Neurological Sciences (2019) 40:1275–1278
https://doi.org/10.1007/s10072-019-03748-z

BRIEF COMMUNICATION

Attenuation of ALS progression during pregnancy—lessons to be learned or just a coincidence?

Mirea Hancevic[1] · Hrvoje Bilic[1] · Barbara Sitas[1] · Gordana Pavlisa[2] · Fran Borovecki[1,3] · Ivana Munitic[4] · Ervina Bilic[1,3]

Received: 20 October 2018 / Accepted: 31 January 2019 / Published online: 11 February 2019

Abstract
ALS is the most frequent motor neuron disorder in adults with suggested complex relationship regarding gender. Studies investigating ALS and hormones have provided varying results. ALS onset during pregnancy is uncommon and pregnancy after the ALS symptom onset is even rarer. We present three patients with the onset of ALS symptoms before or during pregnancy and propose a putative disease modifying mechanism leading to attenuation of disease progression that we observed during the pregnancies.

Keywords ALS · Pregnancy · Hormones · Gender · Immunomodulation · FUS

Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative motor neuron disorder leading to progressive weakness of limb, bulbar, and respiratory muscles. Mean age of onset varies between 60 and 65 years [1]. Epidemiological studies have shown male predominance, especially in patients younger than 51 years of age [2]. Gender ratio is not equal in familial ALS either, being 1.5:1 for most Mendelian ALS genes [3]. Gender influences the clinical phenotype with limb affection being more frequent in males, while bulbar form is more frequent in females. Higher frequency of male cases, particularly in younger age, suggests involvement of hormonal factors through either toxic effect of androgens or protective effect of female sex hormones, both of which may play an important role in modulating ALS risk. Considering epidemiological data, ALS is not frequent in women of reproductive age. Cases of ALS and pregnancy are sporadic and pregnancy after ALS symptom onset/ALS diagnosis is even more infrequent.

Case report

Here, we present three patients treated at the Department of Neurology, Clinical Hospital Centre Zagreb; two of which have become pregnant after the onset of ALS symptoms. All patients were seen in outpatient clinic of neuromuscular department and diagnosed based on physical findings and EMG studies according to revised El Escorial diagnostic criteria. Neurological functional assessment was recorded with the revised ALS Functional Rating Scale (ALS-FRSr) on every clinic visit. Patients had unremarkable past medical history and no familial ALS history.

In summary, two of our patients developed symptoms up to 2 years before pregnancy and delivered healthy babies, whereas one exhibited symptoms in the first trimester and had a stillbirth 2 months later. It is remarkable that for all patients the disease did not substantially progress during the pregnancies. Indeed, ALS FRSr did not show significant worsening during pregnancy in none of our patients as presented in Fig. 1. It is of note that all three of our patients had history of miscarriages/stillbirths, with only one patient being diagnosed with hereditary thrombophilia as the probable cause. Miscarriages have thus far not been

✉ Mirea Hancevic
mhancevic@gmail.com

[1] Department of Neurology, Clinical Hospital Centre Zagreb, Kispaticeva 12, 10000 Zagreb, Croatia

[2] Department of Pulmonology, Clinical Hospital Centre Zagreb, Kispaticeva 12, 10000 Zagreb, Croatia

[3] School of Medicine, University of Zagreb, Salata 2, 10000 Zagreb, Croatia

[4] Laboratory of Molecular Immunology, Department of Biotechnology, University of Rijeka, Radmile Matejcic 2, 51000 Rijeka, Croatia

