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Effect of Perinatal Asphyxia and Body Hypothermia on Hearing Evocated Potentials and Development in the First Two Years of Life

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Abstract

Perinatal asphyxia is associated with a high risk of death as well as neurodevelopmental deterioration both early and late, in addition, severe episodes can have an important effect on auditory function, cochlear damage and retrocochlear neuronal lesions. With the use of body hypothermia therapy as a neuroprotector in the first 72 hours it has been possible to improve the survival of neonates and neurodevelopmental outcomes in cases with moderate to severe Hypoxic Ischemic Encephalopathy (HIE). Objective. To describe the characteristics of Brainstem Auditory Evoked Potentials (BAEP) of infants with moderate and severe HIE treated with body hypothermia, and its connection with the development achieved at one and two years of age. Material and Method. 51 children were studied, who underwent BAEP at 3, 6 and / or 12 months of age, and their development was evaluated at 12 and 24 months of age with the Gesell, Bayley II and Bayley III tests. Results. The BAEP values were similar to those observed in healthy children, and were significantly correlated with development at both ages, especially waves I and III. The Normal / Altered categories in the PEATC showed differences in standard deviation in the developmental score. Conclusions. BAEP showed a relation with later development; the proposed normality / alteration characterization allowed showing the BAEP as an indicator of risk for development, even before frank damage in the auditory pathway.

Keywords: *Perinatal asphyxia, Hypoxic Ischemic Encephalopathy (HIE), hypothermia, child development, BAEP*

Introduction

Perinatal asphyxia is associated with a high risk of death; in Mexico it was reported as the second cause of neonatal mortality between 2008 and 2012 in a tertiary institutional hospital.[1] Survivors have a higher risk of both early and late neurodevelopmental alteration — including functional impairment, cognitive impairment and cerebral palsy —, in addition, serious events can have a significant effect on hearing function, cochlear damage and retrocochlear neuronal lesions.[2,3] With the use of body hypothermia therapy as a neuroprotective in the first 72 hours, it has been possible to improve the survival of neonates, as well as the neurological outcome in cases with moderate to severe Hypoxic-Ischemic Encephalopathy (HIE).[4] Liu et al. followed up for 7 years 325 HIE infants treated with hypothermia and found that at 18 months the risks of cerebral palsy were reduced, and scores on developmental indexes on the Bayley Scales of Infant Development II (BSID-II) and in the Gross Motor Function Classification System were improved.[5] However, although several meta-analyses have analyzed the prognostic capabilities of early clinical tests regarding neurological outcomes between 18 months and 3 years of age, the need for predictive markers has not yet been met.[4, 6]

Regarding auditory function, the brainstem is a region susceptible to damage when events that trigger HIE occur, since it can compromise the function of numerous nuclei, nerve tracts and the reticular formation, with a greater effect being observed in the rostral region of the brainstem.

Romero et al., determined the differences in brainstem auditory evoked potentials (BAEP), between infants with HIE with traditional treatment and healthy children, finding that in the HIE group all the waves showed higher latencies and intervals, moreover, concerning age, they presented faster latency shortening and amplitude increase, probably due to the reorganization process of the nervous system.[7]

Mietzsch conducted a pilot study in HIE newborns treated with hypothermia, and found that peripheral function measured by otoacoustic emissions was disrupted in the first week of life, and normalized by 3 weeks of age; although the BAEP were initially prolonged, especially in waves III and V, over the weeks the central transmission was intact, a behavior comparable to that observed in cardiovascular patients undergoing body hypothermia for surgery.[3]

In the present work, we describe the BAEP of infants with perinatal asphyxia classified with moderate and severe HIE, who received treatment with body hypothermia during the first 72 hours of extrauterine life, and its association with the development achieved at one and two years of age.

Methods

Prospective, descriptive and longitudinal study in which we analyzed the results of BAEP and development of infants with a history of moderate and severe HIE in the neonatal period treated with body hypothermia during the first 72 hours of life in the Neonatal Intensive Care Unit of the Ajusco Medio Hospital. After their discharge they were integrated in the Neurodevelopment Research Center of the National Institute of Pediatrics for follow-up. The BAEP study was performed at 3, 6 or 12 months of age; development was assessed with the Gesell, Bayley II, and Bayley III tests at 12 and 24 months of age. Two children with no measurable response in BAEP were excluded. The final sample included 51 children, from whom 107 BAEP records were obtained (45 at 3 months, 28 at 6 months, and 34 at 12 months of age). In all cases, the parents voluntarily agreed for their children to participate in the study by signing an informed consent letter (INP 075/2014).

The BAEPS were recorded with a Nicolet EDX-Viking equipment at a stimulation rate of 11.5 pulses per second, with a negative polarity click at 80dBHL, surface electrodes were placed according to the international 10-20 technique, with positive in vertex, negative in ipsilateral mastoids and ground in Fpz. The impedance of the electrodes was calibrated to be under 5 kΩ, analysis window of 25ms, and filters of 100-2500 Hz. Monaural stimulation was used, with contralateral masking at 40 dB HL below the stimulation level, averaging 2000 stimulations on two occasions.

All recordings were made during sleep, identifying the latency of waves I, III, and V, as well as interwave intervals I-III, III-V, and I-V, measured in milliseconds (ms); the amplitude of waves I, III and V in microvolts (μV) and the range V/I in percentage (%); the suspected cases presenting central and peripheral deterioration were determined following Pratt's criteria.8 Since there were no significant clinical differences in the side by side comparison, measurements of the right and left ear were averaged, obtaining a single value by indicator for each study. Statistical analysis. For BAEP, measures of central tendency ($\bar{x}$ and SD) were obtained by age group. The z-score was calculated from these measures, to homogenize and categorize the population as Normal —up to $\bar{x}\pm1$SD— or Altered when it was outside that range (prolonged interwave latencies and intervals $\bar{x}+1$SD; decreased amplitude $<\bar{x}$-1SD; and central suspect V/I range $<\bar{x}$-1DS and peripheral suspect $>\bar{x}+1$DS). Subsequently, the components of the BAEP and the scores of the 3 development tests (coefficient for Gesell, developmental index for Bayley II and composite score for Bayley III) were related by correlation and analysis of variance (ANOVA), using the parameters of the BAEP in z-score for the correlations and the categorization of Normality/Alteration for the analysis of variance. The statistical package JMP V.8.0 was used, the level of significance was set at 0.05

Results

The sample was composed of 51 children born at term, 67% of the cases were born vaginally, with the presence of meconium seen in 61%, 48% female and 52% male; the risk events with the highest representation were prolonged expulsive phase and fetal distress (41% and 35%, respectively), distributed by severity degree of asphyxia: 90.7% moderate and 9.3% severe.

The BAEP presented slightly prolonged latencies and interwave intervals in those under 3 months, which showed rapid changes to normal values as age increased, particularly in the most central portions (waves III and V); similarly, the initially small amplitudes had a tendency to increase, normalizing in the older groups. (Table 1)

BAEP and development (correlation). When reviewing the correlation between the components of the BAEP and the areas of development of the three tests at one year of age,

we found that the interval I-III was the indicator that showed the highest correlation with all Gesell and Bayley II areas; amplitudes I and III showed a relationship with all Gesell areas, except with language; wave V amplitude was only related to motor and adaptive. For Bayley III we only found association of the motor component with amplitudes III and V. (Table 2)

For the age cut-off of 2 years, the components of wave III strengthened their correlation with practically all areas of development included in the three tests, proven to be statistically significant. In addition, connections between specific areas of development were added: for Gesell, language was related to amplitude I ($p<0.01$) and, personal-social behavior was associated to interval III-V ($p<0.05$). In the case of Bayley II, the mental area was related to wave I (latency and amplitude) and V/I range, while the psychomotor area was associated to wave V (latency and amplitude) and I-V interval. The Bayley III test, which at the 1-year cut-off only showed a correlation between motor and amplitudes III and V, at 2 years displayed significant associations in its three areas with latencies and amplitudes I and III, intervals I-III and III -V, and with the range V/I; wave V did not showed statistically significant relationships. (Table 2)

Categorization. The indicators with the lowest Normal percentage were range V/I and interwave interval III-V (75.7% and 77.6%, respectively), while amplitude III had the highest percentage (93.5%); the rest of the parameters had at least 80% of normal cases. For the V/I range we present 2 categorizations: 1) the proposal by Pratt,8 from which we obtained a 10.2% with suspected deterioration (6.5% central and 3.7% peripheral), and 2) our proposal based on standardized values, through which we found 24.3% of suspects (15% peripheral and 9.3% central). (Table 3)

Table 1. Distribution of the PEATC components, total population and age groups

		Latency			Interwave Interval			Amplitude			Range
Age groups		I	III	V	I-III	III-V	I-V	I	III	V	V/I
Total	$\bar{x}$	1.66	4.03	6.22	2.38	2.18	4.55	0.25	0.31	0.26	127.23
(107)	ds	0.13	0.26	0.39	0.24	0.26	0.39	0.11	0.12	0.10	77.07
3 months	$\bar{x}$	1.68	4.23	6.52	2.54	2.28	4.82	0.22	0.28	0.23	126.42
(n= 45)	ds	0.13	0.21	0.30	0.21	0.25	0.35	0.09	0.11	0.08	81.08
6 months	$\bar{x}$	1.63	3.96	6.16	2.32	2.20	4.53	0.27	0.32	0.26	116.16
(n=28)	ds	0.12	0.20	0.28	0.17	0.25	0.26	0.11	0.13	0.09	64.86
12 months	$\bar{x}$	1.64	3.84	5.87	2.20	2.02	4.22	0.27	0.34	0.31	137.41
(n=34)	ds	0.15	0.20	0.23	0.17	0.21	0.25	0.13	0.13	0.11	81.60

Table 2. Correlation coefficients between the BAEP standardized parameters and the developmental tests scores by areas at 12 and 24 months of age

		12 months (n=107)										24 months (n=95)									
		Latency			Interval			Amplitude			Rel V/I	Latency			Interval			Amplitude			Rel V/I
		I	III	V	I-III	III-V	I-V	I	III	V		I	III	V	I-III	III-V	I-V	I	III	V	
Gesell	CGD	-0.015	-0.234	-0.115	-0.257 *	0.0786	-0.104	0.1837 *	0.1646 **	0.0386	-0.126	-0.031	-0.294 *	-0.109	-0.314 ***	0.148	-0.102	0.1732	0.1981 +	0.0584	-0.114
	M	-0.077	-0.274	-0.087	-0.262 **	0.1595	-0.052	0.2064 *	0.101 *	0.3096 *	-0.122	-0.026	-0.326 **	-0.121	-0.347 ***	0.158	-0.113	0.1383	0.0757	0.0075	-0.101
	A	-0.051	-0.232	-0.13	-0.239 0.07	0.0588	-0.102	0.2034 *	0.2132 **	0.1771 +	-0.126	-0.003	-0.228	-0.089	-0.262 *	0.1133	-0.087	0.1115	0.158 +	0.0669	-0.093
	L	0.1068	-0.127	-0.12	-0.204 **	-0.043	-0.154	0.0743	0.1074	-0.055	-0.104	-0.053	-0.253 *	-0.144	-0.259 **	0.0481	-0.134	0.2039 **	0.3643 ***	0.1691	-0.063
	PS	-0.007	-0.194 *	-0.099	-0.217 *	0.0614	-0.096	0.1824 ***	0.2016 **	0.0641	-0.119	-0.005	-0.263 +	-0.021	-0.288 **	0.2471 *	-0.03	0.1703	0.1161	-0.042	-0.163
Bayley II	Me	0.0644	-0.142	-0.058	-0.189 *	0.0616	-0.061	0.0816	0.2733 ***	0.0709	-0.042	-0.199 +	-0.307 *	-0.134	-0.238 *	0.1201	-0.071	0.3771 ***	0.3259 **	0.076	-0.222 ***
	Pm	0.0501	-0.194	-0.069	-0.236 **	0.0948	-0.069	0.0331	0.0055	0.056	0.0179	0.0028	-0.343 **	-0.216 *	-0.377 ***	0.0235	-0.21 *	0.1618	0.1511	0.1724 +	-0.063
Bayley III	C	0.0297	0.1334	0.095	0.0466	0.0341	0.1002	-0.077	0.0232	0.013	0.0288	-0.151 *	-0.282 *	-0.052	-0.237 +	0.2245 *	-0.011	0.358 **	0.2959 **	0.0742	-0.247 *
	L	0.1138	0.0152	-0.044	-0.05	-0.072	-0.075	0.0587	0.1229	0.1374	-0.004	-0.148	-0.298	-0.054	-0.259 *	0.2379 +	-0.009	0.4063 **	0.4027 **	0.0847	-0.189 *
	M	-0.068	-0.257	-0.056	-0.187	0.1726	-0.03	0.1847	0.1389 +	0.149 **	-0.0300	-0.149 *	-0.267 *	-0.1	-0.217 +	0.1284	-0.048	0.1931	0.1519	0.0258	-0.142

*p <0.05; **p <0.01; ***p <0.001; +p marginal

GCD: general coefficient of development; M: motor; A: adaptive; L: language; PS: personal-social; me: mental; PM: psychomotor; C: cognitive.

By associating the BAEP categories with the areas of the three development tests, we found that there exist differences between the groups of up to 13.93 points between development mean scores, presenting lower development scores in the groups with some type of alteration. Range V/I, amplitude I, interwave interval I-III and, to a lesser extent, latency III, were the indicators that showed significant differences between groups, both at one and two years. The rest of the BAEP indicators did not show significant differences, although the scores remained higher for those with normal BAEP parameters (Table 4). Similarly, the categorization of Pratt's V/I range did not show significant differences.

Table 3. Population distribution in categories based on the z score normality criterion. (n=107)

	Normal		Prolonged	
Latency	n	%	n	%
I	88	82.2	19	17.8
III	88	82.2	19	17.8
V	88	82.2	19	17.8
IInterwave interval	n	%	n	%
I-III	92	86.0	15	14.0
III-V	83	77.6	24	22.4
I-V	86	80.4	21	19.6
Amplitude	**Normal**		**Decreased**	
	n	%	n	%
I	89	83.2	18	16.8
III	100	93.5	7	6.5
V	89	83.2	18	16.8
Rango V/I	**Normal**		**Suspected impairment**	
			Central	**Peripheral**
	n	%	n %	n %
Pratt	96	89.7	7 6.5	4 3.7
std	81	75.7	10 9.3	16 15.0

Latency and intervals: Normal ≤ $\bar{x}$+1ds; Prolonged >$\bar{x}$+1ds
Amplitude: Normal ≥ $\bar{x}$-1ds; Decreased <$\bar{x}$-1ds
V/I range: Pratt: Normal 50-300%; Central <50%; Peripheral >300%

Discussion

Different studies have addressed the neuroprotective role of treatment with body hypothermia in perinatal asphyxia.[5,6] Its value in the auditory pathway was initially inferred from observations on other populations of patients subject to hypothermia, in which prolongation of conduction times has been described early, as well as the appearance of fast conduction times at older ages, described by some specialists as a compensatory recovery of the maturational pattern.

Although in our population —according to the BAEP records taken at 3 months—, the latencies and interwave intervals showed prolonged values compared to the group of healthy children of a similar age described by Romero, when compared with the group with perinatal asphyxia without hypothermia treatment described in that same study, we found that their means were lower at all times, and even remained close to the values of the healthy group,[7] which supports the use of body hypothermia as a protector of the auditory pathway.

Concerning the neuroprotective role of hypothermia in subsequent neurodevelopment, in our general population the development scores for the three tests at one year of age were within expectations, except for the language (Gesell) and psychomotor areas (Bayley II); however, the mean developmental scores at 2 years of age tended to be lower for the Gesell and Bayley II areas. Bayley III ratings remained relatively similar in both evaluations.

The link between development and functional parameters showed greater importance in the components related to wave III. In this regard, it has been observed that the conduction of the auditory pathway can be delayed in a variety of disorders, including focal damage (demyelination, ischemia, tumors) or diffuse lesions (degenerative disorders, posthypoxic damage, etc.) in any part of the auditory pathway between the generators of wave I (distal VIII nerve) and wave V (superior pons). Amid these alterations, interval I-III — representing the conduction from the cochlear portion of the eighth nerve through the subarachnoid space to the nucleus of the lower pons — has been shown to be susceptible to tumors, inflammation (including inflammation and hemorrhage in the subarachnoid space).[8] Our population had at least one imaging study (CT) during their stay at the Neurodevelopment Research Center and, in cases where it was considered necessary, a transfontanellar ultrasound was performed when they joined the follow-up program, finding that just over half of the cases had presented signs of edema and ischemia at some point.

As we did not have parameters to categorize the PEATC indicators, we resorted to the z-score for the cataloging of our population — setting the cut-off point at the first standard deviation—, in order to achieve a division point that allow us to identify the presence of alterations, from subtle to frank, and to use the BAEP findings as an indicator of risk for subsequent child development. Consequently, it was observed that those patients who had presented some alteration obtained lower scores in their development. Despite this, these results cannot be fully attributed to the presence of functional alterations

Table 4. Analysis of variance of the scores by area of development according to the BAEP components at 12 and 24 months of age.

