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Serum concentrations of brain-derived neurotrophic factor in patients diagnosed with
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Serum concentrations of brain-derived neurotrophic factor in patients diagnosed with gender dysphoria undergoing sex reassignment surgery

Concentração sérica de fator neurotrófico derivado do cérebro em pacientes diagnosticados com disforia de gênero que realizaram cirurgia de redesignação sexual

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Abstract

Introduction: Transsexualism (ICD-10) is a condition characterized by a strong and persistent dissociation with one's assigned gender. Sex reassignment surgery (SRS) and hormone therapy provide a means of allowing transsexual individuals to feel more congruent with their gender and have played a major role in treatment over the past 70 years. Brain-derived neurotrophic factor (BDNF) appears to play a key role in recovery from acute surgical trauma and environmentally mediated vulnerability to psychopathology. We hypothesize that BDNF may be a biomarker of alleviation of gender incongruence suffering.

Objectives: To measure preoperative and postoperative serum BDNF levels in transsexual individuals as a biomarker of alleviation of stress related to gender incongruence after SRS.

Methods: Thirty-two male-to-female transsexual people who underwent both surgery and hormonal treatment were selected from our initial sample. BDNF serum levels were assessed before and after SRS with sandwich enzyme linked immunosorbent assay (ELISA). The time elapsed between the pre-SRS and post-SRS blood collections was also measured.

Results: No significant difference was found in pre-SRS or post-SRS BDNF levels or with relation to the time elapsed after SRS when BDNF levels were measured.

Conclusion: Alleviation of the suffering related to gender incongruence after SRS cannot be assessed by BDNF alone. Surgical solutions may not provide a quick fix for psychological distress associated with transsexualism and SRS may serve as one step toward, rather than as the conclusion of, construction of a person's gender identity.

Keywords: Transsexualism, sex reassignment surgery, BDNF.

Resumo

Introdução: O transexualismo (CID-10) é uma condição caracterizada por forte e persistente dissociação com o gênero atribuído. A cirurgia de redesignação sexual (CRS) e a terapia hormonal (TH) permitem que indivíduos transexuais se sintam mais congruentes com seu gênero e, por isso, têm desempenhado papel importante nos últimos 70 anos. O fator neurotrófico derivado do cérebro (BDNF) parece desempenhar um papel fundamental na recuperação do trauma cirúrgico agudo e vulnerabilidade ambiental à psicopatologia. Nós hipotetizamos que o BDNF pode ser um biomarcador de alívio do sofrimento de incongruência de gênero pós-CRS.

Objetivos: Mensurar os níveis séricos de BDNF no pré e pós-operatório em indivíduos transexuais como biomarcador de alívio de estresse relacionado à incongruência de gênero após a CRS.

Métodos: Trinta e duas pessoas transexuais masculino para feminino submetidas a cirurgia e tratamento hormonal foram selecionadas de nossa amostra inicial. O nível sérico de BDNF foi avaliado antes e depois da CRS pela técnica ELISA. O tempo decorrido entre as coletas de sangue pré e pós-CRS foi medido.

Resultados: Não houve diferença significativa nos níveis de BDNF pré e pós-CRS ou em relação ao tempo decorrido entre a CRS e a coleta.

Conclusão: O alívio do sofrimento relacionado à incongruência de gênero pós-CRS não pode ser avaliado apenas pelo BDNF. Soluções cirúrgicas podem não fornecer uma solução rápida para o sofrimento associado ao transexualismo, e a CRS pode servir como um passo em direção à, em vez de conclusão da, construção da identidade de gênero de uma pessoa.

Descritores: Transexualismo, cirurgia de redesignação sexual, BDNF.