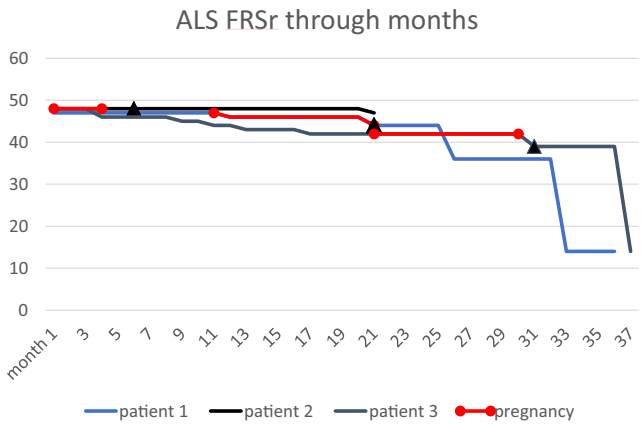

Fig. 1 ALS FRS through months. The time-course of pregnancies and ALS FRSr is depicted since the appearance of the first ALS symptom. The time of diagnosis is marked by Δ. Patient 1 was 41 years old at ALS symptom onset. Two months following a miscarriage, she developed a slight dysarthria. Twelve months after symptom onset she became pregnant again. At that time, she developed non-fluent aphasia and started exhibiting cognitive impairment with her executive functions being most affected but also with some deficiency in her anterograde episodic memory. She delivered full-term healthy baby and was diagnosed shortly after the delivery (i.e. 21 months after the onset of the first symptom) with clinically probable/laboratory supported ALS-FTD. She died 52 months from the onset of symptoms. Patient 2 was 35 years old at symptom onset. In the third month of pregnancy, she noticed a change in the fine motor movements of the left hand. Two months after symptom onset she had stillbirth in 23rd week of pregnancy. Shortly after the miscarriage, i.e. 6 months after symptom onset, she was diagnosed with possible ALS. Patient 3 was 32 years old at ALS symptom onset. Her initial symptom was discreet right hand weakness; 21 months later, she became pregnant; after a full-term pregnancy, she vaginally delivered a healthy baby boy. She was diagnosed with definite ALS 1 month after the delivery. Her disease rapidly progressed shortly after the delivery, reaching ALS-FRSr 14 within 6 months.

characterised as the hallmark of ALS. However, a study of fecundity in ALS has found that ALS patients exhibit retrospective evidence of relative infertility [4].

Discussion

Great patient-to-patient variability is seen in ALS, suggesting that it might not be a single disease [5]. Clinical variability among those rare patients who developed ALS in pregnancy has also been detected, and both cases of disease acceleration and deceleration/plateau were described in literature. Notably, the only two articles that have used ALS FRSr as a means of quantifying ALS progression before, during or after pregnancy showed results similar to ours—that pregnancy was not associated with rapid worsening and was possibly associated with slower disease progression [6, 7].

Pregnancy is characterised by substantially elevated levels of both oestrogen and progesterone. Studies so far have found both oestrogen and progesterone (endogenous as well as exogenous) to be associated with neuroprotection [8, 9]. Oestrogen has been directly linked with neuroprotection via oestrogen receptor (ER)-mediated signalling in neurons and/or via its free radical scavenging potential independent of the ER [10]. Neuroinflammation is an important driving force in ALS; both oestrogen and progesterone substantially modulate immune responses [11] which may also alter the course of the disease [12]. Beneficial effect(s) of increased oestrogen and progesterone levels during pregnancy in ALS could be mediated through the modulation of the immune system. Pregnancy is marked by an increase in regulatory T cells (Treg) and a decrease in the proinflammatory activity of macrophages, T and NK cells, resulting in an increase of various anti-inflammatory cytokines. Such anti-inflammatory skewing in pregnancy leads to remission of a number of immune-mediated diseases [13]. This effect is most pronounced during the peak of the hormone production [14]. Given that Treg numbers and anti-inflammatory status correlate with slower ALS progression in patients and mouse models [15, 16], it is possible that slower disease progression observed in our patients is also linked to hormone-mediated immunosuppression. Of note, all immune subsets, including microglia were shown to harbour oestrogen and progesterone receptors [11]. However, at this point, it is difficult to distinguish the exact effects of individual hormones, and it is possible that they work in concert.

We propose another possible mechanism for disease-modifying effect we observed in ALS during pregnancy that could partially explain gender differences. Research so far has established clear anatomical association between motor neurons and androgen signalling, with androgen receptor being highly expressed in motor neurons of the cranial nerves and motor neurons of the spinal cord [17, 18]. Sex hormones in serum are bound to albumin, corticosteroid binding globulin and sex hormone binding globulin (SHBG). Only unbound (free) hormones can cross blood brain barrier. Dihydrotestosterone binds to SHBG with about five times the affinity of testosterone and about 20 times affinity of estradiol. High oestrogen levels in pregnancy activate SHBG production in the liver and SHBG level increases up to tenfold [19]. This elevated serum SHBG possibly binds significantly more testosterone thus reducing free testosterone fraction and preventing it from crossing the blood brain barrier and exerting its effects on motor neurons. As SHBG also increases with the use of oral contraceptives, this could explain the findings by Rooney et al. [9] who argue that exogenous hormones may exert neuroprotective effects, exhibiting negative association between oral contraceptive use and ALS risk.

