



CASE REPORT

Case Report: Testicular failure possibly associated with chronic use of methylphenidate [v1; ref status: indexed, <http://f1000r.es/48z>]

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Abstract

Methylphenidate is a commonly prescribed treatment for attention deficit hyperactivity disorder (ADHD). However, little is known about its adverse effects on the male reproductive system. We report a 20-year-old male patient whose chief complaint was of delayed puberty. He spoke in a high-pitched voice and complained of lack of body hair, impaired libido, inadequate erectile function, chronic fatigue, and low energy. He had been treated with methylphenidate as an infant and had continued treatment for 17 years. On examination, the patient was lean and visibly lacked facial or body hair. He further explained that he had never been able to grow underarm or facial hair and that he was often mistakenly considered a young teenager rather than a 20-year-old. The patient's genitalia were categorized as Tanner Stage 2. Laboratory studies confirmed low serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone levels. The patient was given exogenous testosterone supplementation with pellets and human chorionic gonadotropin to maintain testicular size. After 4 months his symptoms improved and he demonstrated signs of puberty. Our goal is to further elucidate the possible impact of methylphenidate on the male reproductive system.

Open Peer Review

Referee Status:

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- 1 **Wayland Hsiao**, Emory University USA
- 2 **Matthew Coward**, University of North Carolina USA
- 3 **Jay Sandlow**, Medical College of Wisconsin USA, **Christopher Deibert**, Medical College of Wisconsin USA

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Competing interests: No competing interests were disclosed.

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Introduction

The use of methylphenidate (Ritalin®) has surged over the past decade and is the hallmark therapy for treatment of attention deficit hyperactivity disorder (ADHD)¹. Moreover, the number of individuals diagnosed with ADHD has greatly increased within the past decade². Nevertheless, the long-term effects on various organ systems have not been fully evaluated.

Because of the increasing incidence of ADHD and the widespread use of methylphenidate in the pediatric population³, it is important to determine whether methylphenidate has any adverse gonadotropic effects. Known adverse effects of methylphenidate include the drug's impact on the cardiovascular system (high blood pressure, shortness of breath and irregular heart beat), on behavior, and mood (aggression, restlessness, hallucinations, unusual behavior, or motor tics); yet little information exists in the current literature regarding adverse effects of methylphenidate on the human reproductive system. Juvenile Rhesus monkeys treated with high doses of methylphenidate in a controlled experiment displayed a significant delay in testicular descent and were noted to have lower than normal serum testosterone levels⁴. A parallel experiment was performed using male mice that were given increasing doses of methylphenidate. The mice treated with higher doses of methylphenidate experienced a significant decrease in body weight and reduction in Leydig cell count⁵, indicating that serum testosterone levels and fertility were significantly reduced.

Patient information

The patient, a 20-year-old Latino male, initially came to the clinic with a chief complaint of "delayed puberty". In addition, he complained of his high-pitched voice, lack of libido, low energy level, chronic fatigue and poor erectile function. His height was similar to his friends of the same age although he was very lean and could not gain weight. The patient noted that on the basis of his physical appearance people often perceived him to be an adolescent, around the age of 12. He had never had facial or body hair, although he did have some pubic hair. The patient's past medical history showed use of methylphenidate (dosage varied with age) for approximately 17 years with voluntary cessation a few years ago. The patient currently uses tobacco in the form of an electronic cigar and has been smoking for the past 8 years. He denied alcohol and drug usage. The patient is sexually active and engages in heterosexual sexual activity with no report of sexually transmitted disease. Family history was unremarkable.

Clinical findings

On physical examination, the patient had neither underarm hair nor facial hair. He was 180cm and weighed 55kg. The patient's genitalia were Tanner Stage II, (which is described to be occurring in males aged 8–15 years old and shows enlargement of the testes with pigmentation, minimal to no enlargement of the penis and long, downy hair with a variable pattern). The patient's bilateral descended testes were 6cc in volume.

Diagnostic assessment

Hormone testing revealed that the patient had a follicle-stimulating hormone (FSH) value of 3.0 mIU/ml (normal range is 4.0 – 10.0 mIU/ml), a luteinizing hormone (LH) value of 4 mIU/ml

(normal range is 6.0 – 19.0 mIU/ml), and a serum total testosterone level of 120 ng/dl (normal values range from 200 to 1000 ng/dl). Semen analysis X 2 showed azoospermia both on initial examination and after use of pellet. The patient has a normal 46XY karyotype and no Y-chromosome microdeletion. The results of laboratory tests were consistent with the patient's idiopathic testicular failure and warranted further exploration of the link between chronic methylphenidate use and effects on reproductive parameters.

Therapeutic intervention

The patient was advised to begin testosterone supplementation. He chose to receive testosterone pellets (subcutaneous implantable testosterone). Testopel creates a depot of testosterone that is slowly released over a long period of time (~4–6 months). Because exogenous testosterone suppresses intrinsic testosterone synthesis, the patient was given 1500 IU human chorionic gonadotropin (hCG) therapy per week in order to maintain testicular size⁶.

