes, including increased irritability and mood shifts, as reported by his parents.

Around the age of 57 years, he was found to show sexually and socially inappropriate behaviors toward teenagers whom he frequented at a nearby fishing lake where he used to spend the majority of his time. He was discovered luring adolescents on social media, texting them and sharing videos with sexual content. In his online virtual interactions, the approaches were ambiguous and characterized by sexual allusions with a childish language. Additionally, during fishing sessions, he would inappropriately and rapidly touch pre-adolescents and adolescents'

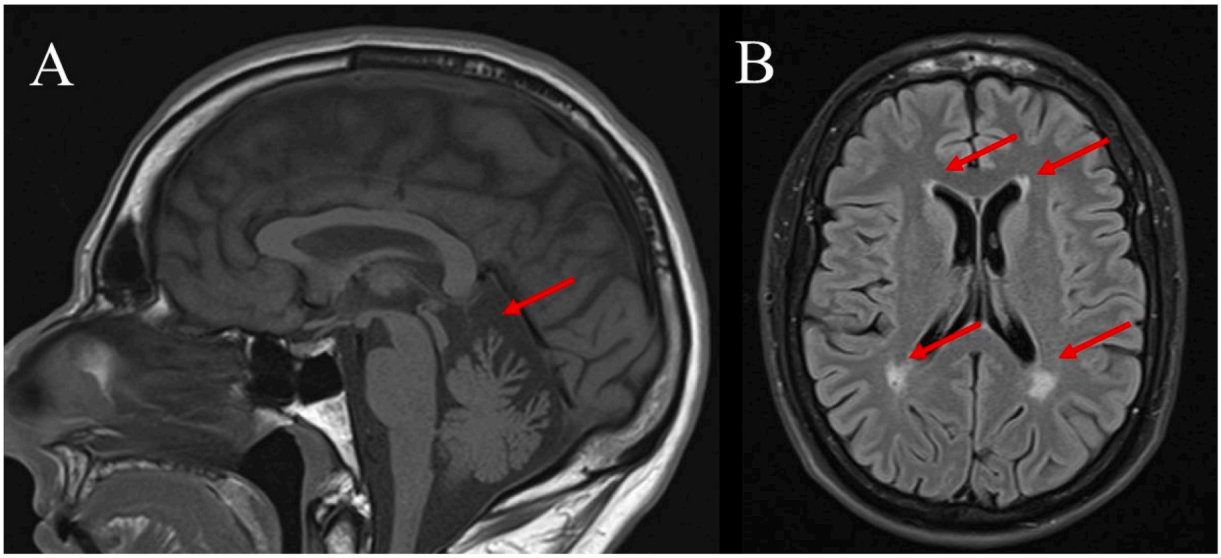

Fig. 1. Brain abnormalities in the patient diagnosed with GHS. (A) the red arrow indicates the cerebellar atrophy; (B) the red arrows indicate the T2/FLAIR-hyperintensities in the periventricular white matter.

genitals pretending it was a joke. These behaviors were never present before the beginning of TRT. The timing of these inappropriate interactions on social media can be traced back to a few weeks before their discovery. The patient was thus prosecuted for hebephiliac behavior, and the judge requested an insanity evaluation.

The patient's lawyer contacted the senior author of this manuscript as defense expert consultant. The patient underwent a full psychiatric examination and a neuropsychological evaluation. He was poorly accessible to the interview, providing brief and limited informative responses and displaying context-inappropriate and childish attitudes throughout the visit. His language content and social attitudes were childish and immature according to his age and socio-cultural level, and markedly inadequate in relation to the assessment context. The patient also presented metacognitive difficulties, which were signs of inability to reflect on his own thought processes and understand his own emotional experiences. His difficulties in metacognition and mentalization likely affected his perception of a sense of responsibility and the understanding of the social and moral negative value of his misconduct. Indeed, when questioned about facts alleged against him, the patient was unable to explain the reasons why his attitudes towards preadolescents and adolescents might be considered illegal, immoral, and inappropriate. Similarly, he also displayed difficulties in mentalization and social cognition, especially a limited capacity to understand others' perspectives. During the clinical evaluation, the patient seemed unable to deduce what the interviewer might or might not know about his life, referring to people and places without providing any suitable context. Additionally, he showed difficulty in attributing a contextual and coherent value to his experiences. For instance, he claimed to be "known and followed throughout Italy" by his Instagram followers, assigning a disproportionate emotional value not aligned with reality. Finally, the patient failed to understand the legal consequences of his actions, exhibiting a fatuous attitude when confronted with the situation and saying that he would not mind going to jail if he still had the opportunity to go fishing while restricted.