		Latency III					Interwave interval I - III					Amplitude I					Relation V / I std				
		Normal		Prolonged		p	Normal		Prolonged		p	Normal		Decreased		p	Normal		Suspicion		p
	Gesell	x̄	ds	x̄	ds		x̄	ds	x̄	ds		x̄	ds	x̄	ds		x̄	ds	x̄	ds	
First year of development	CGD	84.0	13.7	76.5	19.6	*	84.2	13.6	73.7	20.8	**	84.4	13.0	74.0	21.4	**	85.4	13.2	74.2	17.7	***
	M	88.5	19.2	77.4	23.3	*	88.3	19.0	75.9	25.6	*	88.9	17.8	74.9	27.7	**	89.9	18.1	76.0	23.5	***
	A	87.4	14.3	81.1	22.6		87.5	13.9	78.9	25.2	*	88.4	13.5	75.8	23.0	**	88.7	14.0	78.8	20.0	**
	L	72.0	13.6	67.2	15.8		72.5	13.5	63.0	15.1	**	72.1	13.4	66.7	16.7		73.9	13.4	62.8	13.0	***
	PS	88.0	14.2	80.7	19.1	+	88.2	14.1	77.6	19.7	**	88.3	13.4	78.4	21.2	**	89.0	13.3	79.3	18.8	**
	Bayley II																				
	Me	81.7	13.4	77.5	14.2		81.6	13.4	76.9	14.0		81.8	13.0	76.6	15.7		82.7	12.5	75.6	15.5	*
	PM	74.1	14.9	71.3	17.5		74.7	14.6	66.8	18.7	+	74.7	15.0	68.2	16.7		75.6	14.4	67.4	16.9	*
	Bayley III																				
	C	99.0	14.0	100.0	18.5		98.9	14.2	100.5	17.4		100.5	12.7	88.4	22.1	*	99.9	13.8	96.4	16.8	
	L	86.7	11.8	80.8	14.1		86.5	12.3	82.7	11.4		86.9	12.1	79.3	11.3	+	87.3	12.4	81.8	10.6	
	M	88.2	12.6	80.7	19.0		88.2	12.6	81.4	18.9		88.3	12.4	80.3	20.2		89.0	12.8	82.0	15.2	+
Second year of development	Gesell																				
	CGD	77.8	12.2	73.1	21.0		78.2	12.1	69.5	22.1	*	78.5	10.9	68.1	24.3	**	78.8	10.8	70.8	20.8	*
	M	84.6	15.9	77.9	25.0		85.2	15.9	73.0	25.2	*	85.4	13.8	72.5	31.0	**	85.8	13.9	76.1	26.1	*
	A	80.5	11.5	76.8	22.5		80.9	11.5	73.1	23.7	+	81.2	10.5	72.1	25.3	*	82.0	10.1	72.8	21.0	**
	L	72.2	17.4	67.0	20.8		72.7	17.0	62.6	22.1	+	73.0	16.7	61.9	22.6	*	73.0	16.5	66.0	21.9	
	PS	73.0	11.0	68.2	18.4		73.3	10.8	65.5	19.6	*	73.5	9.9	64.9	21.6	*	73.7	9.9	67.2	18.3	*
	Bayley II																				
	Me	73.0	15.3	67.3	13.9		72.8	15.2	67.4	14.4		73.5	14.9	63.6	14.4	*	73.5	15.0	67.1	14.8	+
	PM	71.3	10.7	69.2	12.4		72.3	10.3	62.8	11.6	***	72.0	10.3	64.9	12.7	*	72.4	10.4	66.4	11.6	*
	Bayley III																				
	C	93.6	10.7	86.8	15.0	*	93.4	10.6	85.0	17.2	*	93.9	10.3	84.2	15.7	**	94.8	9.7	83.9	14.5	***
	L	86.4	12.1	77.2	15.7	*	86.0	12.6	76.5	14.7	*	86.1	12.5	78.4	15.2	*	86.5	12.4	79.0	14.5	*
	M	89.1	12.4	83.6	18.4		88.9	12.4	82.4	20.5		89.7	12.0	79.5	18.6	**	90.3	11.6	80.2	17.4	***

*p <0.05; **p <0.01; ***p <0.001; +p marginal

GCD: general coefficient of development; M: motor; A: adaptive; L: language; SP: social personnel; me: mental; PM: psychomotor; C: cognitive.

in the BAEP, since it must be considered that part of our population was subject to a double risk condition (biological and psychosocial) as they came from low and medium low socioeconomic strata.

For the V/I range, we initially used the parameter proposed by Pratt[8] to categorize the population; however, this only allowed us to identify subjects with frank alterations; who we anticipated might show developmental problems. With our z-score categorization, we once again extended the range from subtle to frank alteration, which shows it as an important indicator for predicting later developmental delay.

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Bioinformatic Analysis of Epigenomic Studies for Major Depressive Disorder

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Abstract

Background: Major depressive disorder (MDD) is a common psychiatric entity, being characterized by alterations in mood and in other clinical dimensions. Several epigenome-wide association studies (EWAS) for MDD have been published. Here, we aimed to identify common genes in EWAS and their convergence with multiple lines of genomic evidence. **Methods**: We carried out a computational analysis using data of EWAS, which included a meta-analysis for brain samples of MDD, a convergence analysis for brain and blood samples, and top results from available genome-wide expression and association data. Functional enrichment and protein-protein interaction network analyses were also performed. **Results**: The meta-analysis for brain samples detected a significant gene, FAM53B. A list of forty-four top differentially methylated (DM) candidate genes was found, including GRM8, *NOTCH4* and *SEMA6A*, in addition to known druggable genes. The binding-sites for brain-expressed transcription factors, CREB and FOXO1, were enriched in the top DM genes. The protein-protein interaction networks showed that DM genes for MDD, such as *RPRM* and *TMEM14B*, play a central role. **Conclusion**: In this study, we found integrative evidence for the possible role of novel candidate genes and pathways. These genes are involved in mechanisms of synaptic plasticity, which have been associated with several psychiatric disorders. Analysis of epigenetic factors have a great potential for the identification of the mechanisms involved in the pathogenesis of MDD, taking into account their possible role in the interaction between genetic factors and the environment.

Keywords: *Epigenomics, DNA Methylation, Psychiatric Genomics, Bioinformatics, Major depressive disorder.*

Introduction

Major depressive disorder (MDD) is a common psychiatric entity, being characterized by alterations in mood and in other clinical dimensions, which lead to functional impairment in patients.[1] MDD has an average 12-month prevalence of around 6%[1] and an estimated heritability of 35–45%.[2] A secondary analysis of available global data has shown that the number of incident MDD cases increased from 172 to 258 million in the 1990-2017 period, being one of the psychiatric disorders with the largest impact on burden of disease.[3]

In recent years, several genome-wide analyses have been carried out to identify the molecular risk factors associated with MDD,[2] as well as multiple genome-wide association studies (GWAS)[4] and genome-wide expression studies (GWES).[5] In this context, epigenetic mechanisms have been of interest in the study of the pathogenesis of MDD, as a possible way of finding the interaction between genetic factors and environmental variables (such as psychological stress).[6] Among several epigenetic factors, the analysis of DNA methylation levels has been studied for multiple psychiatric disorders, primarily because of the negative correlation that is found between DNA methylation in promoter regions (in CpG islands) and gene expression.[7]

Epigenome-wide association studies (EWAS) have appeared as important strategies for the analysis of DNA methylation

levels across the genome, based on available microarray platforms that include hundreds of thousands of probes.[6] Several EWAS for MDD and related phenotypes have been published,[8,9] but there is the need for a bioinformatic analysis of the convergence of results from several available EWAS with other genomic evidence.[5,10] In this study, we carried out a computational analysis of available genome-wide DNA methylation studies for MDD and their convergence with multiple lines of genomic evidence. In addition, we performed a meta-analysis for detecting differentially methylated genes in brain samples from subjects with MDD, considering the advantage of this approach to increase statistical power and to obtain more precise results through the combination of individual studies.[11]

Methods

Data processing and convergence analysis of EWAS in brain and blood samples

The NCBI GEO database, an online repository for microarray data,[12] was used to obtain raw data from available epigenome-wide association studies for MDD. Data from five EWAS were extracted from the following published articles: Guintivano, 2013;[9] Chen, 2014;[13] Murphy, 2017BA11 and Murphy, 2017BA25 (both from the same article)[14] and Crawford, 2018[15] (Table 1). The genome-wide DNA methylation data obtained were used to generate two groups for comparison (MDD patients and control subjects), which were then analyzed using the GEO2R tool[12] to identify the differentially methylated (DM) probes for each study. The annotation files from the NCBI GEO database were used for the mapping from microarray probes to human gene identifiers. Convergent differentially methylated genes in these studies were revealed using the Venn diagram tool (http://bioinformatics.psb.ugent.be/webtools/Venn).

Meta-analysis of EWAS in brain samples

Additionally, a meta-analysis was performed using the robust rank aggregation (RRA) method in the R program.[16] In this analysis, four studies that analyzed DNA methylation in brain tissue samples were included (Table 1). The R package "RobustRankAggreg" was employed following the previously described protocol.[17] For the current study, the list of significant DM genes identified by GEO2R was used, which were ranked according to their P values. The RRA method allows to integrate data from different studies and methodologies, and uses a prioritized list of genes.[16] An adjusted P value of <0.05 was considered significant in this analysis.

Table 1. Details of EWAS included

Author, Year	NCBI GEO	Tissue	Sample size	Platform	PMID
Guintivano, 2013	GSE41826	Frontal cortex	49 MDD and 49 controls	Illumina Human Methylation 450K Beadchip (GPL13534)	23426267
Chen, 2014	GSE38873	Cerebellum	17 MDD and 17 controls	Illumina Human Methylation 27K Beadchip (GPL8490)	25243493
Murphy, 2017BA11	GSE88890	Frontal cortex, Brodmann area 11	20 MDD and 20 controls	Illumina Human Methylation 450K Beadchip (GPL13534)	28045465
Murphy, 2017BA25	GSE88890	Frontal cortex, Brodmann area 25	17 MDD and 18 controls	Illumina Human Methylation 450K Beadchip (GPL13534)	28045465
Crawford, 2018	GSE113725	Whole Blood	49 MDD and 48 controls	Illumina Human Methylation 450K Beadchip (GPL13534)	29790996

Abbreviations: PMID: PubMed identifier; NCBI GEO: NCBI GEO database identifier.

Convergence analysis for common genes in EWAS and other genome-wide studies

Records of significant genes from genome-wide expression studies were extracted from a published meta-analysis of GWES for MDD patients and controls (amygdala, anterior cingulate cortex, cerebellum and prefrontal cortex).[18] Lists of significant genes were also extracted from genome-wide association studies for depressive symptoms,[19] personality traits[20] and for the case-control design for MDD.[21] The significant genes obtained from EWAS for MDD, GWAS for depressive symptoms, GWAS for case-control studies of MDD, GWAS for personality traits and meta-analysis of GWES for MDD were analyzed for their convergence, using an online tool (http://bioinformatics.psb.ugent.be/webtools/Venn). The genes found on convergence were compared with the following available lists: genes known to harbor mutations for neuropsychiatric disorders[22] and genes that are highly expressed in human astrocytes and oligodendrocytes.[23]

Enrichment analysis for convergent genes in EWAS

A functional enrichment analysis was carried out using the DAVID online tool, version 6.8,[24] for the following categories: Transcription Factor Binding Sites (TFBS) and Tissue Expression (GNF U133A). The significant genes (that were convergent in five EWAS) were compared with the rest of the genome by using a Fisher exact p value, including a correction for multiple testing using a False Discovery Rate (FDR) method. In the case of TFBS, the significant genes were analyzed for their convergence with transcription factors expressed in the brain.[25]

Protein-protein interaction network for convergent genes in EWAS

An examination of the experimentally validated protein-protein interactions (PPI) was conducted using the online database of the Human Interactome Project [26] for the significant genes that were convergent in EWAS included in this work. The program, Cytoscape 3.8.0,[27] was used to visualize these interactions, in which a connected subnetwork system, using >2 edges, was employed,[28] along with a degree filter (In + Out) of 30-292.

Results

Genome-wide DNA methylation data were extracted from 5 EWAS for MDD, which had samples from different brain regions and whole blood (Table 1). Significant genes from the five EWAS were analyzed; results showed one hundred and seventy-one genes that were differentially methylated in common between the 5 EWAS. Combinations of 4 EWAS identified sixty-five to six hundred and thirty-eight common DM genes (Figure 1, Table S1A). Also, we carried out a meta-analysis for studies performed in brain samples using the robust rank aggregation method. Only one gene, *FAM53B* (family with sequence similarity 53 member B), was identified as significant (Score: 3.3085, P= 0.0160).

A merging of convergent genes from EWAS for MDD with genes available from 1) GWAS for depressive symptoms, 2) GWAS for case-control studies of MDD, 3) GWAS for personality traits and 4) meta-analysis of GWES for MDD, resulted in a list of 44 top candidate genes (Table 2), including *NOTCH4* (Neurogenic locus notch homolog protein 4) and *SEMA6A* (Semaphorin-6A). A number of these 44 genes have been found to harbor mutations for neuropsychiatric disorders (Table S2), such as *COL4A2* (Collagen alpha-2(IV) chain) and *RELN* (Reelin); and to be enriched in astrocytes and oligodendrocytes (Table S2), such as *FAM107B* (Protein Family With Sequence Similarity 107 Member B) and *TNS3* (Tensin-3).

Figure 1. Overview of differentially methylated (DM) genes from five EWAS for MDD.

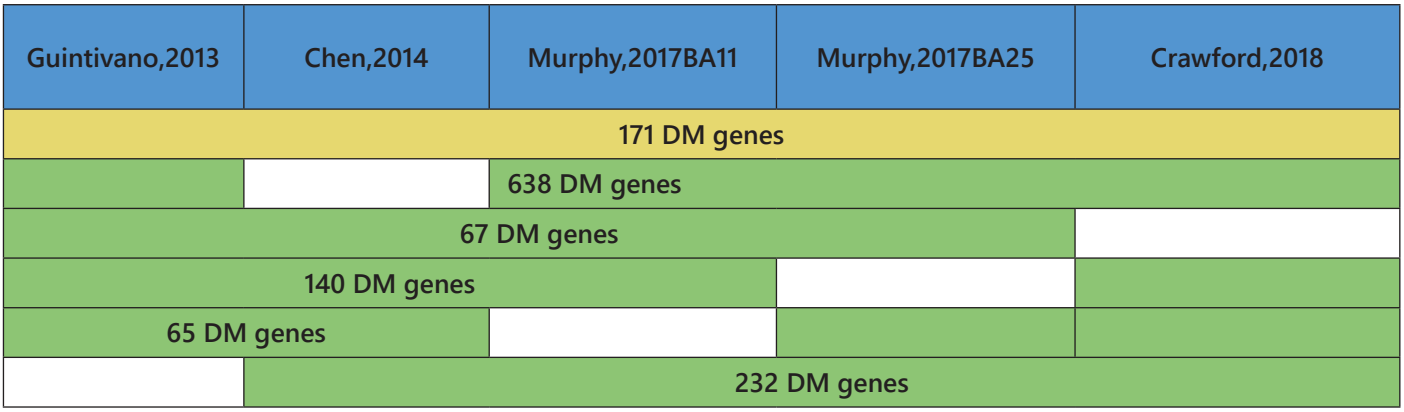


Table 2. Main top candidate genes. EWAS: EWAS for MDD; GWASD: GWAS for depressive symptoms; GWASM: GWAS for case-control studies of MDD; GWASN: GWAS for neuroticism; GWESM: GWES for MDD.