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Introduction

Transsexualism (International Classification of Diseases, version 10 [ICD-10]) is a condition characterized by a strong and persistent dissociation with one's assigned gender.¹ This experience is psychologically taxing and is compounded by distress caused by social stigmatization.² Furthermore, transsexual individuals report a high prevalence of childhood trauma, with particularly high rates of emotional abuse and negligence. Sex reassignment surgery (SRS) and hormone therapy provide a means of allowing transsexual individuals to feel more congruent with their gender, and have played a major role in treatment over the past 70 years.¹⁻⁶

Brain-derived neurotrophic factor (BDNF) is a member of the growth factor family that is involved in promoting synaptic plasticity, including neurogenesis, neuronal survival, and the normal maturation of neuronal developmental pathways.⁷⁻⁹ Low BDNF levels are a biomarker for a range of neuropsychiatric disorders, such as advanced bipolar disease,¹⁰ major depressive episodes¹¹ and schizophrenia.¹² BDNF levels increase in response to antidepressant, lithium, and valproate treatments.⁸

BDNF has also been linked to several recovery situations. While low BDNF levels have been associated with substance abuse disorder, increased levels of brain-derived neurotrophin were found during abstinence in substance abuse disorders, e.g., alcohol withdrawal,¹³ likely signaling neuronal recovery. Additionally, high levels of BDNF have been associated with craving in opiate-dependent patients, signaling a possible maladaptive plasticity associated with drug-seeking behavior during abstinence,¹⁴ and a similar pattern has been observed in patients with cocaine dependence, possibly predicting cocaine abuse relapse.¹⁵

Extensive research has been conducted over the past two decades focusing on the means by which BDNF modulates neuroplasticity. For example, in 1995 Korte et al.¹⁶ showed that BDNF is predominantly synthesized by neurons and Bergami et al.¹⁷ showed that astrocytes play the role of storing and secreting BDNF. Moreover, glia have been found to utilize BDNF in neuroinflammatory and neuroprogressive processes,¹⁸ such as neuronal lesions¹⁹ and inflammatory conditions.²⁰

The way in which hormone therapy in transsexuals may alter BDNF levels has proven a controversial subject. Fuss et al.²¹ conducted a study comparing transsexual females with controls and found no differences in BDNF levels after estrogen therapy, Fontanari et al.²² supposed that the low BDNF levels they found in transsexual individuals could be related to emotional trauma in childhood, while Kauer et al.²³ found that low BDNF levels – as detected, for example, in bipolar individuals – were associated with traumatic life events.

The aim of our study was to explore whether BDNF levels before and after SRS correlate with recovery from psychological distress in transsexual individuals, as they correlate with recovery from distress in other disorders, such as posttraumatic stress disorder (PTSD), acute trauma, and major depression. Although several studies have evaluated psychological recovery using subjective tools, no studies have evaluated the potential of a biological marker as an objective tool for assessing post-SRS alleviation of transsexual suffering.

Materials and methods

Participants and procedures

In this prospective cohort study, male-to-female transsexual people were recruited between February 2009 and December 2015 and monitored after SRS. All patients underwent classic penile inversion vaginoplasty, the surgical gold standard for male-to-female reassignment. All operations were performed by a single surgeon with many years of experience in this technique.

The inclusion criteria were as follows: diagnosis of transsexualism (ICD-10) established by a psychiatrist, age greater than 18 years, and a post-SRS period of at least 6 months. We have chosen to use the term transsexualism based on ICD-10 criteria; however, we are aware of current nomenclature changes. Patients suffering from axis I psychotic disorders, mental retardation, or substance addiction were excluded from the study. Although the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) diagnostic criteria are now no longer used, data collection was carried out between 2008 and 2015, when these criteria were still current, and the Mini International Neuropsychiatric Interview (MINI 6.0) is in accordance with the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (DSM-IV-TR). All patients signed an informed consent form for the study, which was approved by the Research Ethics Committee (CEP HCPA Nº 08-167).

During this period, we evaluated 84 new patients in the clinic. Of these patients, 65 fully fit the surgical criteria and underwent SRS; 33 of these 65 patients were excluded from the analysis due to a lack of data or because they did not meet the inclusion criteria. The final sample contained 32 individuals. All male-to-female transsexuals who underwent both surgery and hormone treatment during this period were selected for the study. Figure 1 illustrates the process of exclusion or inclusion of participants who attended the initial evaluation.

