

# Evaluation the Serum Level of Sex Hormones in Patients With Trigeminal Neuralgia

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## Research Article

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**Evaluation the serum level of sex hormones in patients with trigeminal neuralgia**

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**Research article**

**Evaluation of sex hormones serum level in patients with trigeminal neuralgia  
in comparison with healthy controls**

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## **Abstract**

**Background and Aim:** In this study FSH, LH, Testosterone, Estrogen, Progesterone serum levels in women affected by trigeminal neuralgia have been evaluated.

**Materials and Methods:** This study is a cross sectional study during 2017-2018 in which FSH, LH, Testosterone, Estrogen, Progesterone serum levels in women affected by trigeminal neuralgia, who had referred to Emam Reza clinic and Oral and Maxillofacial Disease Department of Shiraz Dental Faculty, have been evaluated. Twenty-six women with trigeminal neuralgia were recruited in trigeminal neuralgia(TN) group and 26 healthy women whom their age were matched with TN group were enrolled in the healthy control group. Data was analyzed by SPSS version 18.

**Results:** Sex hormone serum level was not significantly different between patients with TN and healthy control group (P value  $\geq 0.05$ ). In spite of this finding, the serum level of FSH in non-menopausal (P value=0.002) participants and progesterone in menopausal (P value=0.016) participants of TN and healthy control group, were significantly different. The serum level for both of these hormones were higher in patients with TN. In contrast to healthy control group, the sex hormone profiles of patients with TN, except LH did not follow the natural pattern changes based on menopausal status.

**Conclusion:** In spite of no significant differences in sex hormonal profile of patients with TN and healthy controls, some hormonal disturbance in FSH and progesterone have been detected in TN patients in comparison between non-menopause and menopausal sex hormones profile.

**Key words:** FSH, LH, Testosterone, Estrogen, Progesterone, trigeminal neuralgia

## **Introduction**

Trigeminal neuralgia is a neuropathic pain, causing sudden, brief, stabbing and recurring pain, limited to a small region of the face[1] . Trigeminal neuralgia onset is usually middle or old age, but it also affects young adults and children. Trigeminal neuralgia can reoccur and lasts for few seconds. The attack might begin with stimulation of trigger zone, located within the trigeminal nerve pathway[2]. Trigeminal neuralgia is a neuropathic pain with different etiologies, causing demyelization in trigeminal zone. Neurovascular compression, multiple sclerosis, tumor, and cysts, diabetes mellitus are the most popular causes[3]. In some studies, neuropathic and neurotropic role were described for sexual hormones, even the effect of hormones on the quality and rate of nerve conduction reported. These studies showed a higher incidence of peripheral neuropathy in menopausal women[4]. Peripheral sensory and autonomic neurons express estrogen receptors[5]. The nerve transmission speed is dependent on velocity and latency (the duration between applying a stimulation and wave form record on nerve conduction study). On the other hand, the degree of myelination can significantly affect velocity and latency in nerve conduction studies[6]. A study showed that sexual hormone replacement therapy were affective on faster velocity and shorter latency, an indication for possible association between sexual hormones and nerve myelination[7]. Another study investigated whether Estrogen(E2) has a proper recovery effect on nerve injury in mice. They reported that local injection of E2 can induce greater nerve conduction velocity and vascularity [8]. In a study by Akanksha Singh explored the relationship between estrogen serum level and progesterone and -peripheral motor nerve neuropathy in postmenopausal women by motor nerve conduction velocity. Their findings reported lower level of serum estrogen in postmenopausal women with peripheral neuropathy[9]. According to these information and higher prevalence of some neuropathic pains, such as burning mouth syndrome and trigeminal neuralgia in female with more variant sex hormone status, the hypothesis of

possible relation between sex hormones and prevalence of trigeminal neuralgia can be evaluated. To the best of our knowledge, there is no study on sex hormones in patient with trigeminal neuralgia; hence, in this study FSH, LH, Testosterone, Estrogen, Progesterone serum levels in women affected by trigeminal neuralgia who had referred to Oral and Maxillofacial Disease Department of Shiraz Dental School, were evaluated.

## **Materials and Methods**

This study is a cross sectional study, performed during 2017-18. The women with confirmed trigeminal neuralgia who had referred to Emam Reza clinic and Oral and Maxillofacial Disease Department of Shiraz Dental Faculty were enrolled in this study. The protocol of this study which was conducted according to the ethical principles of Helsinki [10], was approved by the ethics committee of Shiraz University of Medical Sciences (IR.SUMS.REC.1396.S886).