As a part of the forensic evaluation, the patient underwent a neuropsychological assessment to evaluate objectively his cognitive profile. The patient was administered: i) the Social Intelligence Battery (SIB; Prior et al., 2003), composed of four subtests to evaluate social and emotional skills associated with social intelligence (i.e., Theory of Mind Test, Emotion Attribution Test, Social Situations Test, and Moral/-Conventional Distinction Test); ii) the self-report version of the Behaviour Rating Inventory of Executive Function, Adult Version (BRIEF-A; Roth et al, 2005), a standardized test for assessing executive function in an ecological context. The patient's mother and stepfather were administered the Vineland Adaptive Behavior Scales (VABS-II; Sparrow et al., 2005), a semistructured interview to assess the adaptive skills of individuals with developmental disabilities or disorders. The results of the neuropsychological assessment are reported in Tables 1–3, respectively. Specifically, results of the SIB subtests showed low scores in social intelligence, with impairments in recognizing the inappropriateness of behaviors and in understanding others' mental and affective states (Table 1). Scores on the VABS-II interview, administered to the patient's parents, detected adaptive competencies in the borderline range, in line with the patient's FSIQ examination that showed an IQ of 77. Scores obtained in the single domains of the VABS-II, including Communication, Daily Living, and Socialization, as well as the Composite Adaptive Score, are reported in Table 2. Particularly, the patient exhibited a score in the borderline range in the areas of Communication and Socialization (Table 2). Finally, the report of the BRIEF-A showed scores in the lower normal range and in the deficit range in subscales related to Behavioral Regulation and Metacognition skills (Table 3). Malingering was ruled out because of the patient's borderline IQ score, which would have made basically impossible for him to enact a proper strategy. Of note, the IQ examination had been conducted previously as part of the diagnostic clinical evaluation and well before the patient's involvement in the legal trial, which rules out any attempt or reason for malingering.

Table 1
Raw scores, cut-offs, and qualitative evaluation of the performance obtained by the patient on the Social Intelligence Battery.

Sub-tests SIB	Raw Scores	Cut-off	Qualitative evaluation of the performance
Theory of Mind:	7/13	⩾12	**Impaired**
Emotion Attribution:			
Sadness	6/10	⩾ 6	Norm
Fear	9/10	⩾ 8	Norm
Embarrassment	5/12	⩾ 8	**Impaired**
Disgust	2/3	⩾ 2	Norm
Happiness	9/10	⩾ 10	Norm
Anger	0/10	⩾ 6	**Impaired**
Envy	0/3	⩾ 1	**Impaired**
Social Situations:			
Ability to recognize a normal behavior as normal	14/15	⩾ 13	Norm
Ability to recognize an abnormal behavior as a violation	19/35	⩾ 22	**Impaired**
Ability to judge the severity of behavioral violations	48/75	⩾ 45	Norm
Moral Judgements:			
Moral Behaviours: not allowed	6/6	⩾ 6	Norm
Moral Behaviours: severity	57/60	⩾ 39	Norm
Moral Behaviours: not allowed with no rules	12/12	⩾ 11	Norm
Conventional Behaviours: not allowed	6/6	⩾ 5	Norm
Conventional Behaviours: severity	55/60	⩾ 20	Norm
Conventional Behaviours: not allowed with no rules	10/12	⩾ 6	Norm

Table 2
Raw scores, T-scores, percentile ranks, and qualitative evaluation of the performance obtained by the patient on the Behaviour Rating Inventory of Executive Function, Adult Version.

Self-report BRIEF-A Scales/Indices	Raw scores	T-scores	Percentile Ranks	Qualitative evaluation of the performance
Validity Index:				
	4			Acceptable
- *Negativity*	2			Acceptable
- *Infrequency*	5			Acceptable
- *Incoherence*				
Inhibition	13	57	75	Norm
Shift	9	51	56	Norm
Emotion regulation	19	60	85	***Borderline***
Self-monitoring	15	75	97	**Impaired**
Behavioral Regulation Index	56	63	88	***Borderline***
Start	12	57	77	Norm
Working memory	14	63	90	***Borderline***
Planning/ organization	20	77	98	**Impaired**
Task monitoring	10	60	84	***Borderline***
Task organization	14	60	81	***Borderline***
Metacognitive Index	70	67	92	***Borderline***
Global Executive Index	126	66	92	***Borderline***

Table 3
Raw scores, cut-offs, and qualitative ratings of the patient's parents on the Vineland Adaptive Behavior Scale.

Subscales VABS-II	Raw Scores	IQ equivalent scores	Qualitative evaluation of the performance
Daily living skills	42	IQ=82	Norm
Communication	38	IQ=77	***Borderline***
Socialization	36	IQ=75	***Borderline***
Total	234	IQ=73	***Borderline***

Discussion

Here we reported the case of a patient diagnosed with Gordon-Holmes syndrome at the age of 55 who started displaying hebephiliac attitudes for the first time in his life after the implementation of a TRT. Being GHS characterized by very low testosterone levels, patients with GHS are a natural equivalent of patients whose testosterone levels are chemically reduced through antiandrogens or GnRH agonists.