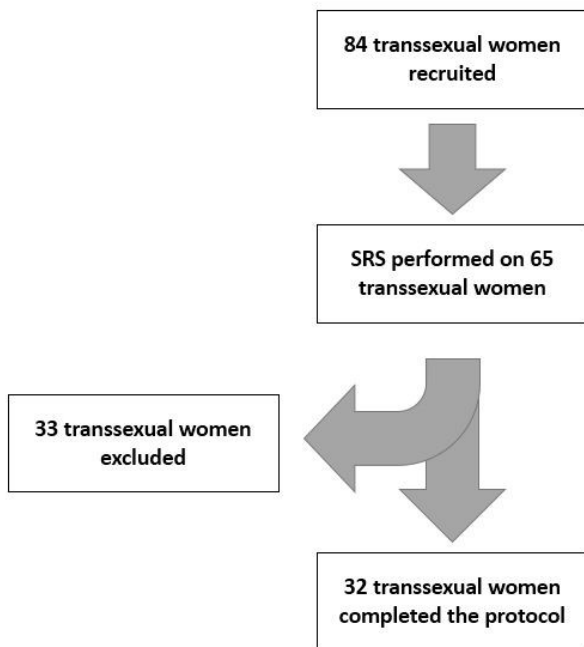


Figure 1 - Diagram of loss and/or exclusion of patients.

Main outcome measures

Five mL of peripheral blood were taken from each subject by venipuncture into an anti-coagulant-free vacuum tube. The blood was centrifuged at 4000 x g for 10 min, and the serum was frozen at -80 °C until assayed. Tests were conducted with sandwich enzyme linked immunosorbent assay (ELISA), according to the manufacturer's specifications (Chemicon, USA). In short, 96-well flat-bottom microtiter plates were filled with the samples (diluted 1:2 in sample diluents) and left for a 24-hour period. The standard curve ranged from 7.8 to 500 pg of BDNF. Plates were then washed four times with wash buffer, monoclonal anti-BDNF rabbit antibody (diluted 1:1000 with sample diluents) was added, and then plates were incubated for three hours at room temperature. After washing, a second incubation with anti-rabbit antibody peroxidase conjugate (diluted 1:1000) was carried out for one hour at room temperature. Next, streptavidin-enzyme, substrate, and stop solution were added, and the amount of BDNF was measured (absorbance set at 450 nm). The standard curve demonstrated a direct relationship between optical density and BDNF concentration. Total protein was measured using Lowry's method, using bovine serum albumin as a standard.

Analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 18.0. Most BDNF value fits were normally distributed and were therefore subjected

to parametric analyses. Two-sided paired t test analyses were conducted to compare BDNF measures, significant at $p < 0.05$. Data were presented as the mean \pm standard deviation. Pearson correlations were used to analyze the relationship between the time of blood collection, in days after SRS, and BDNF levels.

Results

The mean age of transsexual patients was 28.75 ± 6.53 . BDNF serum levels were measured 279.28 ± 190.34 days after male-to-female SRS. The interval between the first and the second blood sample collections was 847 ± 797.09 days. Mean serum BDNF levels were 18.55 ± 5.99 and 17.83 ± 6.47 , pre-SRS and post-SRS respectively. There was no difference between pre-SRS and post-SRS BDNF levels: $\Delta = -0.73$, median difference = -1.36 $t_{32} = 0.67$, $p = 0.50$, 95% confidence interval = -1.46 to 2.92 (Figure 2). There was no significant correlation between the time of blood collection after SRS and post-SRS BDNF levels ($r = -0.11$, $p = 0.54$) or between the time between the pre-SRS and post-SRS blood collections and post-SRS BDNF levels ($r = -0.05$, $p = .77$).

Fifteen HIV+ subjects were included in the sample. These patients were included in the final analysis because we were comparing the same cases before and after SRS and so this confounding factor affected the two data collection times equally.

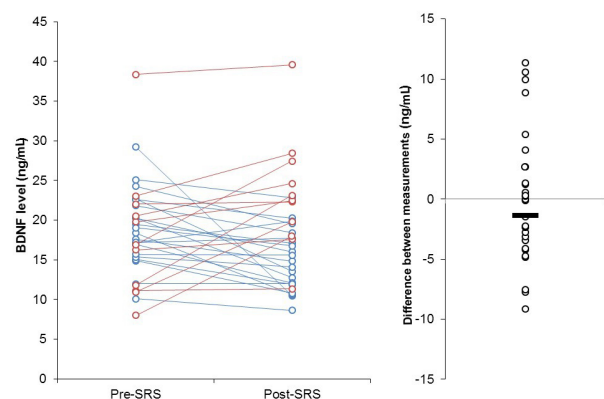


Figure 2 - Brain-derived neurotrophic factor (BDNF) levels before and after sex reassignment surgery (SRS) and differences between them.