A written informed consent was obtained from each participant. The participants who had any disease that could affect sex hormone serum level were excluded from the study. The blood samples were obtained by an expert nurse in day 3 of participant's menstruation of non-menopausal women; the day of sampling for menopausal women was not a specific day. The blood sample was obtained after 2-4 hours after waking up. The serum level of FSH, LH, Testosterone, progesterone, estrogen was evaluated. Patients' demographic data including age, other systemic disease and menopausal situation were registered. Twenty-six women with trigeminal neuralgia were recruited in case group and 26 healthy women whom their age were matched with TN group were enrolled in the healthy control group. The participants in healthy control group were patients who had referred to Shiraz Dental School for routine dental evaluation. Data was analyzed by

SPSS version 18. The pattern of hormonal changes in menopausal and non-menopausal participants were compared by Mann-Whitney test.

## Results

In this study, the mean age of participants in TN group was  $52.73 \pm 15.83$  years old and  $49.93 \pm 12.04$  for the healthy group. The mean serum level of evaluated sex hormones in TN and healthy control groups are presented in table 1. Other statistical data and the P value for comparing the mean of both groups are also in table 1.

Table 1: Mean level of each hormone in TN and healthy control groups and their P value.

Group		Age (years old)	FSH (miu/ml)	LH (miu/ml)	TESTO (ng/ml)	ESTRO (pg/ml)	PROG (ng/ml)
TN group	N	30	30	30	30	30	30
	Mean	52.733	48.31013	23.51427	0.36717	64.57290	1.12663
	Median	50.500	39.20950	18.44950	0.33900	34.06550	0.66400
	Minimum	29.0	0.060	0.031	0.036	4.016	0.055
	Maximum	99.0	105.000	68.055	1.031	263.374	10.000
	Std. Deviation	15.8352	38.094427	17.002634	0.209768	72.854346	1.779472
Healthy control group	N	30	30	30	30	30	30
	Mean	49.933	36.72390	19.60777	0.34317	71.52023	1.19077
	Median	51.500	22.18650	17.30100	0.30300	47.31050	0.41000

	Minimum	26.0	2.120	1.080	0.023	4.820	0.060
	Maximum	70.0	101.900	45.870	0.970	193.000	10.000
	Std. Deviation	12.0400	33.622332	14.333563	0.227073	57.065230	2.251321
Total	N	60	60	60	60	60	60
	Mean	51.333	42.51702	21.56102	0.35517	68.04657	1.15870
	Median	50.500	32.83750	17.71950	0.32450	41.20000	0.55000
	Minimum	26.0	0.060	0.031	0.023	4.016	0.055
	Maximum	99.0	105.000	68.055	1.031	263.374	10.000
	Std. Deviation	14.0177	36.098116	15.714933	0.217069	64.975311	2.012148
	Asymp. Sig. (2-tailed)	0.807	0.135	0.442	0.442	0.095	0.081

FSH=follicle stimulating hormone/ LH=luteinizing hormone/ TESTO=testosterone/ ESTRO= estrogen/

PRO=progesterone

Serum level between TN and healthy control group was not significantly different. The pattern of hormonal changes in menopausal and non-menopausal participants (TN and healthy control groups together) were compared and the P values are reported in table 2.

Table 2: comparison between hormones serum level in menopause and non-menopause participants(TN and healthy control group together)



	Age (years old)	FSH (miu/ml)	LH (miu/ml)	TESTO (ng/ml)	ESTRO (pg/ml)	PROG (ng/ml)
Mann-Whitney U	<0.001	138.000	227.000	297.000	292.000	355.500
Wilcoxon W	465.000	603.000	692.000	762.000	757.000	820.500
Z	-6.658	-4.614	-3.297	-2.262	-2.336	-1.397
Asymp. Sig. (2-tailed)	<0.001	<0.001	0.001	0.024	0.019	0.162

FSH=follicle stimulating hormone/ LH=luteinizing hormone/ TESTO=testosterone/ ESTRO=estrogen/ PRO=progesterone

The hormonal level in all participants based on menopausal status were significantly different, except progesterone. The comparison of hormonal serum level between TN and healthy control group in menopause and non-menopause participants are reported in table 3.