Follow-up and outcomes

The patient was seen 4 months after his initial visit. He described a desirable increase in energy, increased libido, and better erectile function. Physical examination showed new facial and armpit hair, increased thickness of pubic hair, and maintenance of testicular size. Laboratory testing revealed low FSH (2.0 mIU/ml), and low LH (2 mIU/mL) levels, likely related to exogenous testosterone supplementation. On the other hand, the patient's serum testosterone increased dramatically to 861 ng/dL. Overall, the patient was very enthusiastic about the progress associated with the therapy and underwent a second insertion of testosterone pellets. As for his fertility, a testicular biopsy for sperm retrieval with assisted reproduction may give him the best chance of fathering a biological child.

Discussion

Although methylphenidate has been studied for many years, its effects on male gonadal function have only recently become a topic of interest among clinicians. The patient described in our case study seemed to exhibit characteristics related to the effects of chronic use of methylphenidate on development of human reproductive function.

Because the developmental changes that occurred in the human subject occurred over a number of years of treatment with methylphenidate, there is very little information about the patient's condition and how it developed during that period of time. There is also little information for comparison with our observations because there is no much literature available regarding this topic.

Of the few previous studies on the effects of methylphenidate on male gonadal function, one shows results obtained using Wistar rats tested with increasing amounts of methylphenidate. The data show an increase in abnormalities in sperm and a decrease in testicular volume⁷. Another study using Wistar rats showed that increasing levels of methylphenidate led to increased p53 expression and apoptosis of germ cells⁸.

The study involving rats reveals similarities to the case study in question. The case reported describes a possible association between methylphenidate use and testicular failure. The rats were

given increasing doses of the drug over a long period of time; our patient was also taking the drug to treat ADHD for a very long time (~14 years). However, while the rats were monitored from the beginning of the drug treatment, the subject in the case study has only recently come under observation after 14 years of methylphenidate use.

Another of the few existing studies was reported in the *Proceedings of the National Academy of Sciences*. It was conducted on Rhesus monkeys treated with doses of methylphenidate at designed to mimic the amounts given to human ADHD patients⁴. This was one of the first recorded studies displaying altered testicular function in primates following methylphenidate treatment. Over a 40 month time span, the monkeys displayed signs of delayed puberty, including impaired testicular descent and smaller-sized testicles, as well as lower testosterone levels⁹. As noted above, delayed puberty was also observed in our patient, as demonstrated by the Tanner staging and the low testosterone levels in serum. Previous human research yielded similar results. Studies conducted in adolescent boys showed delays in puberty¹⁰. The drug of first choice was methylphenidate, although some subjects were given dexamphetamine. Subjects receiving either methylphenidate or dexamphetamine showed lower weight and BMIs coupled with delayed pubertal development¹⁰. Although the testicular damage induced by methylphenidate is well recognized, the precise mechanisms underlying its toxicity to the testes remains unclear. It is tempting to speculate that methylphenidate could affect the alpha and beta-adrenergic receptors expressed in the testis⁶.

This case report, however, specifically pinpoints methylphenidate and shows an unusual prescription practice for the patient involved. In this case, methylphenidate was started from a very young age compared to normal prescription practices for ADHD. The unknown effects of methylphenidate are currently being studied, but as can be seen, one should exercise caution and patients should be followed closely when prescribing methylphenidate.

Consent

Written informed consent to publish this case report was obtained from the patient.

Author contributions

RR chose the case and evaluated the patient in the manuscript. PD and AD wrote the draft of the manuscript. LIL supervised the process and critically edited the manuscript. All authors discussed the implications and commented on the manuscript at all stages.

Competing interests

No competing interests were disclosed.

Grant information

RR is an NIH K12 Scholar supported by a Male Reproductive Health Research Career (MHRH) Development Physician-Scientist Award (HD073917-01) from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Program.

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Open Peer Review

Current Referee Status:



Version 1

Referee Report 11 September 2014

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Jay Sandlow, Christopher Deibert

Department of Urology, Medical College of Wisconsin, Milwaukee, USA

SUMMARY OF STUDY

The authors present a case report in which there is an association between chronic methylphenidate use from a very young age and delayed puberty and reproductive growth. The use of the term “testicular failure” is a misnomer. His low gonadotropins make this secondary testicular failure. There is no evidence that he has primary testicular failure, as the authors do not present any data to show lack of response to gonadotropins. At best, this may be an association.

SPECIFIC COMMENTS FOR AUTHORS

Introduction

- The introduction should conclude with a restatement of the goal or thesis of the manuscript. It currently ends describing mice fertility.