Gene	Protein Name	Evidence	Gene	Protein Name	Evidence
ASIC2	Acid-sensing ion channel 2	GWASD, GWESM	PIEZO2	Piezo-type mechanosensitive ion channel	GWASM, GWESM
C3orf70	UPF0524 protein C3orf70	GWASM, GWESM	PTDSS2	Phosphatidylserine synthase 2	EWAS, GWESM
CDO1	Cysteine dioxygenase type 1	GWASM, GWESM	RCAN2	Calcipressin-2	GWASN, GWESM
CPLX1	Complexin-1	GWASM, GWESM	RELN	Reelin	GWASM, GWESM
COL4A2	Collagen alpha-2(IV) chain	EWAS, GWASM	RPRM	Protein reprimo	GWASM, GWESM
DAD1	Dolichyl-diphosphooligosaccharide--protein	GWASN, GWESM	RYR2	Ryanodine receptor 2	EWAS, GWASM, GWESM
FAM107B	Protein FAM107B	EWAS, GWESM	SEMA6A	Semaphorin-6A	EWAS, GWASM
FHIT	Bis(5'-adenosyl)-triphosphatase	GWASD, GWASM	SMARCA2	Probable global transcription activator SNF2L2	GWASM, GWESM
GRM8	Metabotropic glutamate receptor 8	GWASM, GWESM	SSB	SPRY domain-containing SOCS box protein 2	EWAS, GWESM
IGSF21	Immunoglobulin superfamily member 21	EWAS, GWESM	STK39	STE20/SPS1-related proline-alanine-rich protein kinase	EWAS, GWESM
IL17RD	Interleukin-17 receptor D	GWASM, GWESM	TM7SF2	Delta(14)-sterol reductase TM7SF2	EWAS, GWESM
LOC102546299	[Uncharacterized]	GWASD, GWASM, GWASN	TMEM14B	Transmembrane protein 14B	GWASM, GWESM
LPCAT1	Lysophosphatidylcholine acyltransferase 1	GWASM, GWESM	TMEM241	Transmembrane protein 241	GWASM, GWESM
MRAP2	Melanocortin-2 receptor accessory protein 2	GWASM, GWESM	TNS3	Tensin-3	EWAS, GWESM
NCKAP1	Nck-associated protein 1	GWASM, GWESM	TRPM3	Transient receptor potential cation channel subfamily M member 3	GWASD, GWASM
NELL1	Protein kinase C-binding protein NELL1	GWASM, GWESM	TUSC3	Tumor suppressor candidate 3	GWASM, GWESM
NELL2	Protein kinase C-binding protein NELL2	GWASM, GWESM	UBA3	NEDD8-activating enzyme E1 catalytic subunit	GWASM, GWESM
NOTCH4	Neurogenic locus notch homolog protein 4	EWAS, GWASM	UNC13C	Protein unc-13 homolog C	GWASD, GWASM, GWASN
OFCC1	Orofacial cleft 1 candidate gene 1 protein	GWASD, GWASM	WIF1	Wnt inhibitory factor 1	GWASM, GWESM
PCP4	Calmodulin regulator protein PCP4	GWASM, GWESM	ZCCHC14	Zinc finger CCHC domain-containing protein 14	EWAS, GWASM
PEX5L	PEX5-related protein	GWASD, GWASM	ZCCHC24	Zinc finger CCHC domain-containing protein 24	GWASM, GWESM
PFKP	ATP-dependent 6-phosphofructokinase, platelet	EWAS, GWESM	ZIC2	Zinc finger protein ZIC 2	EWAS, GWESM

A functional enrichment analysis found an enrichment of binding-sites for brain-expressed transcription factors (Table 3), such as CREB (cAMP responsive element binding protein), FOXO1 (forkhead box O1), and *ZIC1* (Zinc family member 1). In addition, an analysis of the 44 candidate genes showed an enrichment of tissue expression as well, such as Pituitary and Olfactory Bulb (Table 3). A PPI network visualization showed that candidate genes for MDD, such as *TMEM14B* (transmembrane protein 14B) and RPRM (reprimo, TP53 dependent G2 arrest mediator homolog), play a central role in this network (Figure 2).

Table 3. Functional enrichment analysis of top DM candidate genes from EWAS for MDD. TFBS: Transcription Factor Binding Sites; GNF_U133A_QUARTILE: Expression in Multiple tissues.

Category	Term	P value	FDR
UCSC_TFBS	LHX3	9.39E-05	0.009014
UCSC_TFBS	FOXO3	2.92E-04	0.014018
UCSC_TFBS	RP58	6.78E-04	0.015651
UCSC_TFBS	ISRE	6.83E-04	0.015651
UCSC_TFBS	AP2REP	8.15E-04	0.015651
UCSC_TFBS	CDPCR3	0.001284	0.01727
UCSC_TFBS	FAC1	0.001571	0.01727
UCSC_TFBS	CART1	0.001609	0.01727
UCSC_TFBS	HNF1	0.001684	0.01727
UCSC_TFBS	P53	0.00194	0.01727
UCSC_TFBS	IRF2	0.002141	0.01727
UCSC_TFBS	SRY	0.002348	0.01727
UCSC_TFBS	TGIF	0.002659	0.01727
UCSC_TFBS	NFE2	0.002698	0.01727
UCSC_TFBS	CREB	0.00319	0.019138
UCSC_TFBS	AP1	0.003655	0.019969
UCSC_TFBS	IK3	0.004006	0.019969
UCSC_TFBS	ZIC1	0.004134	0.019969
UCSC_TFBS	SREBP1	0.004247	0.019969
UCSC_TFBS	HFH1	0.004501	0.019969
UCSC_TFBS	GATA	0.004576	0.019969
UCSC_TFBS	CDC5	0.004903	0.020465
UCSC_TFBS	TAL1BETAITF2	0.005666	0.022002
UCSC_TFBS	CDPCR1	0.00573	0.022002
UCSC_TFBS	FOXO4	0.006855	0.025311
UCSC_TFBS	STAT3	0.007589	0.026549
UCSC_TFBS	BRACH	0.007743	0.026549
UCSC_TFBS	AREB6	0.009089	0.028731
UCSC_TFBS	FOXO1	0.009868	0.028731
GNF_U133A_QUARTILE	Olfactory Bulb	1.24E-04	0.002084
GNF_U133A_QUARTILE	Dorsal root ganglia	6.72E-04	0.007502
GNF_U133A_QUARTILE	Pituitary	0.005969	0.047689

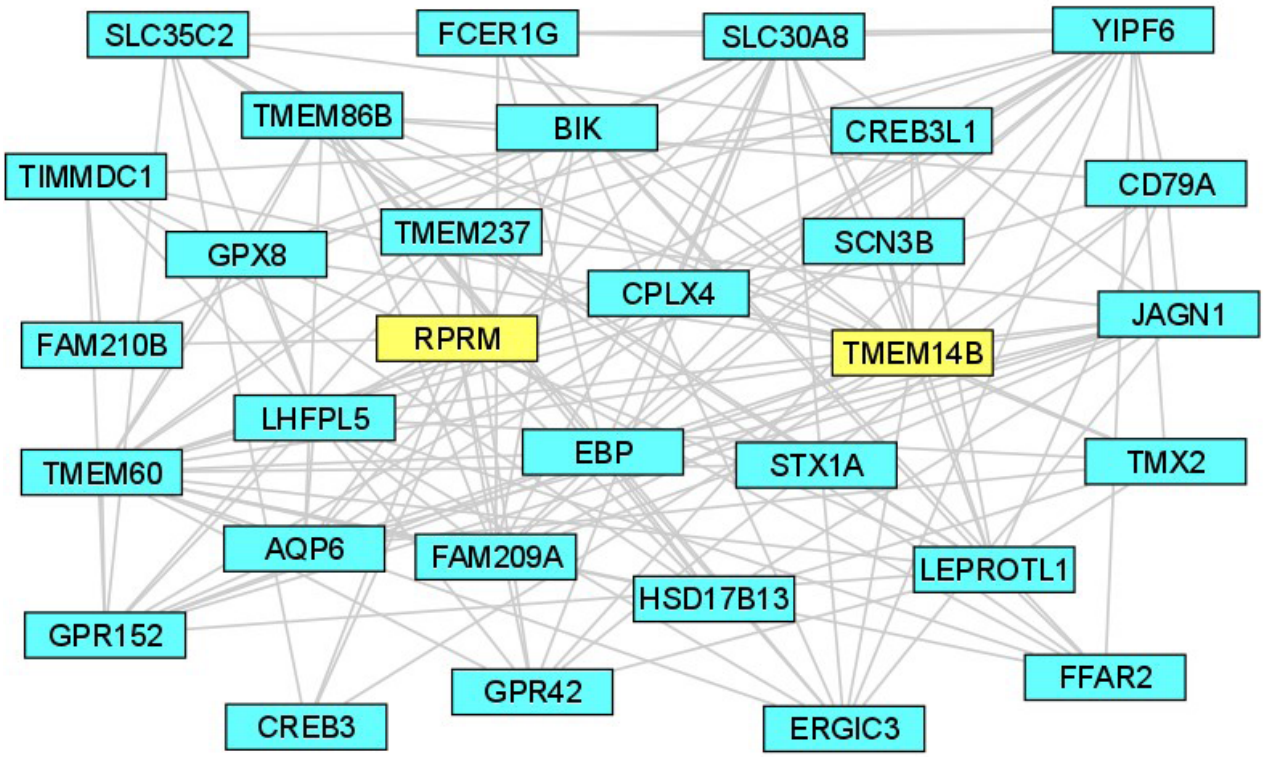
Discussion

Epigenetic factors have been of particular interest in the analysis of the mechanisms involved in the pathogenesis of MDD, considering the possible interaction between genetic factors and the environment.[6] Multiple epigenome-wide association studies for major depression and related phenotypes have been carried out and published in recent years.[6] A bioinformatic analysis of the convergence of results from several available EWAS with other genomic evidence[10,29,30] (D. A. Forero et al., 2017; Niculescu & Le-Niculescu, 2010) can be helpful for the identification of novel genes and pathways for MDD.

In this study, we found integrative evidence for the possible role of novel candidate genes and pathways. Key candidate genes such as *NOTCH4* and *SEMA6A* were found in convergence with those identified in GWAS and GWES. These genes are involved in mechanisms of synaptic plasticity, which have been associated with several psychiatric disorders.[18,31,32] Among the candidate genes found in this investigation, genes which harbor mutations for neuropsychiatric disorders, such as *COL4A2* and *RELN*, have been identified; as well as genes that are highly expressed in astrocytes and oligodendrocytes, such as *TNS3* and *FAM107B*. Furthermore, binding-sites for brain-expressed transcription factors, such as FOXO1 and CREB, are of particular importance, given the previous evidence of involvement in pathophysiology of depression[33,34] — with genes such as *TMEM14B* and *RPRM* observed to play a key role in the protein-protein interaction network.

Previously, Uddin et al found a difference in genome-wide DNA methylation patterns between unaffected and depressed individuals. Functional enrichment showed that methylated and unmethylated genes affect brain development, depending on specific pathways.[35] A study involving post-mortem frontal cortex samples found similar results for genes such as *CPSF3*, *LASS2* and *PRIMA1* having different methylation profiles.[36] Studies with candidate genes have complemented results from EWAS for MDD. A study with MDD patients showed higher levels of methylation at the *BDNF* gene.[37] Another case-control study also showed *BDNF*, *FKBP5*, *CRHBP* and *NR3C1* gene promoters to be significantly hypermethylated in MDD.[38]

Figure 2. Protein-protein interaction network for top candidate genes. Top DM candidate genes from EWAS for MDD were used. A highly connected subnetwork is shown and candidate genes are highlighted in yellow.



It is important for future MDD EWAS to be carried out in other regions of the world (such as Latin America or Africa),[18] that have millions of depression patients.[3]

Concerning the meta-analysis performed in this study, a DM gene, the *FAM53B*, was identified; which encodes a protein that is necessary to regulate the β-catenin-dependent Wnt signal transduction.[39] A GWAS has detected a variant in this gene as a risk for cocaine dependence in African-and European-American subjects.[40] Additionally, other polymorphisms in *FAM53B* are also associated with MDD and Alzheimer´s diseases.[41] Moreover, in a study that analyzed the effects of smoking on DNA methylation, a significant result for 525 genes including *FAM53B* was found.[42] These findings suggest that this gene could play an important role in the molecular mechanisms of different brain disorders. Interestingly, *FAM53B* was convergent with the study performed by Crawford, 2018, that analyzed DNA methylation in whole blood samples (Table S1). Despite the existence of additional EWAS performed in whole blood samples for depressive symptoms in middle-aged and elderly persons,[8] its raw data is unavailable and it was not possible to include their results in our study.

The number of EWASs included is one of the limitations of this study, as several primary EWAS do not have their data publicly available. Comprehensive meta-analyses of available EWAS could be performed if academic journals request for the public availability of such raw data.[28,43] Development of user-friendly computational tools would also facilitate such meta-analyses of large volumes of epigenomic data.[44]

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IntraoperativeNeurophysiological Monitoring: What the Anesthesiologist Should Know. Narrative Review

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Abstract

Intraoperative neurophysiological monitoring (IONM) allows monitoring and evaluating the integrity of the motor and sensory systems in procedures that put the nervous system (NS) at risk and prevents complications. For an appropriate IONM, it is fundamental to comprehend current techniques, how they work, as well as the influence of anesthetics and other variables on the records.

Objective: Review peer-reviewed publications; identify and describe the main IONM techniques and the impact of anesthetic and perioperative management on them.

Methods: A systematic and narrative search and review was carried out in English and Spanish in the Medline, Scopus and PubMed databases, using the MeSH terms: "Intraoperative Neurophysiological Monitoring"; "Anesthesia"; "Neuroanesthesia"; "Perioperative Management"; " Neurological surgery", "Complications", "Safety".

Results: Current national and international clinical guidelines for intracranial and spine surgery recommend multimodal IONM to evaluate the functional integrity of the NS and reduce complications. Total intravenous anesthesia (TIVA) with propofol is recommended as the technique of choice for a better recording of motor evoked potentials (MEP) and somatosensory evoked potentials (SSEP).

Conclusions: It is essential to understand the clinical bases of the different IONM techniques and to interpret alerts and alarm criteria in a timely manner to obtain optimal surgical results and prevent neurological injuries. The neuroanesthesiologist must ensure an adequate state of anesthetic depth, physiological, hemodynamic and cerebrospinal perfusion pressure stability, avoiding modifications that could alter the recordings.

Keywords: *Anesthesia; Neuroanesthesia; Intraoperative Neurophysiological Monitoring; Neurological surgery; Complications; Safety*.

What do we know about this problem and what is the contribution of this study?

Despite the wide circulation and recommendation of the use of IONM by international guidelines, there is little diffusion and understanding among anesthesiologists about techniques, objectives, importance, and impact of anesthetic and perioperative management.

This study identifies and describes the main IONM techniques, as well as the impact of drugs, hemodynamic variables, anesthetic and perioperative management on IONM — all essential knowledge for every anesthesiologist.

Introduction

Intraoperative neurophysiological monitoring (IONM) allows the identification of nerve structures, as well as real-time monitoring and evaluation of the functional integrity of the cerebral cortex, brainstem, spinal cord (SC), nerve roots, and cranial and peripheral nerves, avoiding motor and/or sensory postoperative deficits — transient or permanent — in procedures that put the nervous system (NS) at risk, through various neurophysiological techniques.[1-6] To ensure adequate monitoring, it is recommended to record baseline or reference and control waveforms.[1]

Due to the influence of most anesthetics on the inhibitory pathways,[3,7] the knowledge and understanding of the main IONM techniques and the impact of anesthetic management and various physiological variables on the recordings is crucial for optimal results.

Methodology

A systematic and narrative search and review was undertaken in the Medline, Scopus and PubMed databases — in English and Spanish — using the MeSH terms: "Intraoperative Neurophysiological Monitoring"; "Anesthesia"; "Neuroanesthesia"; "Perioperative Management"; "Surgery neurological"; "Complications"; "Safety". Narrative statistics and recommendations based on the results are presented.