Table 3: the comparison of hormonal level between TN and healthy control groups in menopause and none menopause participants

Group			Age (years old)	FSH (miu/ml)	LH (miu/ml)	TESTO (ng/ml)	ESTRO (pg/ml)	PROG (ng/ml)
Non_Menopause	TN	N	15	15	15	15	15	15
	group	Mean	41.333	33.72120	19.56267	0.39427	77.02840	0.85547
		Median	45.000	19.18700	12.44400	0.35100	38.30700	0.76200
		Minimum	29.0	5.251	0.031	0.109	10.000	0.055
		Maximum	50.0	105.000	68.055	0.737	263.374	2.092

		Std. Deviation	7.5467	32.780559	18.978451	0.171218	81.115178	0.614944
Healthy control group	N		15	15	15	15	15	15
	Mean		39.867	7.53680	12.83933	.43793	104.57293	1.40887
	Median		39.000	5.57000	5.32000	0.30500	90.04700	0.55000
	Minimum		26.0	2.120	1.080	0.220	23.609	0.130
	Maximum		50.0	18.573	42.771	0.970	193.000	8.100
	Std. Deviation		7.2886	5.272371	13.855412	0.229874	63.446536	2.027978
Total	N		30	30	30	30	30	30
	Mean		40.600	20.62900	16.20100	0.41610	90.80067	1.13217
	Median		43.500	9.20900	10.61000	0.34150	59.11050	0.67050
	Minimum		26.0	2.120	0.031	0.109	10.000	0.055
	Maximum		50.0	105.000	68.055	0.970	263.374	8.100
	Std. Deviation		7.3278	26.636281	16.680756	0.200388	72.910467	1.499066
Menopause group	TN N		15	15	15	15	15	15
	Mean		64.133	62.89907	27.46587	0.34007	52.11740	1.39780
	Median		59.000	62.64200	24.22400	0.29200	30.90400	0.62600
	Minimum		51.0	0.060	10.285	0.036	4.016	0.140
	Maximum		99.0	105.000	65.181	1.031	204.194	10.000

	Std. Deviation	13.5640	38.410709	14.324306	0.245476	63.894624	2.454282
Healthy control group	N	15	15	15	15	15	15
	Mean	60.000	65.91100	26.37620	0.24840	38.46753	0.97267
	Median	60.000	68.43000	23.59000	0.24000	39.80000	0.35000
	Minimum	53.0	25.800	11.780	0.023	4.820	0.060
	Maximum	70.0	101.900	45.870	0.670	75.900	10.000
	Std. Deviation	5.4772	22.099776	11.637732	0.186336	19.467676	2.506850
Total	N	30	30	30	30	30	30
	Mean	62.067	64.40503	26.92103	0.29423	45.29247	1.18523
	Median	59.500	66.10450	23.90700	0.29100	34.45000	0.45000
	Minimum	51.0	0.060	10.285	0.023	4.016	0.060
	Maximum	99.0	105.000	65.181	1.031	204.194	10.000
	Std. Deviation	10.3788	30.828220	12.835324	0.219147	46.925686	2.447129
	Asymp. Sig. (2-tailed)	0.617	0.002	0.191	0.852	0.085	0.983
	Asymp. Sig. (2-tailed)	0.852	0.950	0.983	0.351	0.443	0.016

FSH=follicle stimulating hormone/ LH=luteinizing hormone/ TESTO=testosterone/ ESTRO= estrogen/

PRO=progesterone

FSH in non-menopausal participants and progesterone in menopause participants of TN and healthy control group were significantly different. The comparison of hormonal serum level between menopause and non-menopause participants in TN and healthy control groups are presented in table 4.

Table 4: the comparison of hormonal serum level between menopause and non-menopause participants in TN and healthy control groups

Group		Age (years old)	FSH (miu/ml)	LH (miu/ml)	TESTO (ng/ml)	ESTRO (pg/ml)	PROG (ng/ml)
TN group	Mann-Whitney U	0.000	66.000	64.000	86.000	91.000	109.000
	Wilcoxon W	120.000	186.000	184.000	206.000	211.000	229.000
	Z	-4.670	-1.933	-2.012	-1.099	-0.892	-0.145
	Asymp. Sig. (2-tailed)	<0.001	0.053	0.044	0.272	0.372	0.885
Healthy control group	Mann-Whitney U	0.000	0.000	50.000	66.000	42.000	72.000
	Wilcoxon W	120.000	120.000	170.000	186.000	162.000	192.000
	Z	-4.671	-4.666	-2.592	-1.929	-2.924	-1.680
	Asymp. Sig. (2-tailed)	<0.001	<0.001	0.010	0.054	0.003	0.093