Case

- Please clarify for the semen analysis “after use of pellet”. Do the authors mean after the examination of the spun down SA pellet? If so please rephrase this.
- Was delayed puberty ever ruled out in this patient? Was he examined by a pediatric endocrinologist?
- Why was the patient not started on HCG alone to see what his testicular response would be? By giving him exogenous testosterone, his gonadotropins will remain low and his spermatogenesis suppressed.
- In follow up, please describe more clearly the upgrading in his Tanner stage

Discussion

- The second sentence of the discussion is much too strong. To this point, the authors have provided no compelling evidence of the relationship between chronic Ritalin use and reproductive function. Only midway through the discussion do the authors describe this more as an association than a causal mechanism. Clarify at the outset that there is no human data suggesting this relationship currently available.
- For the rat studies, did these rats have exposure prior to adolescence and signs of maturation? Only in this way can the rats possibly be compared to this human and serve as a more direct causal possibility.
- Reference 10, as the only human study cited, should be explored more than the rat and monkey studies. It should probably also be described earlier in this case report.

- The authors should state whether or not there is data from the methylphenidate approval trials that demonstrates suggestion of delayed puberty or delayed development among prepubertal boys taking this medication.
- In the concluding paragraph, the authors again should consider tempering their comments, that this is at most an association and not a direct causal relationship.

We have read this submission. We believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.

Competing Interests: No competing interests were disclosed.

Referee Report 08 September 2014

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Matthew Coward

Department of Urology, University of North Carolina, Chapel Hill, USA

This is a well written case report of an unrecognized, but only possible, association between use of Ritalin[®] and delayed puberty. The discussion offers a very nice commentary on the available literature, and this paper overall generates appropriate consideration for this potential serious adverse effect of methylphenidate. The patient reported had almost lifelong use of methylphenidate throughout childhood and adolescence, but stopped several years prior to presenting with delayed puberty. Another reviewer made several very important comments that I was going to make, so I will not repeat them. A few additional considerations to improve this very nice manuscript are discussed below:

- This patient's particular situation was unusual in that he presented with normal gonadotropins along with hypogonadism, and this should be discussed. Delayed puberty is not typically a testicular problem, but rather one with the HPG axis. The hypothesis would be that the methylphenidate has a direct suppressive effect at the level of the testicles.
- The combined use of exogenous testosterone and hCG has been reported by Hsieh *et al.* to maintain spermatogenesis in hypogonadal men, but the combination has not been previously reported to initiate puberty. It certainly would be the most physiologic manner to initiate puberty, and this point could be highlighted.
- The options for treatment should be discussed. These can include several options such as exogenous testosterone, high dose hCG, or a combination of the two using a lower dose of hCG which was ultimately chosen.
- Please include the dose of Testopel used.
- The androgenization of the patient is noted through the use a exogenous testosterone. An improvement in testicular function is not documented by the authors. This can include post-therapy changes in testicular volume, or more accurately a post-therapy semen analysis.
- In the Follow-up and Outcomes section, the sentence beginning, "As for his fertility..." falls flat with mere speculation. A brief discussion of the potential benefit from ultimately stopping exogenous testosterone and reversing its effects with higher dose hCG is warranted, as it is unclear from this

report that the patient has irreversible testicular atrophy and hypofunction that would result in long-term non-obstructive azoospermia requiring testicular sperm extraction. A simple follow-up semen analysis would be the most accurate way to update the manuscript and frame this discussion.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.

Referee Report 03 September 2014

doi:10.5256/f1000research.5507.r6010



Wayland Hsiao

Department of Urology, Emory University, Atlanta, USA

Very interesting case report of a young man with delayed puberty and primary testicular failure, with no identifiable known cause. The only thing suspicious on their history was long-term use of methylphenidate, with no identifiable genetic cause found otherwise.

The paper talks about the treatment of this patient with testosterone replacement and then reviews the limited animal data on methylphenidate and its effects on spermatogenesis. Of course, as with any case report and retrospective review, it is difficult to say for certain whether this is associated or there is another unknown confounding factor involved, so the authors suggestion that reproductive harm has to be taken into account before giving methylphenidate to children is premature at best.

However, this case does highlight the real dearth of information and studies we have on medications that are widely used and their effects on sperm production and reproductive potential. While this drug is so widely prescribed we only have a number of rat studies and a primate study, all of which have limitations in their ability to be generalized to human results.

As a result, this is a great case report for generating ideas, and raising the idea that maybe some things we commonly prescribe can cause reproductive effects we are unsure of, but to say there is an association, and then say that methylphenidate should be prescribed less because of this is a bit of a stretch.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Competing Interests: No competing interests were disclosed.

Author Response 03 Sep 2014

Ranjith Ramasamy, Baylor College of Medicine, USA

We agree with the reviewer that the association between chronic ritalin use and testicular failure is not direct. The case report is at best hypothesis generating but given some of the strong evidences

available in animal studies, the practitioner should be cognizant of a "possible" association between chronic ritalin use and infertility and delayed puberty.

Competing Interests: None