Results

IONM is a useful technique for evaluating the neurological status of patients under general anesthesia.[8] For over 30 years, it has been used to detect and prevent injuries in various intracranial and spinal surgeries.[3,9,10] It is effective to identify a possible peripheral nerve injury, predict risk of paraparesis, paraplegia and quadriplegia (sensitivity 100%; specificity 91%); predict improvement of the facial nerve in facial hemispasm surgery and guide the resection of epileptogenic areas in epilepsy surgery.[5] Likewise, it is used in endonasal surgery and resection of skull base tumors, for identifying and reducing the risk of cranial nerve injury or critical neurovascular structures;[11-12] prevention of ischemic complications and neurological deficits in endovascular[13] or surgical[14-15] management of intracranial aneurysms; prevention and prediction of perioperative neurological deficits in posterior fossa surgery,[16] aortic[1,17] or thoracic spinal fusion surgery.[9]

Its use has been more widespread in spinal surgery, in which, despite favorable results, nerve elements can be damaged by direct (compression, traction, section laceration, avulsion) or indirect mechanisms (ischemic phenomena due to vascular elongation or compression of the spinal cord), and generate complications secondary to surgical treatment.[18-20]

The recording of evoked potentials (EP) represents the electrophysiological technique with the greatest capacity to provide quantitative, objective and opportune measurements for monitoring the functional integrity of the SC, nerve roots, along with adequacy of the vascular supply to these elements,[4,9,21] since it allows rapid and real-time recognition of functional changes in motor, sensory and nerve structures pathways that comprise them (anterior tracts and posterior cords).[5, 21-22]

Solid Class I evidence ratifies its use —including recording of somatosensory evoked potentials (SSEP) and transcranial motor evoked potentials (TcMEP)—, as a reliable diagnostic adjunct, as well as a valid method to assess SC integrity in the perioperative setting of column surgery.[23]

Multimodal IONM is the combination of different neurophysiological techniques and is the gold standard for preventing and reducing the incidence of postoperative neurological complications[24-26] (Figure 1); the combination of SSEP (Figure 2) and MEP (Figure 3) through sensory and motor cortex stimulation evaluates transmission pathways through the recording of the evoked response (Figure 4), which can suggest modifications during the procedure, detecting, preventing and reducing the incidence of postoperative neurological deficit up to 60% in spinal surgery[22,26] with proven benefit in scoliosis correction;[9,27-29] and as a routine component in surgeries for deformities or intramedullary tumors, reducing complications and maximizing adequate resection.[23]

Despite the evident advantage of IONM to reduce expenses derived from possible complications,[5] the cost-benefit in anterior cervical fusion surgery is considered controversial,[8,30] whereas in the rest of the spine procedures, in duly justified cases, it can be a useful, valid and sensitive tool to detect neurological damage in high-risk conditions or with pre-existing myelopathy, especially with the use of multimodal IONM,[4] provided that it is used as a diagnostic tool and not a therapeutic one.[23]

Current international clinical guidelines recommend multimodal IONM to assess the functional integrity of the NS, SC and nerve roots.[1, 23, 31-32] In Mexico, the Clinical Practice Guide for the Implementation of IONM establishes the degrees of recommendations and levels of evidence for practice.[6]

Figure 1. Multimodal monitoring

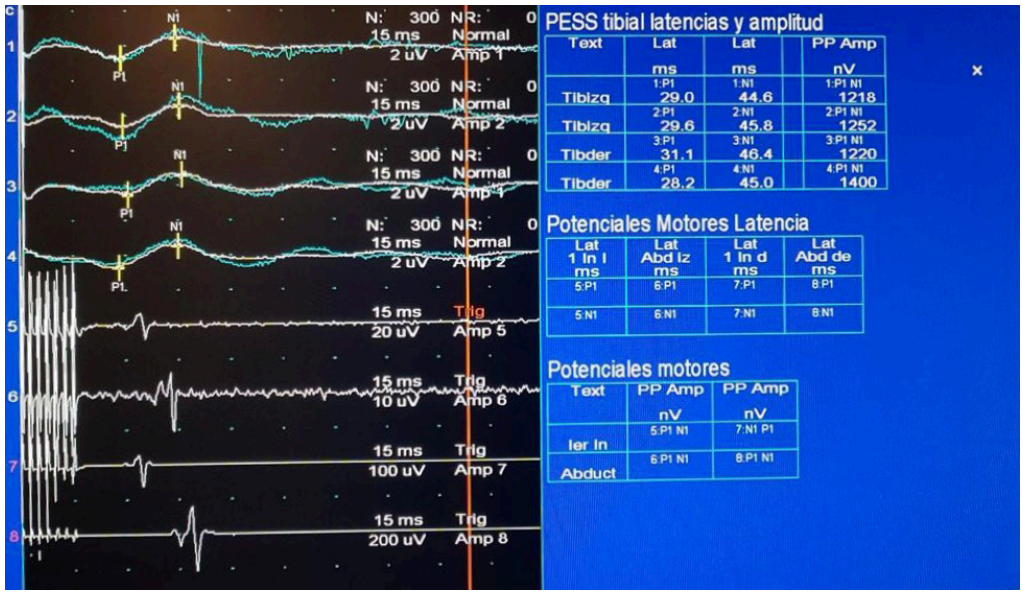


Figure 2. Somatosensory evoked potentials

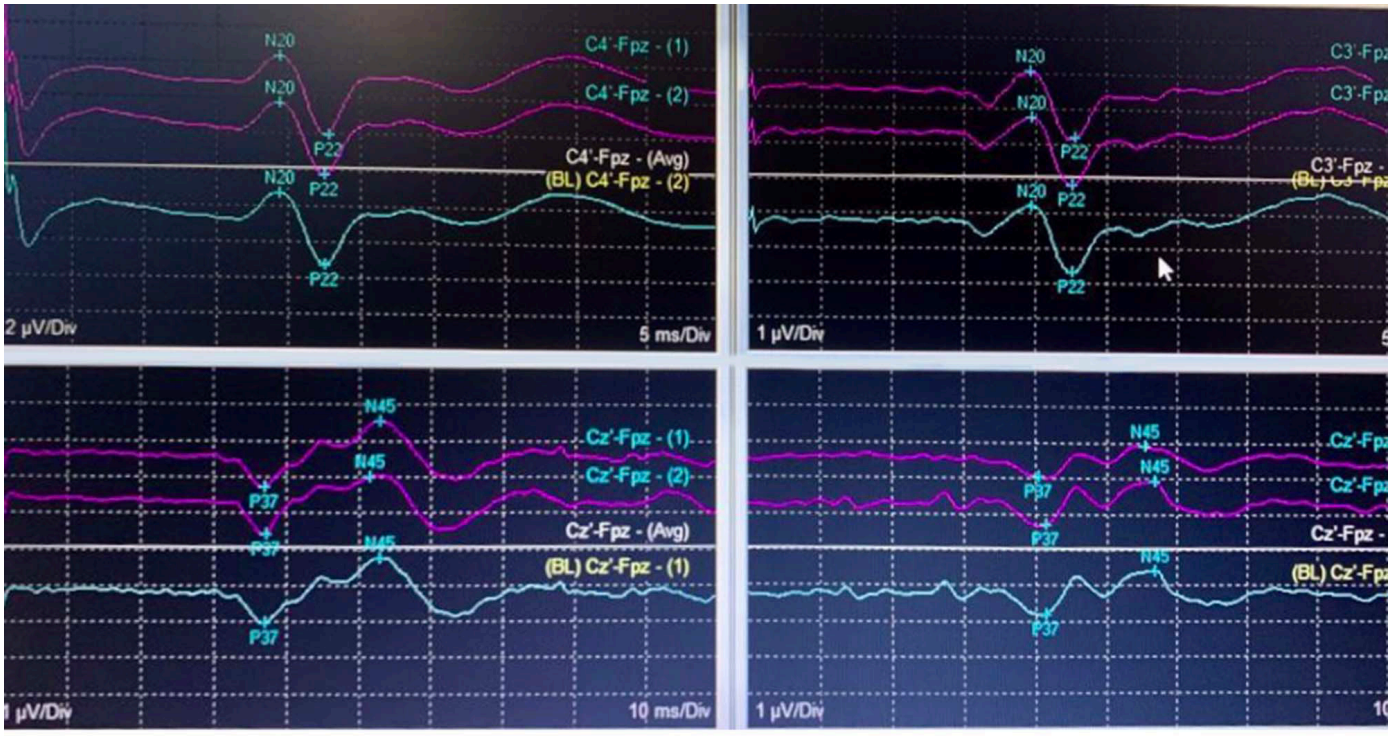


Figure 3. Motor evoked potentials

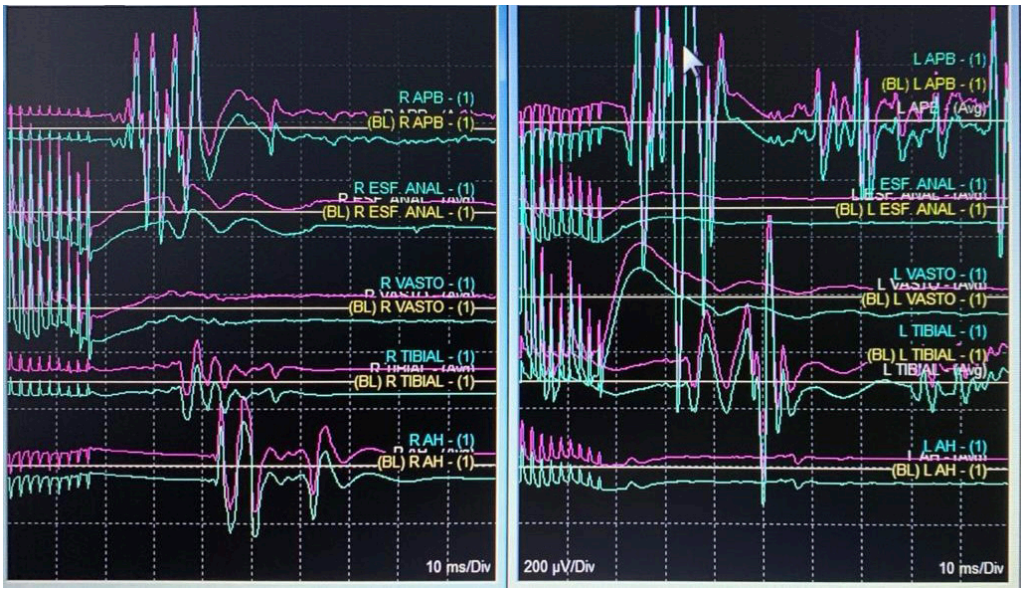
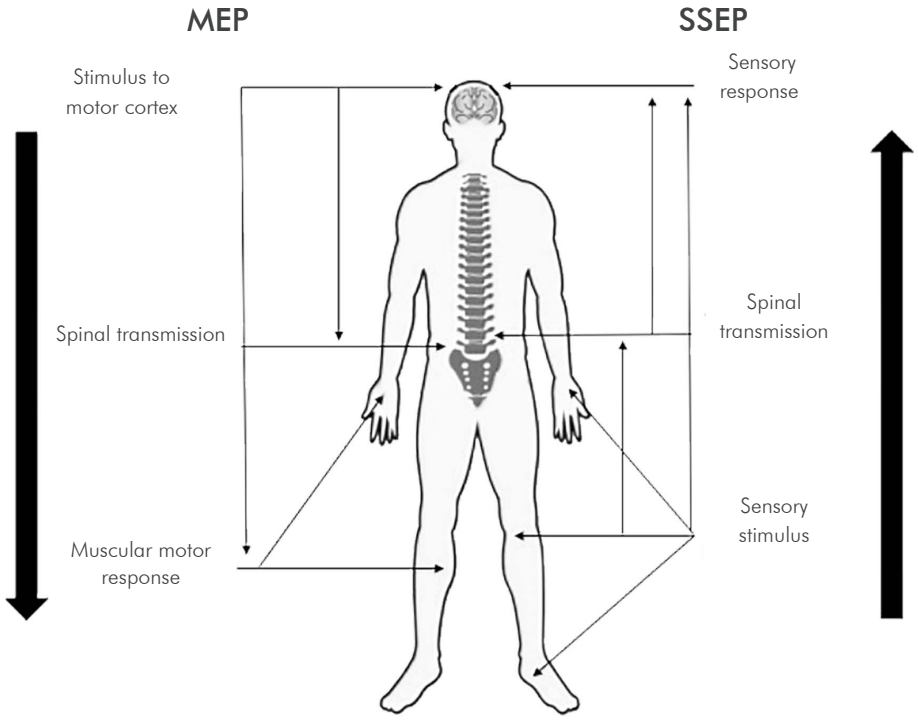


Figure 4. Direction of motor and sensory transmission pathways stimulation in motor and sensory evoked potentials



There are at least eight methods for monitoring SC and spinal nerve root functions during surgical procedures:[33]

1.SCEP: spinal cord evoked potential recorded after its stimulation.
2.SSEP: somatosensory evoked potential with cortical recording after stimulation of a peripheral nerve.
3.SSEP: Somatosensory evoked potential recorded in SC after stimulation of a peripheral nerve.
4.Spinal cord MEP: Transcranial electrical or magnetic stimulation (single pulse) in the motor cortex and recording of the response (D and I waves) in SC with an epidural or subdural electrode.
5.Transcranial motor evoked potentials (TcMEP): Transcranial electrical stimulation (motor cortex) multipulses (train of 5-7 stimuli) and response recording in peripheral muscles.
6. Spinal MEP: SC stimulation and recording in peripheral muscles.
7. Continuous electromyography: recording in rostral and caudal myotomes and muscles innervated by motor roots that emerge at procedure level.
8. Evoked Electromyography: Identifies nerve structures, confirms their integrity, conduction status and proper placement of pedicle screws. It stimulates motor roots at the procedure area, surrounding bone structures, and/or pedicle screws.

Monitoring is specific to the area related to the procedure, such as recurrent laryngeal nerve (RLN) monitoring in thyroidectomy or anterior cervical fixation/decompression surgeries, in which EMG electrodes are attached to the endotracheal tube and placed at the level of the vocal and arytenoid muscles for monitoring.[2]

The complete disappearance of SSEP is associated with limb paralysis and flaccidity,[21] an increase in latency >10% and/or decrease in amplitude >50% in SSEP and 50-100% in MEP compared to the baseline value constitute "**alarm criteria**", indicative of lesion risk in the ascending sensory or descending motor pathway, respectively, which requires timely intervention to avoid permanent damage.[14,21,26] These alarm criteria depend on factors such as response variability, type of anesthesia, positioning and nerve injury,[26,34] presence or absence of pre-existing neurological injury and surgical, metabolic and physiological events at the time of decrease or disappearance, such as mechanical or compressive trauma, or changes due to ischemia, hypoxia, hypotension, hematocrit <15%, hypothermia <32°C, hyperthermia >42°C, PCO2 <20 mmHg, or decrease with ICP >25 mmHg or disappearance with ICP >30 mmHg(17, 35). Loss of signals or reversible decreases (<30-40 min) can predict the absence of new postoperative deficits, while prolonged decreases (>40-60 min) can indicate a risk of permanent injury.[18-19]

In the event of changes in the IONM during surgery, the information must be shared among the multidisciplinary team and measures taken to find and eliminate the cause (LE:1C), whether surgical, due to failure or disconnection of the neuromonitoring or anesthetic equipment as a result of changes in physiological variables, due to anesthetics dose or level of hypnosis (LE: 1D).[1] Once the alteration is identified, it is recommended that the decision to continue the procedure is taken by the entire team. Signal improvement is a predictor of favorable neurological outcome, particularly for SC decompression surgery.[22]

Somatosensory evoked potentials (SSEP)

They were first used in the 1970's to monitor SC function in scoliosis correction. Following stimulation of peripheral mixed nerves, responses are recorded at various points in the somatosensory pathway (peripheral, subcortical, and cortical responses).[24,26]

As an electrophysiological response to a sensory stimulus of the NS, SSEP provide functional and locational information about the somatosensory system, and are the most widely used monitoring modality.[16] They are indicated for any surgery that puts the proprioceptive pathway at risk and to complement the monitoring of MEP.[32]

The afferent pathway begins with receptors in skin, muscle, and tendons, rapidly conducting thickly myelinated afferent Ia fibers, and the first neurons (unipolar or pseudomonopolar) located in the dorsal root ganglion. Neuronal axons travel in the ipsilateral dorsal column to the cervicomedullary junction. At this site they synapse with the second neurons located in the gracile nuclei (medial), for legs, and cuneiform (lateral), for arms. Second neurons axons cross to the opposite side and subsequently travel as a medial lemniscus reaching the ventral posterolateral nucleus of the thalamus, where they synapse with the third neuron, and axons of these neurons reach the primary parietal sensory cortex.[36] The stimulus is performed in a mixed peripheral, median or ulnar (upper limbs) and tibial or peroneal (lower limbs) nerve and electrodes are placed at specific sites along the somatosensory pathway to record electrical responses.