FSH=follicle stimulating hormone/ LH=luteinizing hormone/ TESTO=testosterone/ ESTRO= estrogen/

PRO=progesterone

## Discussion

Sex hormone serum level was not significantly different between TN and healthy control group (P value  $\geq 0.05$ ). In spite of this finding, the serum level of FSH in non-menopausal (P value=0.002) participants and progesterone in menopausal (P value=0.016) participants of TN and healthy control group, were significantly different. The serum level for both these hormones were higher in patients with TN(case group). Although in this study the evaluated hormones in a general pattern confirmed the natural changes of hormonal level in women based on their menopausal status, but in patient of TN group, just LH showed the natural pattern of hormonal change. The importance of this finding is noticeable when comparing to natural pattern of these hormones in healthy controls. This imbalance might be related to incidence of TN in the case group. The effect of sex hormones (especially estrogen and progesterone) on neurons was evaluated in previous studies, but the reports are controversial. Some studies indicated a neuroprotective role for these hormones;[11-15] while others did not confirm this role [16-20]. In a study, the relationship between peripheral motor nerve status, estrogen serum level and progesterone was evaluated by Motor Nerve Conduction Velocity(MNCV) in post-menopausal women. In spite of significant lower serum level of estrogen in post-menopausal patient with peripheral neuropathy, no significant effect was reported for progesterone[9]. In another study, higher levels of progesterone was accompanied with reduced optic nerve conduction

velocity[16]. Also elevated level of progesterone was considered to be effective in reducing the nerve conduction velocity in an evaluation[17]. On the other hand, animal model evaluation did not consider noticeable influence of estrogen and progesterone therapy on nerve repair[21]. The findings of these studies are in accordance with what we have reported in our study, in menopause participants which are considerably more prone to neuropathies, where a significant higher level of progesterone was reported in patients with TN compared to healthy controls. On the other hand, some other studies showed a neuroprotective and neurotrophic properties for progesterone. This role was reported in electrophysiological alteration of diabetic induced neuropathy in rats[15, 22]. This neuroprotective effect was also reported for estrogen in some studies. A study proposed the protective effect of estrogen against neural death mediated by estrogen receptors. Estrogen can also regenerate the damaged nerves or enhance the nerve velocity and vascularity[8, 12]. Several neuroprotective mechanisms in the literature have been proposed; for example, progesterone can induce regeneration and nerve demyelination which plays an important role in pathogenesis of most neuropathies [22-40]. In damaged nerves, progesterone prevents secondary neural losses by reducing edema, inflammatory cytokines and reactive gliosis[41]. Some studies reported that estrogen treatment can increase vascular epithelial growth factor expression, which suggests the pro-angiogenic properties of estradiol [42]. In the result of present study, rather than confirming the neuroprotective role of progesterone and estrogen, an imbalance of sex hormones in patients with TN was shown. Menopause patients with TN had higher level of progesterone in comparison with healthy controls. According to pathogenesis of TN and role of demyelinated affected trigeminal nerve and following neuropathies, the higher level of progesterone cannot be indicative of neuroprotection. On the other hand, in non-menopause participants who were less prone to TN,

the serum level of FSH in patients with TN was significantly higher than healthy controls. Since there is no study on the possible effect of FSH on neurons, this hormone can impose its effect by estradiols. FSH is a gonadotropin hormone that regulates the secretion of estradiol. Any alteration in serum level of estradiol can affect FSH. Although in menopause TN patients' progesterone level was higher than healthy patients, significant higher level of FSH in non-menopause TN patients was noticeable. Hormonal imbalance for FSH and progesterone in TN patients was significant. This can be a novel point when evaluating new methods for adjuvant treatment. Considering the sex hormonal profile evaluation in patients affected by TN and improving these imbalances, might affect patients' response to routine treatment. The sample size was small due to financial limitation and low prevalence of TN; hence, it would be wise to recruit larger sample size. To the best of our knowledge there is no similar study on TN patients. Previous studies evaluated different types of neuropathies by several methods and designs. These diverse methodologies make the comparison difficult and sometimes inaccurate, which explains the controversies in their findings. As we proposed, in contrast to healthy controls, the sex hormone profiles of patients with TN, except LH did not follow the natural pattern changes based on menopausal status. This can show sex hormonal imbalance in these patients. Perhaps small sample size in our study limited the study power to discriminate the quality of these imbalances and their possible association with pathogenesis of TN. Further case-control studies with larger sample size, as well as recruiting men can be suggested for further studies.

