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Aging males' symptoms in relation to the genetically determined androgen receptor CAG polymorphism, sex hormone levels and sample membership

Gudrun Schneider [a,*], **Kathrin Nienhaus** [a], **Jörg Gromoll** [b], **Gereon Heuft** [a], **Eberhard Nieschlag** [b], **Michael Zitzmann** [b]

[a] *Department of Psychosomatics and Psychotherapy, University of Münster, Domagkstrasse 22, 48149 Münster, Germany*
[b] *Department of Reproductive Medicine, University of Münster, Germany*

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Summary Late-onset hypogonadism describes the co-occurrence of a range of physical, psychological and sexual symptoms in aging men, with the implication that these symptoms are caused by androgen deficiency. Previous investigations examined mostly population samples and did not take into account the testosterone modulating effects of the genetically determined CAG repeat polymorphism (CAGn) of the androgen receptor (AR) gene.

This is the first study which investigates aging male symptoms (AMS) in relation to the genetically determined androgen receptor CAG polymorphism, estradiol and testosterone levels in men ≥50 years of age in a healthy population sample ($n = 100$), outpatients of an andrological department ($n = 76$) who presented with sexual and "aging male" symptoms and a psychosomatic/psychiatric sample ($n = 120$) who presented with various psychological and medically unexplained somatic complaints.

Although the population sample was significantly older than the two patient groups, they reported significantly fewer AMS and had higher testosterone levels and shorter CAG repeats of the AR. Regression analysis revealed influences of CAGn on the AMS global score and the psychological and somatic subscale only in the two patient samples, while testosterone had some impact on the sexual subscale. Our results suggest that the so-called aging male symptoms show a certain association to androgenicity, but that they are rather unspecific and of multifactorial origin. Other factors contributing to AMS need further clarification.

1. Introduction

1.1. Current state of knowledge

Serum testosterone levels decrease progressively in aging men, but the rate and magnitude of decrease vary consider-

* Corresponding author. Tel.: +49 251 8352902; fax: +49 251 8352903.
E-mail address: schneig@mednet.uni-muenster.de (G. Schneider).

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ably between individuals. Serum testosterone decreases of about 1% each year and age-related increases in sex hormone-binding globulin result in even lower free and bioavailable testosterone levels (Harman et al., 2001; Zitzmann and Nieschlag, 2001; Feldman et al., 2002; Tancredi et al., 2005; Kazi et al., 2007). Manifestations of hypogonadism are supposed to include low libido, erectile dysfunction, decreased muscle mass and strength, increased body fat, decreased bone mineral density, osteoporosis, decreased vitality and depressed mood; results of studies on the association between supposedly "aging male symptoms" and low total or free testosterone levels, however, are somewhat contradictory in clinical and population settings (Perry et al., 2001; Kratzik et al., 2004; T'Sjoen et al., 2004; Beutel et al., 2005).

As none of these symptoms are specific to testosterone deficiency, questionnaires which inquire for these symptoms (Aging Male Symptoms Score (AMS), Heinemann et al., 1999; Androgen Deficiency in Aging Men (ADAM), Morley et al., 2000) are not recommended as the sole diagnostic procedure because of their low specificity. According to the ISA, ISSAM, EAU, EAA and ASA recommendations (Wang et al., 2008), one or more of these symptoms must be associated with a low serum testosterone level for a diagnosis of late-onset hypogonadism (LOH), which is defined as a clinical and biochemical syndrome. The terms "male climacterium" or "andropause" are obsolete.

The most widely accepted parameter to establish the presence of hypogonadism is the measurement of serum total testosterone. However, setting a lower limit of normal testosterone has attracted considerable controversy, as there is no clear testosterone threshold associated with symptomatic hypogonadism. In a study of andrological outpatients who presented with various "aging male symptoms", prevalence of loss of libido or loss of vigor increased below testosterone concentrations of 15 nmol/l, whereas depressive mood was significantly more present in testosterone concentrations below 10 nmol/l and erectile dysfunction only below testosterone concentrations of 8 nmol/l (Zitzmann et al., 2006). The recommendations of ISA, ISSAM, EAU, EAA and ASA (Wang et al., 2008) agree that total testosterone levels above 12 nmol/l (350 ng/dl) do not require substitution. The consensus that patients with serum testosterone below 8 nmol/l (230 ng/dl) will usually benefit from testosterone treatment is mainly based on the data of younger men.