The dorsal proprioceptive pathway conveys discriminative touch, vibration, and proprioception, while the anterolateral exteroceptive pathway conveys pain, temperature sensation,

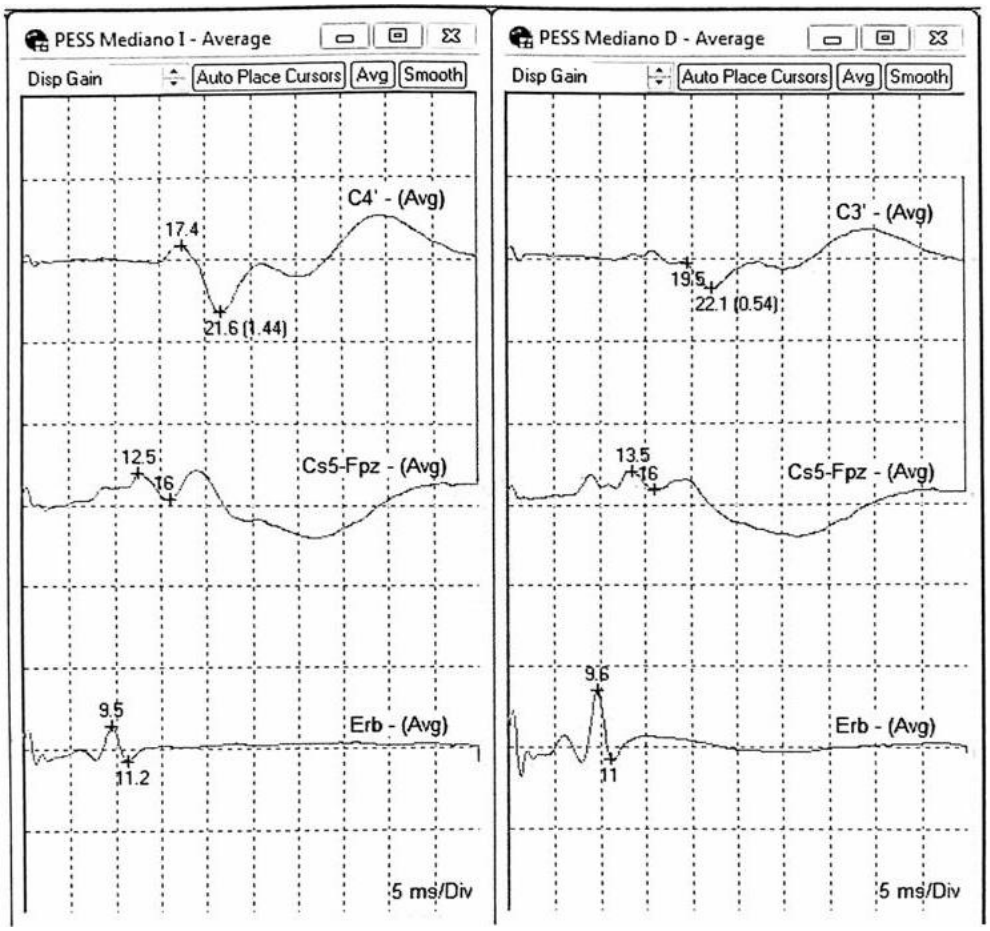
and superficial touch. This technique does not evaluate the anterolateral system because the axons are thinner, with higher thresholds, and slower and more variable conduction. The nerves stimulated will depend on the location of the surgical site.[32]

The nomenclature to designate the peaks and troughs of the SSEP waveforms is by means of a letter that represents its polarity; an ascending deviation means negative polarity (N), a descending one is positive (P); a number is also assigned based on the latency (time between the stimulus and the response), which is measured in milliseconds (ms);[17] similarly, the amplitude represents the number of functional fibers —these last two, amplitude and latency, are used to demonstrate changes in neuronal activity. The peaks called N20 and P22 result from the stimulation of the median nerve, of thalamic and cortical origin, whereas the cortical responses are P37 and N4536 correspond to the posterior tibial nerve or the peroneal nerve (Figure 5).

Intraoperative injury causes acute neuronal or axonal disruption that primarily reduces the amplitude of the SSEP and has less effect on latency. Demyelination increases latency and produces less effect on amplitude; amplitude is the main parameter to consider in intraoperative monitoring.[32,36]

Cortical SSEP responses of the median nerve are generated by the primary somatosensory cortex supplied by the middle cerebral artery and are useful for detecting ischemia associated with aneurysm clipping during temporary internal carotid occlusion. The tibial nerve has been used in ischemic events associated with anterior cerebral artery aneurysms.15 Cortical SSEP amplitude decreases with regional CBF <20 ml/min/100 g and is completely lost with <15 ml/min/100 g.17 An abrupt loss of the cortical SSEP response (<1 min after clipping)15 or decrease in MEP amplitude >50% can predict postoperative neurological dysfunction.[14]

Figure 5. SSEP of upper limbs



In posterior fossa surgery there is a high risk of brainstem injury; in this regard, SSEP are useful for monitoring the integrity of the medial lemniscus.[16] In carotid endarterectomies, the use of electroencephalogram (EEG), MEP, and SSEP of the median and tibial nerve is recommended for arterial bypass decisions, intraoperative brain neuroprotection, and risk reduction of cerebral ischemia.[5]

Unilateral amplitude decrease in upper extremity SSEP responses with or without MEP impairment detects peripheral nerve or brachial plexus conduction abnormality in 2% to 3% of scoliosis surgeries.[27] Descending aortic procedures have a high risk of SC infarction and paraplegia by temporarily or permanently interrupting blood flow; in this cases IONM detects incipient ischemia prior to permanent damage.[17]

Motor Evoked Potentials (MEP)

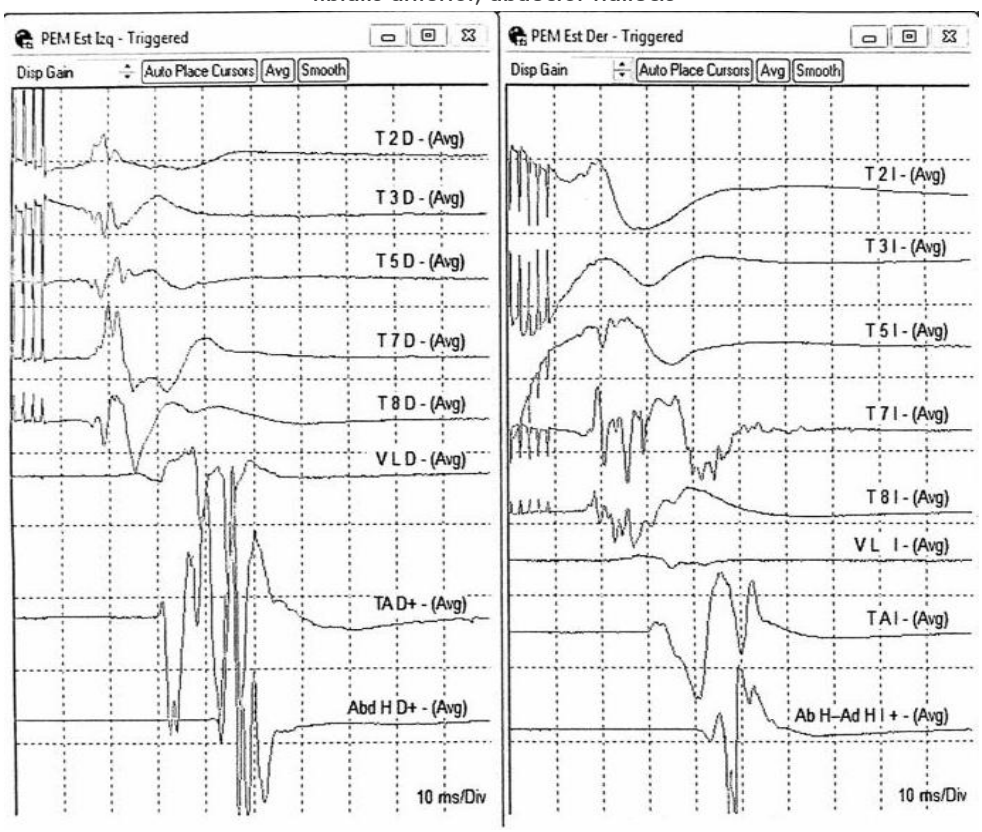
They evaluate functional integrity of the motor pathway, through transcranial electrical stimulation and depolarization of corticospinal neurons; descending impulses are recorded in SC and extremities[2] (Figure 6).

In 1980, Merton and Morton recorded muscle action potentials after transcranial motor cortex stimulation in humans, prompting the development of SC monitoring.10 Subsequently, in the 1990s, muscle motor evoked potentials (mMEP) and epidurals (eMEP or D wave) were introduced.[24]

MEP can be spinal, neurogenic and muscular, they facilitate a selective and specific evaluation of the integrity of the motor pathway, from the cortex to the peripheral nerve fibers and muscles,[24] and allow detecting the functional integrity of the corticospinal pathway with high sensitivity and specificity.[25] Monitoring of the motor system can be performed by short-train transcranial stimulation (5-7 stimuli) or single stimulation with recording in SC.[33] Lesions of axons, neurons or motor support systems show a threshold that ranges from the reduction of amplitude until its disappearance.[32]

The disappearance of the mMEP response does not always indicate permanent motor deficit; the sensitivity of PEM monitoring to detect decreased cerebral blood flow (CBF) in aneurysm surgery has already been validated,[14] but its sensitivity

Figure 6. Lower extremity motor evoked potentials, T2, T3, T5, T7, T8, vastus lateralis, tibialis anterior, abductor hallucis



to ischemic aggression and spinal cord compression is high, so false positives increase if the trial is based solely on this potential.[33] A >50% decrease in eMEP amplitude (D wave) correlates with postoperative motor deficit; variations in mMEP and eMEP amplitude allow predicting postoperative motor function.[24]

Spinal cord evoked potentials

Developed in Japan in the 70's, they consist of the stimulation of the SC with an epidural electrode, recording a proximal or distal response, which corresponds to the sum of neuronal activities originating in ascending and descending tracts near the recording electrode.[33]

Stimulation can also be performed cranially and recorded caudally or vice versa. Due to the different conduction properties (speeds) of the SC pathways, the recorded potentials take the form of two different waves. The recorded potentials are very robust and represent combined activity of the dorsal columns (DC), corticospinal tracts, and other spinal cord pathways. This method is largely abandoned, but retains value in severe pre-existing neuropathies, research, or when determining the degree of conduction is important.

Electromyography

It is the real-time graphic recording of muscle electrical activity, in order to evaluate the integrity of nerve structures. Two variants are used intraoperatively with different purposes: continuous and evoked EMG; two subdermal needles are placed 2-3 cm apart into the muscle innervated by the peripheral nerve, cranial nerve, or nerve root involved in the procedure.

Continuous EMG: Myogenic activity is recorded to show if a nerve structure is being damaged (nerve irritation or injury). It is based on the property of the motor nerve to respond to thermal or mechanical injury with the consequent activation of the muscles innervated by said nerve.

Evoked EMG: Direct or indirect electrical stimulation is used to identify a nerve structure, demonstrate its integrity and/or estimate the degree of injury; it allows corroborating the adequate placement of the pedicle screws (PS) by means of indirect stimulation of a nerve root. When the PS is poorly placed, medially or laterally, or there is a fissure in the pedicle, the electric current in the head of the PS spreads and stimulates the adjacent root, obtaining a compound muscle action potential at low amperage. If the PS is well placed, it will be surrounded by bone resistant to the passage of current, it will not stimulate the adjacent root and there will be no responses. Safety values vary depending on the spinal segment involved.

Nerve action potential (NAP)

It is one of the most useful techniques in peripheral nerve procedures, since it provides fast and reliable information on the status of peripheral nerves during surgery. It is useful for detecting regenerating peripheral nerve axons and determining the corresponding surgical action in a procedure.

It can be recorded with stimulation and recording electrodes placed directly on the nerve. Stimulation is done with a tripolar electrode that allows the current to be concentrated, minimizing its spread; recording is done with a bipolar electrode.

Anesthetics and their influence on intraoperative neurophysiological monitoring

Most anesthetics increase the activity of inhibitory pathways, decreasing neuronal activity and attenuating IONM responses, specially neuromuscular blockers (NMB) and inhaled halogenated drugs;[1,3,7] for an optimal IONM, it is important to understand the influence of drugs and other variables on the records[21, 35, 37, 38] (Table 1).

Table 1. Anesthetic drugs and their effects on Somatosensory Evoked Potentials and Motor Evoked Potentials.

Drug	Effect on SSEP	Effect on MEP
Propofol(*)	Minor decrease	Minor decrease
Etomidate	Increase	No effect
Midazolam	Decrease	No effect
Ketamine	Increase	Little effect - Decrease
Fentanyl	Little effect - Decrease	Decrease
Remifentanil	Little effect - Decrease	Little effect - Decrease
Sufentanil	Little effect - Decrease	Decrease
Dexmedetomidine	Little effect - Decrease	Little effect - Decrease
Sevoflurane	Larger decrease	Larger decrease
Desflurane	Larger decrease	Larger decrease
Rocuronium	No effect	No response
Succinylcholine	No effect	No response

NMB block the transmission of signals from motor nerves to muscle fibers at the level of the neuromuscular plate; when monitoring the functional integrity of a nerve structure is through myogenic activity, it is imperative that the muscle group be sensitive to changes in root, peripheral nerve, or cranial nerve function when pulled or compressed, therefore it is recommended not to use them or to use NMB with a short half-life and always monitor their activity, communicating any decision with the neurophysiologist.[14]

Benzodiazepines at induction doses greater than 30 mcg/kg cause depression in cortical, subcortical, and peripheral SSEP. They also have depressant effects in MEP.[7] Despite not being contraindicated, they are rarely used in neurosurgery due to their impact on postoperative evaluation.

Inhaled halogenated anesthetics have a significant dose-dependent effect on IONM,[1,3] decreasing MEP amplitude and increasing the possibility of false positives,[38] cortical SSEP are also affected to a lesser extent.[7] Isoflurane causes a greater reduction in amplitude and dose-dependent increase in latency, followed by sevoflurane and desflurane. At molecular level, they cause a reduction in neuronal excitability due to its effect on potassium channels and by means of inhibiting the activation of lower motor neurons by upper motor neurons.[7,33]

Opioids cause mild decrease in amplitude and prolongation of latency of cortical potentials; their depressant effect is not comparable to those inhaled, making them a useful alternative in IONM.[35]

Adjuvants are recommended to generate synergy, post-anesthetic analgesia, and to reduce doses of hypnotics and anesthetics; perfusion lidocaine 15-60 mcg/kg/min generates hemodynamic stability, less need for opioids and postoperative analgesia; magnesium sulfate 1-5 mg/kg/h is an analgesic adjuvant, provides hemodynamic stability and lower opioid requirement; dexmedetomidine has little effect or decreased EP at doses <0.5 mcg/kg/hr and with adequate infusion stability they can be continued for analgesia in the postoperative period in continuous infusions, single or associated, for 24-48 hours depending on the type of surgery or number of levels operated. Ketamine increases amplitude of SSEP and MEP of SC and is a useful alternative in patients with previous neurological damage,[35] it is recommended in spinal surgery as well to improve the recording of EP, less use of opioids, and as postoperative analgesia in infusions of 0.3 mg/ kg/hr. Etomidate and ketamine generate a dose-dependent increase in EP amplitude.[7] Bolus doses of etomidate 0.3 mg/kg increases cortical SSEP amplitude, without changes in subcortical and/ or peripheral responses; a slight decrease in the amplitude of the MEP is observed, with no changes in latency.[35]

The technique of choice

In addition to the selection of the anesthetic protocol for the baseline and control recording, measures to maintain a constant level of hypnosis and muscle relaxation are crucial to immediately detect changes in EP responses during or after surgical manipulation (LE:1C).[1]

Both desflurane and sevofuran decrease SSEP and MEP amplitudes and prolong SEP latencies in a dose-dependent manner; when used, <0.5-0.6 CAM[3,7] and adjuvants are recommended.[38] Intravenous bolus administration or abrupt changes in the CAM of halogenated drugs can compromise records.

TIVA with propofol allows better recording of MEP and SSEP (LE: 2C);[6] the dose recommendation is 3.0-4.5 mcg/ml PC based on hemodynamics and anesthetic depth monitor with processed or unprocessed EEG of the patient; its effect on latency is minimal, which, along with the pharmacokinetic profile that allows infusions at constant concentrations and less depressant effect than inhaled ones, makes it the hypnotic of choice.[1] Most studies agree on the use of infusions or TIVA-TCI with intravenous anesthetics such as propofol as a hypnotic, remifentanil TCI, sufentanil TCI or ketamine, as an anesthetic and short-acting NMB or for intubation, but not during surgery.[4,14,22,26,35]

The level of hypnosis and muscle relaxation must be kept constant; the use of neuromuscular and anesthetic depth monitors, ideally EEG, is recommended.[1]

Physiological variables such as temperature, blood pressure, heart rate, blood oxygen concentration, partial pressure of carbon dioxide, should be maintained without significant changes; the neuroanesthesiologist must ensure adequate positioning of the patient and sustain clear objectives of hypnosis and metabolic and physiological homeostasis, maintaining adequate saturation and systemic oxygenation, hematocrit, normotension, normothermia and normocapnia, avoiding modifications that alter the recordings.[14]

Stimulation of the motor cortex can cause involuntary movements of the hand, jaw and other parts of the body

with the risk of self-biting and other injuries. Therefore, it is important to anticipate and prevent possible adverse events associated with IONM. Informed consent should include not only the goals and methods of monitoring, but also the risk of associated adverse events.[1]

Conclusions

Multimodal IONM is a useful method that allows the functional state of the motor and sensory systems to be evaluated in real time with the aim of preventing postoperative injuries in procedures that put the nervous system at risk and pose important challenges for the neuroanesthesiologist.

It is essential to understand the clinical bases of the different IONM techniques and interpret alerts and alarm criteria in a timely manner, through close cooperation between the neurosurgeon, neurophysiologist and neuroanesthesiologist, for early decision-making and better surgical results.

In turn, the neuroanesthesiologist must ensure adequate positioning, anesthetic depth status, hemodynamic stability, and cerebral/spinal cord perfusion pressure, avoiding changes that alter the recordings.

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Conflict of interest

The authors declare that they have no conflict of interest.

Ethical Responsibilities

The authors state that no experiments have been performed on humans or animals for this research, and that no patient data appears in this article.

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Effects of strength training in people with multiple sclerosis: literary review

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Abstract

Introduction: Multiple sclerosis (MS) is the most common cause of non-traumatic neurological disability in young people. Its rehabilitation treatment focuses on improving symptoms and restoring functionality. Muscle strength training has been studied recently as a rehabilitation method, simultaneously with balance exercises, and improvement of gait and coordination. The objective of this review is to analyze the application of these training programs in subjects with MS.