## **Conclusions**

In spite of no significant differences in sex hormonal profile of patients with TN and healthy controls, the serum level of FSH in non-menopause TN participants and progesterone in

menopause TN patients were significantly higher. These findings confirmed the sex hormonal imbalance of TN patients.

## **List of abbreviations**

TN: Trigeminal neuralgia

EST: Estrogen

FSH: Follicle Stimulating Hormone

LH: Luteinizing Hormone

PROG: Progesterone

TESTO: Testosterone

ESTRO: Estrogen

MNCV: Motor Nerve Conduction Velocity

## **Declarations**

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## **Authors' contributions**

Fateme Lavaee and Parisa Mohaghegh Zahed were involved in study design, patients' evaluation and data interpretation. Fateme Zarei and Maryam Shahrokhi Sardo were involved in data acquisition and preparing the manuscript. All the authors read and approved the manuscript.

## **Data Availability**

The readers can access the data supporting the conclusions of the study by a request through an email to the corresponding author.

## **Funding Statement**

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## **Availability of data materials**

The datasets used and/or analyzed during the study are available from the corresponding author on reasonable request.

## **Ethical approval and consent to participate**

An informed consent was taken from all the participants before the study. This study was approved by the ethics committee of Shiraz University of Medical Sciences.

## **Consent for publication**

Not applicable

## Competing interest

The authors declare that they have no competing interests.

## References

- [1.] Amanat D, Ebrahimi H, Lavaee F, Alipour A, “The adjunct therapeutic effect of lasers with medication in the management of orofacial pain: double blind randomized controlled trial,” *Photomedicine and laser surgery*, vol. 31, no. 10, pp. 474-9, 2013.
- [2.] Love S, Coakham HB, “Trigeminal neuralgia Pathology and pathogenesis,” *Brain*, vol. 124, no. 12, pp. 2347-60, 2001.
- [3.] Toda K, “Etiology of trigeminal neuralgia,” *Oral Science International*, vol. 4, no. 1, pp. 10-8, 2007.
- [4.] Lobo R, “Menopause: endocrinology, consequences of estrogen deficiency, effects of hormone replacement therapy, treatment regimens,” *Comprehensive Gynecology 5th ed Philadelphia, PA: Mosby Elsevier*, vol., no., pp. 1039-71, 2007.
- [5.] Jeon KW. *International Review of Cytology: A Survey of Cell Biology*: Elsevier Science; 2003.
- [6.] Takeo T, Sakuma Y, “Diametrically opposite effects of estrogen on the excitability of female rat medial and lateral preoptic neurons with axons to the midbrain locomotor region,” *Neuroscience Research*, vol. 22, no. 1, pp. 73-80, 1995.
- [7.] Kim H, Ku SY, Sung JJ, Kim SH, Choi YM, Kim JG, et al., “Association between hormone therapy and nerve conduction study parameters in postmenopausal women,” *Climacteric*, vol. 14, no. 4, pp. 488-91, 2011.
- [8.] Sekiguchi H, Ii M, Jujo K, Renault M-A, Thorne T, Clarke T, et al., “Estradiol Triggers Sonic-hedgehog-induced Angiogenesis During Peripheral Nerve Regeneration by Downregulating Hedgehog-interacting Protein,” *Laboratory investigation; a journal of technical methods and pathology*, vol. 92, no. 4, pp. 532-42, 2012.
- [9.] SiNgh A, ASif N, SiNgh PN, Hossain MM, “Motor Nerve Conduction Velocity In Postmenopausal Women with Peripheral Neuropathy,” *Journal of clinical and diagnostic research: JCDR*, vol. 10, no. 12, pp. CC13, 2016.
- [10.] Lewis JA, Jonsson B, Kreutz G, Sampaio C, van Zwieten-Boot B, “Placebo-controlled trials and the Declaration of Helsinki,” *The Lancet*, vol. 359, no. 9314, pp. 1337-40, 2002.
- [11.] Suzuki S, Brown CM, Wise PM, “Mechanisms of neuroprotection by estrogen,” *Endocrine*, vol. 29, no. 2, pp. 209-15, 2006.
- [12.] Wise PM, Dubal DB, Wilson ME, Rau SW, Böttner M, Rosewell KL, “Estradiol is a protective factor in the adult and aging brain: understanding of mechanisms derived from in vivo and in vitro studies,” *Brain Research Reviews*, vol. 37, no. 1-3, pp. 313-9, 2001.
- [13.] Sekiguchi H, Ii M, Jujo K, Thorne T, Ito A, Klyachko E, et al., “Estradiol promotes neural stem cell differentiation into endothelial lineage and angiogenesis in injured peripheral nerve,” *Angiogenesis*, vol. 16, no. 1, pp. 45-58, 2013.
- [14.] Sekiguchi H, Ii M, Jujo K, Renault M-A, Thorne T, Clarke T, et al., “Estradiol triggers sonic-hedgehog-induced angiogenesis during peripheral nerve regeneration by downregulating hedgehog-interacting protein,” *Laboratory Investigation*, vol., no., pp. 532, 2012.
- [15.] Sameni H, Panahi M, Sarkaki A, Saki G, Makvandi M, “The neuroprotective effects of progesterone on experimental diabetic neuropathy in rats,” *Pakistan Journal of Biological Sciences*, vol., no., pp. 1994-2000, 2008.
- [16.] Azarmina M, Soheilian M, Azarmina H, “Increased latency of visual evoked potentials in healthy women during menstruation,” *Journal of ophthalmic & vision research*, vol. 6, no. 3, pp. 183, 2011.