Mechanism by which testosterone may be modifying ALS progression rate could be also through its interaction with DNA transcription as the case of FUS (FUsed in Sarcoma)

gene seems to suggest. FUS is a multifunctional DNA/RNA binding protein with over 50 mutations found in ALS families. It regulates DNA transcription and is involved in mRNA processing. It also repairs DNA damage and has a role in regulating miRNA activities in gene silencing [20]. Yamaguchi & Takanashi have found that FUS represses androgen receptor (AR)-mediated transcriptional activity [21]. It is therefore possible that, in the cases of mutation in FUS, AR transcriptional activity is not repressed and contributes to disease by contributing to further formation of cytoplasmic aggregates. Lower levels of free testosterone (due to pregnancy or use of oral contraceptives) would decrease this transcriptional activity (and need for its repression) thus modifying the disease progression.

In two of our patients with full-term pregnancies disease appeared to have postpartum acceleration. Another neurological disorder shows similar pattern in pregnancy; studies investigating multiple sclerosis show significant decrease in relapse rate during pregnancy and increased relapse rate in months following delivery [22]. Reasons for this increase include abrupt drop in oestrogen, progesterone and glucocorticoid levels with rapid normalisation of immune function to pre-pregnancy conditions [23].

It is of note that free testosterone levels increase after 28th week of pregnancy due to increased production rate [24]. Possible link to disease acceleration could be trough increased AR binding and slower genomic effects taking place towards the end of pregnancy.

In conclusion, a review of literature has shown that, although infrequent, ALS in pregnancy has been reported in 45 patients since 1920 with differing impressions regarding the effect of pregnancy on the disease progression. Cases with documented ALS FRSr have shown disease progression attenuation during pregnancy. Our proposed disease-modifying mechanism could possibly encourage further research into the effect of hormones on the disease progression, especially in the cases of ALS mutations known to affect hormone receptor transcription.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