Methods: In February 2020, the CINAHL and Medline databases were consulted using the MeSH descriptors "multiple sclerosis" and "resistance training". The search retrieved 89 results; 17 of which fitted the review objective and were analyzed.

Results: The effects of isolated strength training programs were analyzed using high-intensity continuous or interval aerobic protocols, with increases in workload or progressive resistance, as well as suspension training (TRX), resistance training with body weight, hatha yoga, and its combination with cardiovascular exercise, self-guided physical activity, neuromuscular electrostimulation, functional training or functional gait training. The variables of strength and neuromuscular function (spasticity, proprioception), functionality (mobility, motor capacity, balance, fatigue and fatigability), metabolic parameters (glucose tolerance, brain-derived neurotrophic factor (BDNF), sphingosine-1-phosphate (S1P), body composition, cortisol and DHEA, inflammatory mediators, immunomodulatory markers, aerobic capacity, and parameters such as quality of life, satisfaction, adherence and participation.

Conclusions: Strength training protocols, used alone or combined with other methods, improve muscle strength and gait functionality in subjects with MS, as well as their metabolic parameters. However, its involvement in the regulation of neuroprotective factors has not been demonstrated.

Keywords: *Multiple Sclerosis. Strength Training. Physiotherapy. Rehabilitation. Neurological disease.*

Introduction

Multiple sclerosis (MS) is classified as a demyelinating, chronic, autoimmune and inflammatory pathology,[1–12] with an unregulated evolution that complicates rehabilitation treatment.[4] Its affectation directly involves the axons of the central nervous system (CNS),[12,13] which leads to the loss of the myelin that sheath it and affecting neuronal continuity,[5] covering the affected area with scar tissue that produces sclerotic plaques.[1–5] Some patients register a single outbreak, however, this can be multiple and cumulative, which generates a progressive physical disability[1–5,7,14–19] that affects them functionally both at the motor and sensory levels, which has repercussions on fatigue and pain levels that influence their autonomy.[20]

MS is identified as the most frequent cause of non-traumatic neurological disability in the young population,[1–5,7,9,21-23] being predominant in women, with a proportion that varies between 2:1 and 3:1.[1 ,2,5,7,19,21,22]

The etiology of MS is not clear,[9,21] despite there is scientific consensus that relates it to genetic and environmental factors, in addition to risk factors such as smoking and vitamin D deficiency,[1,7,19,24-26] as well as viral causes,[5,7,24] such as the Epstein-Barr virus.[1,5,19] Regarding environmental factors, these cause the growth of autoreactive T cells that, after a few decades of latency , are activated by a systemic or local factor.[1,2,5,26]

As it is a disease with no cure, treatment focuses on reducing the frequency, severity and duration of relapses, improving symptoms and restoring functionality.[1,8–13,21,23,27–35] Physiotherapy, a multidisciplinary perspective, focuses on working on spasticity and muscle weakness[9,17,33,36] through muscle training that improves both[17] through balance, gait, strength and body skill exercises,[8–13,15,16,21,23,27–35,37,38] either isolated or combined.[8,32–34,38] Following this context, the objective of this literature review is to analyze the application of strength training programs in subjects with MS.

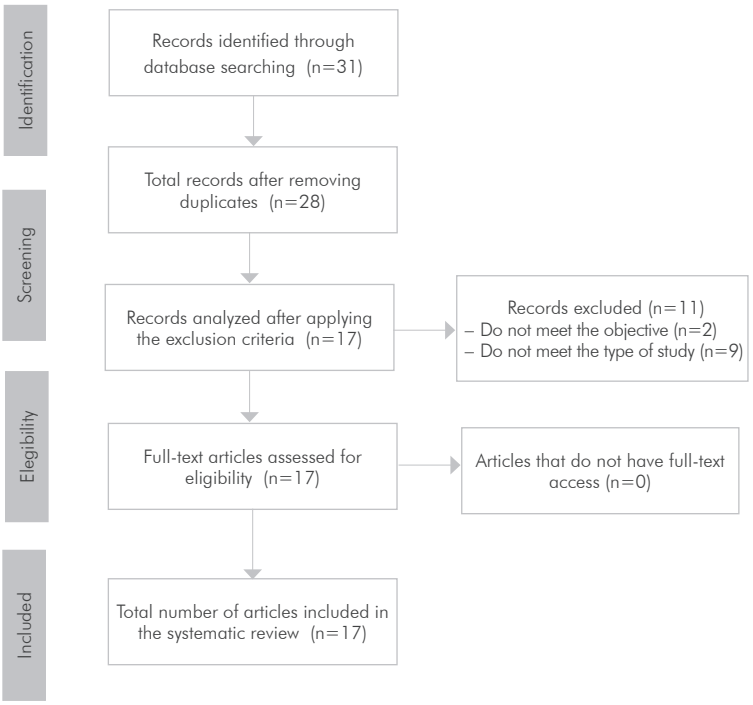
Material and methods

A literature search was conducted in February 2020 for recently published studies examining resistance training in people with MS.

The Medline and CINAHL databases were consulted, using the MeSH terms "multiple sclerosis" and "resistance training", as well as a variation of the term -- "muscle strengthening" -- in CINAHL.

As inclusion criteria, publications in English or Spanish from the last 5 years were selected, excluding those that did not fully analyze the effects of the application of strength training programs in subjects with MS. 89 results were obtained which, after applying the selection criteria and omitting three repeated results, constituted a sample with a total of 17 studies. See Figure 1.

Figure 1. Flow chart according to Prisma guidelines (2009)



Results

We analyzed the effects of isolated resistance training programs using high-intensity continuous or interval aerobic protocols, with increases in workload or progressive resistance, suspension training (TRX), body-weight resistance training, hatha yoga, and its combination with cardiovascular exercise, self-guided physical activity, neuromuscular electrostimulation, functional training or functional gait training. The variables of strength and neuromuscular function (spasticity, proprioception), functionality (mobility, motor capacity, balance, fatigue), metabolic parameters (glucose tolerance, brain-derived neurotrophic factor (BDNF), sphingosine-1-phosphate (S1P), body composition, cortisol and DHEA, inflammatory mediators, immunomodulatory markers, aerobic capacity, and other parameters such as quality of life, satisfaction, adherence and participation.

Tables 1 and 2 show the results of randomized controlled trials and quasi-experimental studies.

Discussion

All the studies analyzed examine the effects of resistance training programs in subjects with multiple sclerosis. Considering the methodological design, a distinction is made between randomized controlled trials (RCT) and quasi-experimental studies. Interventions are based on the application of a strength improvement program, either alone or in combination with other techniques.

RCTs with an isolated strength training intervention

The most used intervention was the application of a muscle strength training protocol with increases in workload or conventional progressive resistance work.[10,13,21,32]

Table 1. Results of randomized controlled studies

Author	Sample Age	Experimental group / Control group	Duration and Frequency	Variables and measurement instruments	Improvements (↑) Differences between groups (GE-GC)
Isolated strength training application					
Hosseini et al.[21]	26 subjects 15W/12M 32 y/o	Strength G: weight(25-30min) Yoga G: 60-70 min CG: usual activity	8 weeks 3 TW	-Extensor strength BLE (1RM) -Motor capacity (10MTW) -Balance (eyes open, closed, and monopodal support)	↑S en FG>YG>CG Motor capacity ↑ Monopodal support balance ↑
Aidar et al.[13]	23 subjects 15W/8M 43 y/o	EG: Progressive Strenght Training GC: Sedentary	12 weeks 3 TW	BLE function: TUG -BLE strength: T25FWT and Sit to stand test -Balance and fall risk: BBS	EG-CG in TUG, T25FWT, up and go test and BBS
Wens et al.[32]	41 subjects 22W/12M 46 y/o	EG: Progressive strength training CG: Sedentary HG: Healthy group	24 weeks 2-3 TW	-BDNF -S, exercise tolerance, body composition	BDNF: EG: ↑13,9%-8,8% / CG: ↓10,5%-4,1% S, exercise tolerance and body composition CG=EG
Jørgensen et al.[10]	30 subjects 22W/8M 44 y/o	EG: High intensity progressive resistance training CG: Usual activity	24 weeks 2 TW	-BDNF y S1P (análisis agudo y crónico) -Función y actividad neuromuscular Flex y Ext rodilla (MCV dinamómetro isocinético y EMG.	BDNF o S1P no cambios GE-GC: actividad neuromuscular y la fuerza muscular mejoró más en GE
Wens et al. [8]	34 subjects 15W/8M 45 y/o	HIIT G HIACT G CG: Sedentary	12 weeks 2-3 TW	-Glucose tolerance: oral test - Skeletal muscle: vastus lateralis biopsy	Glucose ↑ HIIT G and HIACT G Insulin and GLUT4 ↑ HIIT G
Brændvik et al.[31]	26 subjects 17W/9M 48 y/o	EG: Treadmill CG: Strength training	12 weeks 3TW	-Functional walk (GAITRite walkway) -Walking economy and balance (accelerometer)	Treadmill G > S training G Gait functionality, walking economy and balance
Moghadasi et al.[29]	34 subjects - 36 y/o	EG: Full body suspension training CG: Usual activity	8 weeks 3 TW 30 min	-Mobility (TUG, 2MTW, 10MWT and 5STS) -Propioception and knee S flex-Ext (isokinetic dynamometer)	↑:EG TUG, 2MTW, 10MWT and 5STS EG-CG: Non dominant LL propioception EG-CG: ↑ Knee Ext and reflexes on both lower extremities
Combined strength training application					
Deckx et al.[23]	45 subjects 26W/19M 48 y/o	EG: cardiovascular exercise + Progressive strength and resistance training CG: Sedentary subjects	12 weeks 2-3 TW	-Cortisol and DHEA -Inflammatory mediators -Inmunomodulatory markers: blood analysis	EG-CG in ↓inflammatory mediators and ↑ inmunomodulatory markers
Kjølhede et al.[11]	29 subjects - 43 y/o	EG: Progressive strength and resistance training + self guided physical activity CG: Usual activity	24 weeks 2-3 TW + 24 weeks follow-up	--Walking performance (T25FWT, 2MWT, 5STS, stair-climbing test y MSWS-12) -Neuromuscular knee function Ext and Flex (S isometric isokinetic dynamometer, EMG and thigh perimeter: MRI)	EG-CG: ↑Walking performance: T25FWT, 2MWT, 5STS, stair-climbing test, MSWS-12 an neuromuscular function
Coote et al.[30]	25 subjects 17W/8M 52 y/o	EG: Progressive resistance training + NMES CG: Progressive resistance training	12 weeks 2-3 TW	-Hip S Ext and knee S: dynamometer -Spasticity (nm VAS) -Function: BBS, TUG, MSWS-12MS, MSIS-29v2, MFIS -ENM device usability (questionnaire)	CG-EG: MFIS EG: ↑S quadriceps, balance, MSIS-29v2 and MFIS highly usable device

HIIT: high intensity interval training, HIACT: high intensity aerobic continuous training, BBS: Berg balance scale, BDNF: brain-derived neurotrophic factor, T: training, ECW: energy cost of walking, EMG: electromyography, ESES: Exercise Self-Efficacy Scale, NMES: neuromuscular electrical stimulation, Ext: extension, S: Strength, FSMC: fatigue scale for motor and cognitive functions, Flex: flexion, CG: control group, EG: experimental group , GLUT4: glucose transporter type 4, M: man, W: woman, LE: lower extremity, BLE: bilateral lower extremities, MVC: maximal voluntary contraction, MFIS: modified fatigue impact scale, MSIS-29v2: 29-item multiple sclerosis impact scale version 2, MSWS-12MS: 12-item multiple sclerosis walking scale, MRI: magnetic resonance imaging, S1P: sphingosine-1-phosphate, T: test, TUG: timed up and go test, T25-FW: timed 25-foot walk test, TW: times per week, 1RM: 1 repetition maximum test, 2MWT: 2 minutes walk test, 5XSST: 5 times sit to stand test, 6MWT: 6 minutes walk test, 10MWT: 10 meter walk test.

Table 2. Results of quasi-experimental studies

Author	Sample Age	Intervention Training	Duration and Frecuency	Variables and measurement instruments	Improvements (↑) Differences between groups (EG-CG)
Patrocinio Oliveira et al.[9]	52 33W/19M 48 y/o	EG: eccentric S CG: resistance S ↑ load (according place of residence)	12 weeks 2 TW	-Knee Ext S: maximum isometric contraction and 1RM -TUG and CST	EG and CG ↑ S, 1RM, TUG Y CST EG-CG: no differences
Zaenker et al.[33]	26 19W/7M 44 y/o	High intensity training + resistance S with weight G1 and G2 (EDSS 0-3 y 3,5-5)	12 weeks 2 TW	-Aerobic capacity: VO2 Max, maximum tolerated and lactatos -Quadriceps and hamstrings isokinetic strength -Quality of life	G1 and G2: VO2 Max, maximum tolerated ↑ Quadriceps and hamstrings isokinetic strength ↑ Quality of life↑ Women> ↑ Men
Heine et al.[12]	10 6W/3M 49 y/o	CG: healthy subjects EG: subjects with MS: resistance training + walking	16 weeks 3 TW	-Ankle thrust (dynamometer) -Muscular, cardiopulmonary and self-report tests - Gait functionality (3D analysis and 10MWT) -Energy Consumption (ECW) -MFIS, FSMC, MSWS-12 and ESES	EG<CG: ankle thrust, and MSWS-12 in more affected lower extremity Post-program: ↑walking distance, ankle thrust, and speed in less affected lower extremity
Hameau et al.[34]	23 13W/10M 39/59 y/o	Intensive physiotherapy focused on gait and balance, strength and endurance	4 weeks 4 TW	-Fatigue and fatigability -Isokinetic dynamometer and MFIS -Flex and Ext knee S -Neuromuscular efficiency (EMG)	MFIS↓, fatigue ↑ immediately, but after rest = S↑ in isometric contraction as concentric EMG↑
Mañago et al.[28]	10 9W/1M 54 y/o	Isotonic and isometric strength training Ankle plantar flexors, hip abductors and trunk muscles strengthening	8 weeks Supervised and at home	-Satisfaction (Likert test) -Adherence (attendance at sessions) -Plantar flex, hip abductor, trunk musc. S Function T -Walking speed (T25FW) -Walking resistance (6MWT) -Participation (MSWS-12MS)	Satisfaction:100% Adherence: (Supervised training: 87%; at home: 75%) S ↑ in all muscles T25FWT ↑ 6MWT↑ MSWS-12MS↑
Keytsman et al.[35]	CuasiExp 16 7W/9M 52 y/o	HICT high-intensity interval cycle ergometer with strength training	12 weeks 5 TW	-Body composition -Blood pressure and resting heart rate -Oral glucose tolerance 2h. -Blood lipids -C-reactive protein	Better: resting heart rate (-6%), glucose concentration (-13%) and insulin sensitivity (24%)
Manca et al.[27]	CuasiExp 8 6W/2M 39 y/o	High intensity S training ankle dorsiflexors (less affected side) Subject, asymmetric affectation	6 weeks 3 TW	-S dorsiflexors (isokinetic dynamometer) -Gait functionality -6MWT, TUG, 10MTW, -Quality of life MS: MSQoL-54	Trained BLE (less affected) and untrained (more affected) improved similarly

HIIT: high intensity interval training, HIACT: high intensity aerobic continuous training, BBS: Berg balance scale, BDNF: brain-derived neurotrophic factor, CST: chair stand test, T: training, ECW: energy cost of walking, EDSS: Expanded Disability Status Scale, EMG: electromyography, ESES: Exercise Self-Efficacy Scale, Ext: extension, S: Strength, FSMC: fatigue scale for motor and cognitive functions, Flex: flexion, CG: control group, EG: experimental group, M: man, W: woman, LE: lower extremity, BLE: bilateral lower extremities, MVC: maximal voluntary contraction, MFIS: modified fatigue impact scale, MSIS-29v2: 29-item multiple sclerosis impact scale version 2, MSQOL-54: Multiple Sclerosis Quality of Life - 54, MSWS-12MS: 12-item multiple sclerosis walking scale, MRI: magnetic resonance imaging, S1P: sphingosine-1-phosphate, T: test, TUG: timed up and go test, T25-FW: timed 25-foot walk test, TW: times per week, 1RM: 1 repetition maximum test, 2MWT: 2 minutes walk test, 6MWT: 6 minutes walk test, 10MWT: 10 meter walk test.