- [17.] Amir D, Fessler DM, "Boots for Achilles: Progesterone's reduction of cholesterol is a second-order adaptation," *The Quarterly review of biology*, vol. 88, no. 2, pp. 97-116, 2013.
- [18.] Henderson V, Popat R, "Effects of endogenous and exogenous estrogen exposures in midlife and late-life women on episodic memory and executive functions," *Neuroscience*, vol. 191, no., pp. 129-38, 2011.
- [19.] Nachemson AK, Lundborg G, Myrhage R, Rank F, "Nerve regeneration and pharmacological suppression of the scar reaction at the suture site: An experimental study on the effect of estrogen-progesterone, methylprednisolone-acetate and cis-hydroxyproline in rat sciatic nerve," *Scandinavian journal of plastic and reconstructive surgery*, vol. 19, no. 3, pp. 255-60, 1985.
- [20.] Kim H, Ku S, Sung J, Kim S, Choi Y, Kim J, et al., "Association between hormone therapy and nerve conduction study parameters in postmenopausal women," *Climacteric*, vol. 14, no. 4, pp. 488-91, 2011.
- [21.] Hale G, Burger H, "Hormonal changes and biomarkers in late reproductive age, menopausal transition and menopause," *Best practice & research Clinical obstetrics & gynaecology*, vol. 23, no. 1, pp. 7-23, 2009.
- [22.] Leonelli E, Bianchi R, Cavaletti G, Caruso D, Crippa D, García-Segura LM, et al., "Progesterone and its derivatives are neuroprotective agents in experimental diabetic neuropathy: a multimodal analysis," *Neuroscience*, vol. 144, no. 4, pp. 1293-304, 2007.
- [23.] Yin X, Crawford TO, Griffin JW, Tu P-h, Lee VM-Y, Li C, et al., "Myelin-associated glycoprotein is a myelin signal that modulates the caliber of myelinated axons," *Journal of Neuroscience*, vol. 18, no. 6, pp. 1953-62, 1998.
- [24.] Keirstead HS, Nistor G, Bernal G, Totoiu M, Cloutier F, Sharp K, et al., "Human embryonic stem cell-derived oligodendrocyte progenitor cell transplants remyelinate and restore locomotion after spinal cord injury," *Journal of Neuroscience*, vol. 25, no. 19, pp. 4694-705, 2005.
- [25.] Koenig HL, Schumacher M, Ferzaz B, Thi AN, Ressouches A, Guennoun R, et al., "Progesterone synthesis and myelin formation by Schwann cells," *Science*, vol. 268, no. 5216, pp. 1500-3, 1995.
- [26.] Chan JR, Phillips LJ, Glaser M, "Glucocorticoids and progestins signal the initiation and enhance the rate of myelin formation," *Proceedings of the National Academy of Sciences*, vol. 95, no. 18, pp. 10459-64, 1998.
- [27.] Jung-Testas I, Schumacher M, Robel P, Baulieu E, "Demonstration of progesterone receptors in rat Schwann cells," *The Journal of steroid biochemistry and molecular biology*, vol. 58, no. 1, pp. 77-82, 1996.
- [28.] Magnaghi V, Cavarretta I, Galbiati M, Martini L, Melcangi RC, "Neuroactive steroids and peripheral myelin proteins," *Brain research reviews*, vol. 37, no. 1-3, pp. 360-71, 2001.
- [29.] Chan JR, Rodriguez-Waitkus PM, Ng BK, Liang P, Glaser M, "Progesterone synthesized by Schwann cells during myelin formation regulates neuronal gene expression," *Molecular biology of the cell*, vol. 11, no. 7, pp. 2283-95, 2000.
- [30.] Groyer G, Eychenne B, Girard C, Rajkowski K, Schumacher M, Cadepond F, "Expression and functional state of the corticosteroid receptors and 11 $\beta$ -Hydroxysteroid dehydrogenase type 2 in Schwann cells," *Endocrinology*, vol. 147, no. 9, pp. 4339-50, 2006.
- [31.] Sereda MW, zu Hörste GM, Suter U, Uzma N, Nave K-A, "Therapeutic administration of progesterone antagonist in a model of Charcot-Marie-Tooth disease (CMT-1A)," *Nature medicine*, vol. 9, no. 12, pp. 1533, 2003.
- [32.] Lubetzki C, Demerens C, Anglade P, Villarroya H, Frankfurter A, Lee V, et al., "Even in culture, oligodendrocytes myelinate solely axons," *Proceedings of the National Academy of Sciences*, vol. 90, no. 14, pp. 6820-4, 1993.
- [33.] Baumann N, Pham-Dinh D, "Biology of oligodendrocyte and myelin in the mammalian central nervous system," *Physiological reviews*, vol. 81, no. 2, pp. 871-927, 2001.
- [34.] Ghomari A, Ibanez C, El-Etr M, Leclerc P, Eychenne B, O'malley B, et al., "Progesterone and its metabolites increase myelin basic protein expression in organotypic slice cultures of rat cerebellum," *Journal of neurochemistry*, vol. 86, no. 4, pp. 848-59, 2003.