Discussion

BDNF has been identified as a possible predictor of treatment response in some types of psychiatric distress.²⁴ There is also evidence to suggest that patients remain

satisfied after SRS and that it alleviates the suffering caused by living in non-conformity with their gender identity.²⁵⁻²⁷ In alignment with this extant research, this study posited that alleviation of this suffering after SRS would be traceable through BDNF serum levels.

However, contrary to this hypothesis, the difference between preoperative and postoperative BDNF levels was not significant. One way to interpret these findings is to consider that SRS could serve as one step toward, rather than the conclusion of, a person's gender identity construction and so the molecular response may require extensive recuperation, not occurring immediately after SRS. This interpretation can be sustained considering that SRS cannot reverse the effects of the chronic psychological trauma associated with transsexuals' life experiences, at least not in the short term or as an isolated intervention.

Another important point to consider is the effect on BDNF levels of the neuroactive steroids used by patients. All of our participants were undergoing hormonal sex reassignment therapy. A myriad of *in vitro* studies have evaluated the type of neuronal effects exerted by the steroids we currently use in the reassignment process. Estradiol and progesterone have been shown to directly and indirectly increase neuroplasticity, via BDNF augmentation and glutamate respectively.²⁸ These *in vitro* models have demonstrated that steroidal hormones augment release of BDNF from neurons or astrocytes.²⁹

Notably, Fuss et al.,²¹ found a negative correlation between estradiol treatment during the reassignment process and BDNF levels in their group of transsexual women. Their finding was somewhat surprising, because earlier studies had found the opposite. There is a correlation between the menses cycle and brain neurotrophin secretion, for example, with positive BDNF fluctuation in response to estradiol³⁰ at the end of the follicular phase. On one hand, we expect elevation of BDNF levels after SRS – consistent with other psychiatric models of suffering alleviation (anxiety, major depression, bipolar disease, schizophrenia, and PTSD) – but on the other hand, we have information that BDNF levels diminish with estradiol treatment. We can therefore hypothesize that the effects of these interventions are opposite and neutralizing when conjugated. Any augmentation of BDNF due to alleviation of distress would be neutralized by the negative effects of estradiol on BDNF in transsexuals.

Nevertheless, studying transsexuals may be subject to certain peculiarities compared with studying non-transsexual individuals. The majority of neurobiological models of neuroactive steroids are tested in non-transsexual individuals or in animals. The significance of this must be considered. There are indications that transsexual individuals respond differently to steroids

than cissexuals do. For a long period of time, it was believed that the brain would be dimorphic in some aspects for men and women, with a type of intermediate variation of some structures for transsexuals,³¹ and estrogen exerts an effect on neuronal development.³² Although new evidence of brain morphology and functional magnetic resonance imaging contest the idea of macroscopic dimorphisms across gender,³³ we do not know exactly what happens microscopically in treatment with estradiol, an XY chromosome: Molecular responses might be "dimorphic." There may be microscopic – beyond molecular – properties intrinsic to the sexual chromatin that dictate different responses between transsexual and non-transsexual individuals, e.g., the second messenger machinery and the neurokinin system.

Increasing sample sizes to ensure that there BDNF serum levels are truly non-significant biologically, and not a result of our meager participant pool, would be advisable for forthcoming research.

Conclusion

Although this particular study has proven non-significant, it has provided a critical inference: surgical solutions may not provide a quick fix for psychological distress associated with transsexualism. Although BDNF levels may be able to recover rapidly from acute trauma, it appears that transsexualism may require more extensive rehabilitation, in accordance with the hypothesis that the early and continual neurological effects of prejudice that transsexual patients suffer throughout their lives could be observed as continuous trauma that influences neuroplasticity, resulting from social vulnerability.^{34,35} These results have opened up avenues for more comprehensive research opportunities that could evaluate the association of BDNF levels in transsexualism. While ensuing studies will need to readdress confounding factors in this methodology, these results should allow for a more extensive and informed support system for medical interventions in transsexual individuals.

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