Due to the much delayed GHS diagnosis, the patient was not taken in charge and did not receive any adequate treatment or specialized interventions he would have needed since early adolescence or even earlier, with serious repercussions on his psychosexual and psychosocial development as well as on the brain maturation process. As a consequence, the late administration of testosterone-based hormone replacement therapy for the management of the hypogonadal condition resulted in a "*delayed puberty*." This condition, combined with a profile of intellectual, cognitive, and affective disabilities, clearly prevented the harmonious development of behavioral regulation skills, metacognitive abilities, and sexual instincts inhibition.

In the case presented here, the temporal proximity between the beginning of TRT and the onset of hebephiliac urges and behaviors appears to sustain the causal role of increased plasmatic testosterone levels in the acting out of this illegal behavior. To corroborate the existence of a causal link between TRT and the patient's behavior, there is also evidence of increased irritability and mood swings, as reported in the clinical documentation and by the patient's parents during the clinical interview, also known to be influenced by testosterone levels (Batrinos, 2012; Archer, 1991). In other words, the administration of testosterone resulted in a behavioral fracture in this patient, somehow making him experience most of the aspects that are associated with the transition from childhood to adolescence, including sexual urges and behavioral changes.

The sexual acts of palpation of pre-adolescents and adolescents' genitals were configured as driven by libidinal stimuli that the patient experienced for the first time in his late 50 s and thus struggled to manage and regulate, in a way that could be described in an impulsive-compulsive continuum which clearly resembled the one typically observed during adolescence. Similarly, the allegations of harassing pre-adolescents and adolescents on social media, also find their genesis in the inability to plan, organize, and finalize one's own behavior, to understand the mental and affective states of others in order to assess the appropriateness of one's own conduct and thus to be able to appropriately evaluate the consequences of one's actions in order not to act or do otherwise.

Unfortunately, it is not possible to disentangle whether TRT unmasked a latent pre-existing hebephilia (Prado et al., 2021) or whether the patient was sexually attracted by underage as they are closer to his mental age. In other words, it is not clear whether the patient has a pre-existing sexual orientation toward pre-adolescents and adolescents (Seto, 2012).

Overall, this case is relevant for its social and forensic implications. Under the Italian legal framework, there is a distinction between total insanity, when the ability to understand or will is completely abolished, and partial insanity, when the ability to understand or will is greatly diminished but not fully abolished. In this specific case, the Italian Court considered the defendant to be totally insane, as the offending behaviors against pre-adolescents and adolescents were recognized to be in direct causal link with the testosterone-based hormone replacement therapy performed to treat GHS symptoms. Critically, the defendant, like most patients with GHS, not only manifested HH, requiring hormonal replacement therapy, but also a low cognitive profile (borderline IQ). This co-occurrence of symptoms explains the sexual offenses toward under-ages in light of the Insufficient but Non-redundant parts of Unnecessary but Sufficient conditions (INUS) model of causation that needs to be applied in forensic reasoning (Anckarsater et al. 2009). In other words, both the administration of TRT and the borderline IQ configured as INUS causes that account for the illegal behavior. The INUS model of causation asserts that there are no deterministic causes for complex behaviors like violence. On the contrary, it posits that many probabilistic causes should be concomitantly present to originate such a behavior. Each one of the probabilistic causes, by itself alone, could not account for the illegal behavior, but if they are present all together, they are able to explain the violent act. In this specific case, the TRT-driven abnormal sexual interest for pre-adolescents and adolescents, alone, could not be considered sufficient to cause the hebephiliac behavior, because humans have moral reasoning that prevents them from acting in behaviors that they know to be illegal or morally wrong. However, in this patient, sexual attraction toward pre-adolescents and adolescents was coupled with an impaired neuropsychological profile (probably related to the low IQ) as well as with a childish-like personal and relational life that prevented him from understanding the social and moral disvalue of his behavior as well as its legal consequences.

Conclusion

To conclude, here we report a case of acquired hebephilia that emerged, and was in a INUS causal link, with the iatrogenic normalization of abnormally reduced serum testosterone levels in a patient with GHS. In this case, a multidisciplinary approach that integrates psychiatric evaluation, generic (IQ) and specific (social cognition) neuropsychological evaluation, as well as brain structural MRI was important to characterize the clinical and functional profile of the patient (Scarpazza, Finos et al. 2021a, 2021b). At trial, the defendant was acquitted by the Italian Court because of his insanity at the time and in relation to the allegations.

Consent to publish

Written informed consent was obtained for this manuscript from the patient.

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CRediT authorship contribution statement

Riccardo Loconte: Writing – original draft, Data curation, Conceptualization. **Gianluca Sesso:** Writing – original draft, Conceptualization. **Cristina Scarpazza:** Writing – original draft, Conceptualization. **Pietro Pietrini:** Writing – review & editing, Project administration, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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