- [35.] Dusart I, Airaksinen MS, Sotelo C, "Purkinje cell survival and axonal regeneration are age dependent: an in vitro study," *Journal of Neuroscience*, vol. 17, no. 10, pp. 3710-26, 1997.
- [36.] Ghoumari AM, Wehrle R, De Zeeuw CI, Sotelo C, Dusart I, "Inhibition of protein kinase C prevents Purkinje cell death but does not affect axonal regeneration," *Journal of Neuroscience*, vol. 22, no. 9, pp. 3531-42, 2002.
- [37.] Notterpek L, Bullock P, Malek-Hedayat S, Fisher R, Rome L, "Myelination in cerebellar slice cultures: development of a system amenable to biochemical analysis," *Journal of neuroscience research*, vol. 36, no. 6, pp. 621-34, 1993.
- [38.] Baulieu E, Schumacher M, "Neurosteroids, with special reference to the effect of progesterone on myelination in peripheral nerves," *Multiple Sclerosis Journal*, vol. 3, no. 2, pp. 105-12, 1997.
- [39.] Roof RL, Duvdevani R, Stein DG, "Gender influences outcome of brain injury: progesterone plays a protective role," *Brain research*, vol. 607, no. 1-2, pp. 333-6, 1993.
- [40.] Roof RL, Duvdevani R, Braswell L, Stein DG, "Progesterone facilitates cognitive recovery and reduces secondary neuronal loss caused by cortical contusion injury in male rats," *Experimental neurology*, vol. 129, no. 1, pp. 64-9, 1994.
- [41.] VanLandingham JW, Cutler SM, Virmani S, Hoffman SW, Covey DF, Krishnan K, et al., "The enantiomer of progesterone acts as a molecular neuroprotectant after traumatic brain injury," *Neuropharmacology*, vol. 51, no. 6, pp. 1078-85, 2006.
- [42.] Hamada H, Kim MK, Iwakura A, Ii M, Thorne T, Qin G, et al., "Estrogen receptors alpha and beta mediate contribution of bone marrow-derived endothelial progenitor cells to functional recovery after myocardial infarction," *Circulation*, vol. 114, no. 21, pp. 2261-70, 2006.