In the study by Jørgensen et al.,[10] progressive resistance work was of high intensity; in turn, Wens et al.[8] compared the effects of a high-intensity continuous aerobic program versus an interval program. Other interventions were based on suspension training (TRX),[29] treadmill walking,[31] or hatha yoga.[21] All of the aforementioned conventional progressive resistance training programs contributed to a significant improvement in strength,[10,13,21] motor capacity,[21] neuromuscular activity,[10] lower limb function[13] and balance.[13,21] Through these studies it was shown that conventional strength improvement programs produce greater benefits than a yoga training program,[21] as well as participants continuing their usual activity[10,21,29] and not being sedentary.[8,13,32]

Studies on high-intensity programs analyzed their effects according to metabolic parameters (acute and chronic study of BDNF and S1P, glucose tolerance, insulin and GLUT4) and functional parameters (strength, function and neuromuscular activity of knee flexors and extensors, exercise tolerance and body composition). Wens et al.[32] observed an increase in BDNF in the intervention group in contrast to its decrease in the sedentary group, without changes in the functional parameters of strength, exercise tolerance and body composition. On the other hand, the high-intensity progressive resistance intervention by Jørgensen et al.[10] demonstrated functional improvements in neuromuscular activity and strength of knee flexors and extensors, without metabolic changes of BDNF or S1P.

Suspension training programs improved mobility, non-dominant lower limb proprioception, and knee extension strength and reflexes in both lower limbs, compared to participants who continued with their usual activity.[29]

Treadmill gait training[31] was found to be more beneficial for gait functionality, walking economy, and balance compared to a conventional strength training program.

RCTs with a combined strength training intervention

Protocols to increase strength combined with cardiovascular exercise[23] improve the concentration of inflammatory mediators and immunoregulatory markers, but do not modify cortisol and DHEA levels. Those combined with self-guided physical activity[11] improve walking performance and neuromuscular function. The combination of progressive resistance strength training with neuromuscular electrostimulation[30] provides greater benefits in the strength of hip extensors and knee flexors and in gait functionality, compared to resistance strength training without such stimulation.

Quasi-experimental with two intervention groups

Quasi-experimental studies present two types of design, those that have two intervention groups and those that only include one. Those with two groups assigned participants according to their place of residence, the degree of impairment according to the Expanded Disability Status Scale (EDSS), or depending on whether they were healthy subjects or subjects with MS. The study by Patrocinio de Oliveira et al.,[9] which divided its participants according to place of residence, applied an eccentric strength training program to one group and a resistance strength training program with increases in workload to the other, obtaining the same results after the two interventions.

The study that divided its participants according to the level of affectation -- in the first group the most affected, G1: EDSS 0-3, and in the second, the least affected, G2: EDSS 3.5-5 -- applied a combined program of high-intensity strength training together with weight-resistance strength training, obtaining an improvement in MaxO2 consumption, max. tolerated, isokinetic strength of quadriceps and hamstrings, and quality of life, with no differences between groups. The study by Heine et al.[12] applied a strength training program combined with walking in a group of healthy subjects and another of subjects with MS. After the program, walking distance, ankle thrust, and speed increased in the less affected inferior limb.

Quasi-experimental with a single intervention group

The 4 studies that had a single intervention group applied intensive physiotherapy focused on gait and balance, as well as strength and resistance,[34] and obtained benefits in participation, fatigue, isometric and concentric strength, and neuromuscular function. Similarly, an isotonic and isometric strength training program was used to strengthen ankle plantar flexors, hip abductors and trunk muscles,[28] observing improvements in satisfaction, adherence, strength in all the muscles analyzed and in gait functionality. The other two studies applied high-intensity programs. The study by Keytsman et al.[35] applied HICT (high-intensity interval cycle ergometer with strength training) and observed better resting heart rate, decreased glucose concentration, and better insulin sensitivity. Manca et al.[27] performed a contralateral ankle dorsiflexor training on the less affected side, and obtained similar improvements, both in trained (less affected) and untrained (more affected) lower limbs.

In general, most of the studies analyzed use the combined method of strength training. Starting from the theoretical basis that an individual strength intervention produces physical-functional improvements,[15,16,37,38] combined methods are based on a multiperspective attention and multiple and simultaneous action of strength, gait, resistance, balance and proprioception, in order to achieve a comprehensive improvement.[38] Wens et al.[8,32] asserts that combined strength and resistance training improve physical parameters, since they not only increase people's tolerance to exercise, but also the physical strength and endurance of the muscles.

Regarding intervention times, they range between 6 and 24 weeks. The most common intervention time is 12 weeks,[8,9,13,23,30,33,35] followed by those that use a time of 8 weeks[21,28,29,31] and those of 24 weeks;[10,11,32] including Kjølhede et al.,[11] who used a follow-up period of 24 additional weeks, added to the 24 of the main intervention. Most of the studies are based on an intervention of medium-long duration, with the aim of increasing adherence to training and reducing reversibility effects. Likewise, Wens et al.[8,32] affirm that a longer intervention over time has greater effects at a physical-functional and physiological level, while Moghadasi et al.[29] point out the need to include the evolution in long-term studies and protocols, justifying it with the causes listed in previous lines. In contrast, Hosseini et al.[21] state that, despite the fact that long-term training is more beneficial, short-term training also produces positive results.

Concerning the muscles to be treated, most studies focus on the upper, lower limb and trunk,[8,10,11,13,21,23,28,29,32,34,35] while the rest of studies center on the lower limb.[9,12,27,30,31,33] This is justified since focusing all efforts on a single area produce greater improvement. Additionally, the gait limitation

produced by MS is important and therefore the combined use of strength, balance and resistance training is recommended. As stated by Moghadasi et al.,[29] proprioception improves balance during walking. On the other hand, Mañago et al.[28] indicate that a lower limb treatment produces a significant improvement in gait, which represents the most compromised functional activity of subjects with MS.

In view of the obtained results, both general and by protocol, a stability of the variables is identified in all the control groups analyzed, while the opposite occurs in the intervention groups. The programs based on some type of training -- resistance, strength or combined -- present changes in the pre/post intervention score, in which improvement of the extensor and flexor musculature of both the upper and lower extremities is noticeable,[9,10,12,13,21,27-30,32-34] but more recurring in the later, as it is the area of the body most trained in the different interventions. This improvement is significant in almost all studies, although to a greater extent in programs based on a combination of resistance and strength training,[8,12,23,32-34] and it derives not only on the improvement in muscle tone, but also variables such as the reduction of fatigue in the MFIS scale,[34] decrease in heart rate,[12] and other cardiorespiratory parameters, including resistance to exercise,[32,34] decrease in mean response time[32] and mobility.[12] Metabolic improvements, namely an increase in the concentration of brain-derived neurotrophic factor (BDNF)[32] or an increase in VO2 peak and lactate[33] are also observed in combined training. Finally, in the study by Decks et al.,[23] increase of cortisol, decrease of inflammatory mediators secretion, and maintenance of DHEA concentrations was confirmed.

As one of the most compromised functions in MS, gait assessment was carried out using different functional mobility tests.[12,27-29] In all of them, an improvement was observed due to the increase in muscle function, although only Mañago et al.[28] identified this vinculation, which, in the case of Heine et al.,[12] is also associated with an increase in the maximum voluntary contraction of the plantar flexors.

In regard to the evaluation of physiological factors,[8,10,23,32,35] both Wens et al.[32] and Jørgensen et al.[10] carried out a pre/post comparison of BDNF concentration, one of the most important immune cells for pathologies such as MS; these studies recommend a line of action based on the coupling of strength exercise and combined exercise, in order to increase BDNF segregation. Wens et al.[32] associated an increase in BDNF concentration to strength and endurance improvements, proposing combined exercise as a useful tool not only to for the increasing of BDNF segregation, but also for the improvement of the main risk factors and symptoms of MS. On the contrary, Jørgensen et al.[10] did not observe a significant difference in BDNF concentrations, nor suggest any association between BDNF production and the rest of the physical improvements reported in their study.

Pertaining to adherence and satisfaction with the training programs, only two of the studies, Zaenker et al.[33] and Mañago et al.[28], conducted surveys, reporting a positive response in both variables.

Kjølhede et al.[11] and Manca et al.[27] carried out a one-year follow-up of the training programs results: the former observed an initial decrease in strength and resistance improvement, mainly on the non-dominant member. Manca et al.[27] identified reversibility in all variables related to strength, mobility and functional capacity, although they remained higher than the baseline level. This reversibility, reported in a higher dregree in the second study, could be associated with the intervention period. It should be noted that the Kjølhede et al.[11] program lasted 24 weeks and the one in Manca et al.[27] of 6 weeks; according to observed data, high training adherence and a longer intervention generate greater stability over time.

Finally, this review has limitations to be considered. In the first place, the heterogeneity of the studies and analyzed variables imply that the results should be interpreted with caution, taking into account the differences according to gender and between populations, both important in multiple sclerosis research. Future analysis of the same variables, including meta-analysis, could contribute to obtain more consistent findings.

Conclusion

Most of the analyzed studies carried out a combination of strength training with other methods, obtaining physical-functional improvements such as increased strength and endurance, improved balance and functional capacity, decreased fatigue, improvement of cardiocirculatory parameters and improvement of the quality of life of people with MS. Both types of training, whether simple or combined, produced an improvement of MS symptoms. However, it is postulated that the combination of several methods is more favorable for the improvement of all variables and their persistence over time, this due to the enhancement of several functional parameters.

The implication of strength training in the regulation of neuroprotective factors has not been demonstrated, and its influence on other metabolic parameters has produced contrasting results among studies, thus future research on both subjects could be of interest.

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Declaration of interests

The authors have no conflicts of interest to declare.

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Therapeutic potential of dehydroepiandrosterone for Parkinson's disease: scoping review protocol

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Abstract

Background: Parkinson's disease (PD) is a neurodegenerative disorder characterized by a progressive loss of nigrostriatal dopaminergic neurons. Its treatment is symptomatic and shows limited efficacy. Dehydroepiandrosterone (DHEA) is a hormone produced in the brain. Several studies have reported beneficial effects of said steroid in experimental models of PD and various human diseases, but its potential for PD is inconclusive. Therefore, it is necessary to evaluate current evidence to determine the therapeutic potential of DHEA administration for PD since it could be an effective and low-cost treatment.

Objectives: This scoping review protocol aims to evaluate the therapeutic potential of dehydroepiandrosterone administration in patients with PD. **Inclusion criteria**: Studies describing patients with PD receiving DHEA, and reporting an outcome --on disease course, severity, or adverse effects-- compared to either placebo, an inactive treatment or a standard treatment will be included. Also, PD experimental models reporting an effect of DHEA treatment on measures of neuroprotection (cell death, motor activity, oxidative stress) will be considered. **Exclusion criteria**: Studies written in languages different than Spanish or English that could not be appropriately translated, or whose full-text files could not be retrieved will be discarded. Information sources: Studies will be retrieved from Web of Science, PubMed, Scopus, EBSCOhost, Cochrane Library, Google Scholar, and author's collections. No other sources will be considered. **Data charting**: Data will be extracted by one researcher and verified by another using a pilot-tested predefined format. Non-systematic review articles (narrative, scoping or similar) will only be considered for narrative synthesis. This protocol complies with the PRISMA 2020 statement and its main related extensions (PRISMA-A, PRISMA-P, PRISMA-Scr). It also complies with the Manual for Evidence Synthesis of the Joanna Briggs Institute.

Keywords: *Central Nervous System, Dehydroepiandrosterone, Parkinson Disease, Mechanisms, Neuroprotection*

Introduction

Parkinson's disease (PD) involves a neurodegenerative process of generally sporadic presentation. James Parkinson initially described it in 1817. PD symptoms include bradykinesia, rigidity, tremor, and postural instability; an asymmetric damage to the extremities is sufficient to suspect its diagnosis.[1] In addition, PD is characterized by marked changes in gait, such as shuffling and short steps, a low-speed walk with a small angular displacement, and alterations in posture and balance.[2] PD is the most common form of parkinsonism. Its overall incidence varies between 1.5 and 22 patients/100,000 inhabitants/year;[3] which increases in patients over 60 years old, being the male sex the most affected, this has been related to exposure to estrogens and their neuroprotective effect.

The characteristic lesion of PD occurs in the substantia nigra pars compacta (SN), which is part of the mesencephalic dopaminergic groups that innervate the basal ganglia. In PD, there is a progressive loss of the dopaminergic neurons of the nigrostriatal system –with depigmentation and gliosis– while Lewy bodies appear in the surviving neurons.

Currently, there is no cure for this disease. The treatments are symptomatic and often show limited efficacy.

Dopaminergic medications are the mainstay of symptomatic therapy for motor symptoms in PD[4], but may lead to neurological and psychiatric side-effects. Some potential treatments like noninvasive deep brain stimulation, gene therapy, immunotherapy, cell transplantation, and circuit neuromodulation have been proposed. However, as mentioned above, all therapies are symptomatic and do not seem to slow down or reverse the natural course of the disease. Furthermore, about 40% of patients experience ostensible complications after five years despite medication use, so the treatment for this condition remains a challenge for medical sciences.

Several studies have shown a neuroprotective effect of DHEA in PD models, from cell cultures to non-human primates (reviewed in [5]). Dehydroepiandrosterone (DHEA) is a hormone produced predominantly at the adrenal glands and, to a lesser extent, at the gonadal level, but it is also produced de novo in the brain.

DHEA concentrations are usually higher in the brain than in the bloodstream. DHEA is an essential precursor of androgens and estrogens; in men, 50% of androgens come from DHEA and DHEAS, and, in the case of premenopausal women, 75%. DHEA and DHEAS progressively decrease with age [6, 7], which is associated with chronic and neurodegenerative diseases.

There are studies of DHEA supplementation in older adults demonstrating beneficial effects for lupus erythematosus[8], depression[9], ulcerative colitis[10], and reduced ovarian reserve[11,12]. There is also positive evidence of its use as an adjuvant during immunization against tetanus and influenza[13], pulmonary hypertension, and chronic obstructive pulmonary disease.[14]

The neuroprotective effects of DHEA follow complex pathways of cellular genomic and nongenomic events through their conversion to testosterone and dihydrotestosterone (DHT). In turn, this effect activates androgen receptors (AR), its conversion into estradiol, and the subsequent activation of estrogen receptors (ER). A study on cortical and hypothalamic astrocytes isolated from neonatal rats showed its capacity to synthesize both testosterone and estrogen from exogenous DHEA. On the other hand, DHEA itself can bind and modulate some receptors.

Injury with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) provides a model of PD that allows studying the neuroprotective effects of hormones. Sex differences in sensitivity to MPTP have been reported, with a more significant neurotoxic effect observed in male rodents than females[15–17]. Animal studies have shown that DHEA administration is as effective as 17β-estradiol to produce a neuroprotective effect against MPTP toxicity.[18] This treatment modulates the dopaminergic system at different levels.

Nowadays, PD treatment can be expensive in contrast with other neurological disorders. Moreover, with the epidemiological and demographic transition underway, it can become a public health problem that will put enormous pressure on governmental health systems.

Study rationale

As the disease progresses, the treatment alternatives for PD lose efficacy, which leads to a worse quality of life, primarily due to motor and non-motor complications. This reinforces the necessity to evaluate current evidence and determine the therapeutic potential of DHEA administration in the PD treatment since it could be an effective and low-cost option for patients.

Registration or publication of systematic review protocols is important for several reasons: "planning and documentation of review methods, act as a guard against arbitrary decision

making during review conduct, enable readers to assess for the presence of selective reporting against completed reviews, and, when made publicly available, reduce duplication of efforts and potentially prompt collaboration"[19]. However, this is not performed in most cases. According to some studies, only 20% of systematic reviews have a registered or published protocol.[20]

Methods

Research questions

Research questions for this review are described in Table 1. In addition, secondary research question three –related to the financial impact of the treatment– was included as recommended by the Cochrane Handbook for Systematic Reviews of Interventions.[21]

Table 1. Research questions for the scoping review protocol

Question type	Framework	Description
Main research question	CoCoPop (Condition, Context, Population)[38]	What is the therapeutic potential (Co) of dehydroepiandrosterone administration (Co) in patients with Parkinson´s Disease (Pop)?
Secondary research question 1	PICOC (Population, Intervention, Comparison, Outcome, Context) [39]	In Parkinson's disease (**P**), could dehydroepiandrosterone administration (**I**), compared to an inactive treatment (**C**), decrease symptomatology (**O**) according to clinical and preclinical studies (**C**)?
Secondary research question 2	CoCoPop (Condition, Context, Population)[38]	What are the possible side-effects (**Co**) of dehydroepiandrosterone administration (**Co**) in patients with Parkinson's disease (**Pop**)?
Secondary research question 3	MIP (Methodology, Issues, Participants) (40)	Which could be the financial cost (**M**) of dehydroepiandrosterone administration (**I**) in patients with Parkinson disease (**P**)?
Secondary research question 4	CIMO (Context, Intervention, Mechanisms, Outcomes)[41]	According to published studies (**C**) regarding dehydroepiandrosterone administration (**I**), which mechanisms of action (**M**) may be beneficial for Parkinson disease (**O**)?
Secondary research question 5	MIP (Methodology, Issues, Participants) [40]	Does dehydroepiandrosterone administration (**M**) modify quality-of-life measures (I) in patients with Parkinson disease (**P**)?