Contradictory results on the association of testosterone with "aging male symptoms" may be in part due to sample selectivity and also to the fact that testosterone effects are modified by the genetically determined CAG repeat polymorphism of the androgen receptor (AR) gene. The AR gene contains in exon 1 a polymorphic trinucleotide CAG repeat, whose length (CAGn) modulates AR action. Longer CAG repeats are associated with lower transcription activity of those genes activated by testosterone binding to the androgen receptor, i.e. lower testosterone effects. This has been shown in vitro and also in different populations in testosterone sensitive tissues (Zitzmann et al., 2001, 2003b; Canale et al., 2005; Zitzmann and Nieschlag, 2007).

Testosterone is metabolized by 5-alpha-reductase in target organs to the more potent androgen dihydrotestosterone, which itself is metabolized by aromatase to estradiol. The role of estradiol is not clear in the context of late-onset hypogonadism (LOH): Ponholzer et al. (2002), Beutel et al. (2005) and Miwa et al. (2006) reported no correlations between AMS and ADAM scores and estradiol, while Basar et al. (2005) reported higher estradiol levels in men with an AMS score of 29 or higher.

So far no study investigated aging male symptoms in the context of testosterone, estradiol and the AR polymorphism and only one study, which was community-based, investigated aging male symptoms in the context of androgen levels and the AR polymorphism (Härkönen et al., 2003). They found no correlations between testosterone and aging male symptoms, but a positive correlation between CAG repeat number and depressed mood, anxiety, deterioration of general well-being and decreased beard growth. Paradoxically, men with CAG repeat length in the uppermost quartile ($\geq$23 CAG repeats) reported less often decreased potency. As the initial participation rate was 35.5% in this study, Härkönen et al.'s sample is bound to be selective. Especially in studies of older adults, life satisfaction is a predictor of participation (Lütdke et al., 2003). It therefore seems reasonable to expect that more impaired subjects may decline participation and thus be underrepresented in studies of community samples. This could lead to underestimation of associations between certain risk factors (genetic, hormonal) and symptoms.

In healthy individuals with intact hypothalamic–pituitary–gonadal feedback mechanisms, a compensatory upregulation of testosterone concentrations can occur in subjects with longer CAG repeats: In population-based samples from different European countries, the European Male Aging Study found significant positive associations between testosterone, estradiol and AR CAG repeat length (Huhtaniemi et al., 2009), while Härkönen et al. (2003) and T'Sjoen et al. (2005) reported no such association. In men with disturbances of the feedback mechanism, hence LOH, this compensation is not likely to happen. Thus, such individuals might present with hypogonadal features in the presence of low-normal testosterone concentrations and longer than average CAGn. This is a patient group which could look for medical care for their somatic or psychic symptoms in different specialities and are most likely missed by normal diagnostic procedures.

In conclusion, the associations between supposedly "aging male symptoms", sex hormone levels and the AR polymorphism need further clarification.

1.2. Description/objective of the study

The purpose of the present study was the investigation of the relation between "aging male symptoms", serum sex hormone levels and the CAG repeat polymorphism of the AR gene in 3 different samples.

Because of the differing results in clinical and population settings (Perry et al., 2001; Kratzik et al., 2004; Beutel et al., 2005; T'Sjoen et al., 2004) and the non-specific nature of the symptoms assigned to LOH, our aim was to investigate the relations between aging male symptoms, sex steroids and AR polymorphism in a population sample, in a psychosomatic/psychiatric outpatient setting, where patients presented with psychiatric and so far medically unexplained somatic symptoms and in a sample of andrological outpatients with "aging male symptoms". We expected higher "aging male" symptom levels in subjects with low testosterone levels and