Informed consent Informed consent was obtained from all individual participants for whom identifying information is included in this article.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. del Aguila MA, Longstreth WT, McGuire V, Koepsell TD, van Belle G (2003) Prognosis in amyotrophic lateral sclerosis: a population-based study. Neurology 60(5):813–819
2. Manjaly, Z.R., Scott, K.M., Abhinav, K., Wijesekera, L., Ganesalingam, J., Goldstein, L.H., Janssen, A., Dougherty, A., Willey, E., Stanton, B.R., Turner, M.R., Ampong, M.-A., Sakel, M., Orrell, R.W., Howard, R., Shaw, C.E., Leigh, P.N., and Al-Chalabi, A., 2010. The sex ratio in amyotrophic lateral sclerosis: a population based study. Amyotroph Lateral Scler, 11 (5), 439–442
3. Blasco, H., Guennoc, A.-M., Veyrat-Durebex, C., Gordon, P.H., Andres, C.R., Camu, W., and Corcia, P., 2012. Amyotrophic lateral sclerosis: a hormonal condition? Amyotroph Lateral Scler, 13 (6), 585–588
4. Byrne S, Heverin M, Bede P, Elamin M, Hardiman O (2014) Fecundity in ALS. Amyotrophic Lateral Sclerosis & Frontotemporal Degeneration 15(3–4):204–206
5. Hardiman O, Al-Chalabi A, Chio A, Corr EM, Logroscino G, Robberecht W, Shaw PJ, Simmons Z, van den Berg LH (2017) Amyotrophic lateral sclerosis. Nat Rev Dis Primers 3:17071
6. Martínez HR, Marioni SS, Escamilla Ocañas CE, Gonzalez Garza MT, Moreno-Cuevas JE (2014) Amyotrophic lateral sclerosis in pregnancy: clinical outcome during the post-partum period after stem cell transplantation into the frontal motor cortex. Cytotherapy 16(3):402–405
7. Sarafov S, Doitchinova M, Karagiozova Z, Slancheva B, Dengler R, Petri S, Kollewe K (2009) Two consecutive pregnancies in early and late stage of amyotrophic lateral sclerosis. Amyotroph Lateral Scler 10(5–6):483–486
8. Jong S, Huisman M, Sutedja N, Kooi A, Visser M, Schelhaas J, Schouw Y, Veldink J, den Berg L (2013) Endogenous female reproductive hormones and the risk of amyotrophic lateral sclerosis. J Neurol 260(2):507–512
9. Rooney JPK, Visser AE, D'Ovidio F, Vermeulen R, Beghi E, Chio A, Veldink JH, Logroscino G, van den Berg LH, Hardiman O (2017) A case-control study of hormonal exposures as etiologic factors for ALS in women: euro-MOTOR. Neurology 89(12): 1283–1290
10. Nakamizo T, Urushitani M, Inoue R, Shinohara A, Sawada H, Honda K, Kihara T, Akaike A, Shimohama S (2000) Protection of cultured spinal motor neurons by estradiol. Neuroreport 11(16): 3493–3497
11. Robinson DP, Klein SL (2012) Pregnancy and pregnancy-associated hormones alter immune responses and disease pathogenesis. Horm Behav 62(3):263–271
12. Villa A, Vegeto E, Poletti A, Maggi A (2016) Estrogens, Neuroinflammation, and neurodegeneration. Endocr Rev 37(4): 372–402
13. Markle JG, Fish EN (2014) SeXX matters in immunity. Trends Immunol 35(3):97–104
14. Confavreux C, Hutchinson M, Hours MM, Cortinovis-Tourniaire P, Moreau T (1998) Rate of pregnancy-related relapse in multiple sclerosis. Pregnancy in multiple sclerosis Group. N Engl J Med 339(5):285–291
15. Zhao W, Beers DR, Liao B, Henkel JS, Appel SH (2012) Regulatory T lymphocytes from ALS mice suppress microglia and effector T lymphocytes through different cytokine-mediated mechanisms. Neurobiol Dis 48(3):418–428
16. Beers DR, Zhao W, Wang J, Zhang X, Wen S, Neal D, Thonhoff JR, Alsuliman AS, Shpall EJ, Rezvani K, Appel SH (2017) ALS patients' regulatory T lymphocytes are dysfunctional, and correlate with disease progression rate and severity. JCI Insight 2(5):e89530

17. Sar M, Stumpf WE (1977) Androgen concentration in motor neurons of cranial nerves and spinal cord. Science (New York, NY) 197(4298):77–79
18. Waragai M, Yamada T, Moroo I (1993) [The distribution of androgen receptor like protein in the central nervous system of rat and human medulla and spinal cord–immunohistochemical study]. No To Shinkei 45(7):661–667
19. Male hypogonadism (2017) Springer Berlin Heidelberg, New York, NY
20. Zhang T, Wu Y-C, Mullane P, Ji YJ, Liu H, He L, Arora A, Hwang H-Y, Alessi AF, Niaki AG, Periz G, Guo L, Wang H, Elkayam E, Joshua-Tor L, Myong S, Kim JK, Shorter J, Ong S-E, Leung AKL, Wang J (2018) FUS regulates activity of microRNA-mediated gene silencing. Mol Cell 69(5):787–801.e8
21. Yamaguchi A, Takanashi K (2016) FUS interacts with nuclear matrix-associated protein SAFB1 as well as Matrin3 to regulate splicing and ligand-mediated transcription. Sci Rep 6(1)
22. Amato MP, Bertolotto A, Brunelli R, Cavalla P, Goretti B, Marrosu MG, Patti F, Pozzilli C, Provinciali L, Rizzo N, Strobelt N, Tedeschi G, Trojano M, Comi G (2017 Oct) Management of pregnancy-related issues in multiple sclerosis patients: the need for an interdisciplinary approach. Neurol Sci 38(10):1849–1858
23. Bammann BL, Coulam CB, Jiang NS (1980) Total and free testosterone during pregnancy. Am J Obstet Gynecol 137(3):293–298
24. Ysrraelit MC, Correale J (2019 Jan) Impact of sex hormones on immune function and multiple sclerosis development. Immunology 156(1):9–22