Objectives

The primary objective of this scoping review will be to evaluate the therapeutic potential of DHEA administration in patients with PD. Secondary objectives are as follows:

- To evaluate if DHEA administration, compared to an inactive or standard treatment, could decrease symptomatology in PD according to clinical and preclinical studies.
- To evaluate what are the possible side-effects of DHEA administration in patients with PD.
- To estimate which could be the financial cost of DHEA administration in patients with PD.
- To determine which DHEA's mechanisms of action may be beneficial for PD.
- To estimate if DHEA administration could modify quality-of-life measures in patients with PD.

Protocol development

We determined the appropriate type of review article according our research questions and objectives using an online tool, as previously reported.[22] The result was "scoping review" and is available https://whatreviewisrightforyou.knowledgetranslation.net/map/results?id=5413&code=GAkWQRoevx.

We consulted the International Prospective Register of Systematic Reviews (PROSPERO, https://www.crd.york.ac.uk/prospero/), the JBI Clinical On-line Network of Evidence for Care and Therapeutics (JBI COnNECT+, https://connect.jbiconnectplus.org/), and the Open Science Framework (OSF, https://osf.io/), to search ongoing protocols for systematic or scoping reviews related to our research questions. However, no relevant records were retrieved (July 2nd, 2021). Our protocol was drafted by the research team and revised as necessary. Supporting materials [appendix A (see below) and guideline checklists] are available through the Open Science Framework (https://osf.io/np2jr/?view_only=ffe214c3396a4c06b21b60e8a3b9188e), as previously reported[23] (registration date Sept.14th, 2021; last updated Oct. 2nd, 2021).

Our investigation team comprises different profiles: clinical, preclinical, and socio-medical science research specialists. The protocol for this scoping review complies with the JBI Manual for Evidence Synthesis[24], complemented with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA 2020[25]), and the PRISMA extensions for abstracts (PRISMA-A[26]), protocols (PRISMA-P[19]), and scoping reviews (PRISMA-Scr [27]). We applied these guidelines to the most possible extent for a scoping review protocol.

Search strategy

A trained researcher elaborated our search strategy, which was peer-reviewed by another specialist using the Peer Review of Electronic Search Strategies (PRESS [28]), – this strategy was not adapted from any previous protocol and is reported according to PRISMA-S.[29]

Published studies (all publication types) will be retrieved from Web of Science (Clarivate), MEDLINE (PubMed), Scopus, EBSCOhost (Academic Search Ultimate), Cochrane Library, from database inception to the date of the research.

Sources or grey literature will be: the Conference Proceedings Citation Index- Science (Web of Science Core Collection), OpenDissertations (EBSCOhost), and Scopus (which includes conference proceedings). In addition, the first 100 results from Google Scholar (https://scholar.google.com/, accessed from Mexico City in incognito mode) sorted by relevance without citations, will be retrieved.[23] Finally, the author's collections will also be consulted. No other sources will be considered.

Search algorithms were elaborated using an online tool and are publicly available (https://app.2dsearch.com/new-query/6128c7e22bde1000048c6380). Those algorithms were adjusted, if necessary, according each database during line-by-line analysis. Databases to be consulted, their providers, and coverage dates (if available) are listed in Table 2. Line-by-line evaluation of all search algorithms is described in Appendix A (available at https://osf.io/np2jr/?view_only=ffe214c3396a4c06b21b60e8a3b9188e). No search filters or limits will be applied.

Table 2. Databases to be consulted, along with providers and dates of coverage

Database	Interface
Science Citation Index Expanded (1900-present)	Web of Science
Social Sciences Citation Index (1900-present)	
Arts & Humanities Citation Index (1975-present)	
Conference Proceedings Citation Index- Science (1990-present)	
Conference Proceedings Citation Index- Social Science & Humanities (1990-present)	
Book Citation Index– Science (2005-present)	
Book Citation Index– Social Sciences & Humanities (2005-present)	
Emerging Sources Citation Index (2015-present)	
Biological Abstracts (1993-present)	
Current Contents Connect (1998-present)	
Derwent Innovations Index (1963-2019)	
KCI - Korean Journal Database (1980-present)	
Russian Science Citation Index (2005-present)	
SciELO Citation Index (2002-present)	
Zoological Record (1976-present)	
Academic Search Ultimate	EBSCOhost
Applied Science & Technology Source Ultimate	
Art & Architecture Source	
Audiobook Collection (EBSCOhost)	
Business Source Ultimate	
CINAHL with Full Text	
Communication & Mass Media Complete	
Dentistry & Oral Sciences Source	
eBook Collection (EBSCOhost)	
EconLit with Full Text	
E-Journals	
Environment Complete	
ERIC	
Family & Society Studies Worldwide	
Food Science Source	
FSTA - Food Science and Technology Abstracts	
Gender Studies Database	
Historical Abstracts with Full Text	
Humanities Source	
Inspec	
Inspec Archive - Science Abstracts 1898-1968	
Left Index	
Library & Information Science Source	
MathSciNet via EBSCOhost	
MedicLatina	
MLA Directory of Periodicals	
MLA International Bibliography	
Newspaper Source Plus	
Newswires	
OpenDissertations	
Philosophers Index with Full Text	
Regional Business News	
Research Starters - Business	
Research Starters - Education	
Research Starters - Sociology	
RILM Abstracts of Music Literature	
Textile Technology Complete	
Web News	
World Textiles	
MEDLINE	**Pubmed**
Scopus	**Scopus**
Cochrane Library	**Cochrane Library**
Google Scholar	**Google Scholar**
Authors' collections	**Authors' collections**

Articles written in languages different from English and Spanish will be included if they can adequately translated using Google Translate[30] or if English or Spanish translations are available [31], as previously reported.

We will de-duplicate retrieved references using the default algorithm of Rayyan QCRI.[32] Identified duplicates will be manually revised to confirm duplicated publications to be eliminated[32]. Both reference and study duplicates (i.e., articles published more than once) will be identified through Rayyan, followed by their visual inspection; only the earliest publications will be included.

The screening process (title/abstract stage) will be performed using an online tool (Sysrev[33]) and will be pilot-tested with a random sample of 25 studies.[24] Two screening stages will be performed: title/abstract and full-text.[24] The second screening process will be performed in those studies whose inclusion/exclusion could not be decided by title/abstract screening. Full-text will be retrieved for all studies selected for inclusion or left undecided after the first screening stage. Besides the screening process, further studies could be excluded if their full-text is not available. Eligibility will be assessed by two independent researchers using Sysrev [33] according to predefined criteria. As previously reported, one decision will be considered sufficient for inclusion, while two decisions will be required for exclusion.[23] A third researcher will re-assess all excluded studies, and this decision will be considered final.

Agreement between reviewers will be assessed using Sysrev tools.[33] We will retrieve all studies selected for inclusion using Scite[34], in order to identify retracted studies, which will be eliminated. After six months of initial searches, and before the final analysis, we will re-run the search strategy to identify more recent studies for possible inclusion. A PRISMA flow diagram will be used to describe search results.[35] Also, the number of included/retrieved references (precision of literature retrieval), will be reported.

Eligibility criteria

Inclusion criteria

- Studies describing patients with PD (or Parkinsonism) receiving DHEA (or its sulfated ester DHEAS, any treatment regime) independently of their age, race, sex/gender, current treatment, or any other PROGRESS equity characteristic.[36]
- No specific diagnostic criteria for PD (or Parkinsonism) will be considered if the studies describe their population as presenting the condition, as previously reported.[37] The analysis will not be limited to any clinical setting. All types of quantitative, qualitative, or mixed-method studies will be considered.
- Any experimental model of PD reporting and effect of DHEA (or DHEAS) treatment (any pharmacological regime). Studies will be analyzed separately by type of experimental model (cell cultures, rodents, or non-human primates).
- Any theoretical study discussing the effects, advantages, disadvantages, side-effects, or therapeutic implications of administering DHEA (or DHEAS) to PD (or Parkinsonism) patients.

Exclusion criteria

- Studies written in languages different than Spanish or English that can not be appropriately translated
- Duplicated references or studies
- Studies whose full-text files can not be retrieved

No restrictions regarding follow-up time, year of dissemination, language, or publication status will be considered. These criteria may be adjusted during the screening process, as in previous studies.[23]. At least 75% agreement among reviewer team members will be required to introduce changes in these criteria.[24] Adjustments will be applied to all studies and reported accordingly.

Data charting

Data will be extracted by one researcher and verified by another using Sysrev [33] and predefined criteria [19]. Discrepancies will be solved through discussion. Although we will pilot-test the extraction format with a random sample of 25 studies [24], the format may be adjusted as necessary.

Either clinical or preclinical studies will be analyzed separately (for summary tables), even though they might be discussed jointly in the narrative synthesis. The results will be presented in the order established in the research questions.

The main outcomes of interest are the following:

- For clinical studies: clinical scales scores (any) for PD, quality-of-life scales (any), incidence of side-effects (any), interaction with conventional treatments (changing dose regimens, modifying incidence or severity of side-effects for conventional treatments).
- For preclinical studies: brain dopamine content (either in specific brain regions or the whole brain), motor activity (measured in an activity chamber), biochemical/histological/histochemical evidence of neuronal death

(caspase activity or expression, markers of necrosis/apoptosis/autophagy, markers of free radicals/oxidative stress/antioxidant mechanisms).

Additional variables to be extracted include sample size (per treatment group), type of study (clinical/preclinical, randomized/quasi-randomized/non-randomized, trial/observational), clinical setting, treatment comparator (placebo/inactive treatment, active treatment), concomitant conventional treatments, age (years for humans, or months/bodyweight for experimental animals), sex/gender (male, female, other), animal species, DHEA dose (mg, mg/day, or mg/kg), administration route, duration of treatment if more than a single administration (hours or days).

Data synthesis

Data summaries from original studies and systematic intervention reviews will be presented in graphs, figures, tables, and narrative synthesis. Other types of review articles (scoping, narrative) will only be considered for narrative synthesis. Results will be presented as originally reported, no conversions will be applied if different units are involved.

Conclusions

This protocol has some strengths and limitations, it is intended to provide an integrative perspective of the therapeutic potential of dehydroepiandrosterone for PD based on both clinical and preclinical studies. Also, possible side-effects of this treatment are considered to suggest an objective recommendation of its use. Finally, the costs of current treatment for this disease are included to estimate the generalizability of its application.

In contrast to other protocols[23], our research questions comply with systematic frameworks supporting our search strategy, which was peer-reviewed. Efforts will be made to include articles written in any language. The multidisciplinary research group provides complementary perspectives from several profiles.

This protocol complies to the most possible extent with several guidelines, including several for systematic reviews (PRISMA 2020, PRISMA-A, PRISMA-P, PRISMA-S, PRESS) besides those for scoping reviews (PRISMA-Scr, JBI Manual for Evidence Synthesis).

Only a narrative analysis of the evidence will be presented. No risk-of-bias analysis or certainty of evidence assessment will be applied. We consider the heterogeneity of the included studies to be an asset, since it allows an exhaustive analysis of the research topic. However, it is also a limitation, considering it precluded us from performing a systematic review of intervention or meta-analysis.

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Authors' contributions

- I.P.N. provided methodological expertise, topic expertise, original idea; and contributed developing the protocol's methodology (including search strategy), coordinating co-author's participation and activities; drafting, correcting, and approving the protocol; documenting and implementing protocol amendments, and is the guarantor of the review.
- C.E.D.C. provided topic expertise, original idea; contributed with the drafting, correcting, and approval the protocol.
- H.S. provided methodological expertise; contributed to the protocol's methodology; drafted the manuscript; revised, corrected, and approved the protocol, and participated in the peer-reviewing of the search strategy.
- V.A.C.P. contributed with the protocol's methodology, and the drafting, revising, and approval the protocol.
- E.C.M. provided topic expertise, and contributed to revising, correcting, and approving the protocol.
- C.R. provided topic expertise; contributed by supervising the reviewer team, and revising, correcting, and approving the protocol.

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Guillain-Barré Syndrome Related to the application of Vaccine Against Sars-CoV2 and Seasonal Influenza. Case Report

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Abstract

Summary: Guillain-Barré Syndrome (GBS) is the principal cause of acute flaccid paralysis in the world. During mass vaccination campaigns, implemented in previous decades for the influenza virus and currently for the SARS-CoV2 virus, an increase in GBS cases has been reported. Recently, both vaccines have been implemented in adult immunization schedules. **Objective**: to report a case of GBS with a history of vaccination against seasonal influenza and SARS-CoV2 in a short period of time. **Results**: A 53-year-old woman with no previous infectious disease received a trivalent inactivated seasonal influenza vaccine [Virus A (A/Victoria/2570/2019(H1N1pm09), Virus A (A/Cambodia/e0826360/2020(H3N2), Virus B (B/Washington/02/2019(B/Victoria line)] and a SARS-CoV2 vaccine (Oxford/AstraZeneca, ChAdOx1-S) 22 days apart. The patient then developed progressive and ascending symptoms of weakness predominantly in the lower extremities, with areflexia. **Paraclinical examinations**: lumbar puncture with albuminocytological dissociation, nerve conduction study fulfilling criteria for AIDP variant, classifying for GBS with level of certainty 1 by Brighton criteria. **Conclusion**: due to the SARS-CoV2 pandemic, mass vaccination schedules against this virus were implemented, which coincide with vaccination against seasonal influenza virus in the winter season; consequently, cases of GBS may occur with a history of recent application of both vaccines.

Keywords: *SARS-CoV2, influenza, Guillain-Barré syndrome, vaccination, AIDP*.

Introduction

Guillain Barre Syndrome (GBS) is the leading cause of acute flaccid paralysis in the world. In 70% of the cases, the mechanism of peripheral nerve damage is attributable to an aberrant immune response after infection. Other cases have been related to the application of certain vaccines, for example, against seasonal influenza, hepatitis B and hepatitis A, to name a few.[1] Even when patients are diagnosed and treated promptly (immunoglobulin human G or plasma exchanges), 20-40% present short term severe disability (non-independent gait).[1,2]

The main electrophysiological variants are acute inflammatory demyelinating polyradiculoneuropathy (AIDP) and acute motor axonal neuropathy (AMAN).

The AIDP variant is more frequent in European countries and in the USA, and is related to viral infections (e.g., cytomegalovirus) and post-vaccination. The AMAN variant is the most frequent in some Latin American countries, such as Mexico, and in Asia; this variant is related to gastrointestinal infection by the agent Campilobacter jejuni.[1,2]

In 2011, as a consequence of the increase in GBS cases linked to different vaccines, a group of experts created the Brighton Criteria, which offer recommendations to define GBS cases related to vaccination, and classify them in levels of diagnostic certainty.[3]

Currently, due to the SARS-CoV2 pandemic, health systems in all countries have implemented mass vaccination against this virus. Worldwide, secondary reactions to vaccines against the SARS-CoV2 virus have been reported, ranging from mild symptoms such as fever, myalgia and flu-like symptoms, to cases of GBS.[4] However, it should be noted that there are few cases of GBS related to vaccination against SARS-CoV2.[5] In addition, during the winter season and in accordance with WHO recommendations, countries such as Mexico implement vaccination against seasonal influenza with a trivalent inactivated virus vaccine in the adult population.[6]

To our knowledge, there is little information on cases of GBS with a history of vaccine application against two respiratory viruses. In this work we report the case of a patient who presented GBS after receiving the vaccines against seasonal influenza and the SARS-CoV2 virus in a short period of time.

Clinical Case

A 53-year-old woman with a diagnosis of type 2 diabetes mellitus and systemic arterial hypertension, had been on treatment for a year with losartan 50 mg every 12 h and metformin 500 mg every 12 h with adequate control. She denied any gastrointestinal or respiratory infection in the last 4 weeks. She was vaccinated against seasonal influenza with a trivalent inactivated virus vaccine [Virus A (A/Victoria/2570/2019 (H1N1pm09)), Virus A (A/Cambodia/e0826360/2020 (H3N2)), Virus B (B/Washington/ 02/2019 (line B/Victoria))], and 22 days later, she received the third vaccine against the SARS-CoV2 virus (Oxford / AstraZeneca, ChAdOx1-S [recombinant] vaccine). That same day, 8 hours later, the patient presented distal paresthesias in the upper extremities, adding in the following days progressive weakness of the four extremities, predominantly in the lower extremities, until requiring a wheelchair to move. The patient was admitted to the emergency department 14 days after symptom onset. In the general physical examination, vital signs were in normal parameters, without fever, and no pathological findings in the lung fields. At neurological examination, the patient showed no abnormalities in the cranial nerves. Regarding the motor system, muscle strength —quantified with the MRC scale— was 4/5 in the upper limbs (deltoid, biceps and hand extensor muscles), 1/5 in the lower limbs (iliopsoas muscle, quadriceps and tibialis anterior), with a score of 4 on the Hughes scale. Muscle stretch reflexes were found to be generally abolished. She had no alterations in sensitivity. General tests (hematic cytometry, blood chemistry, serum electrolytes, liver function tests, CPK levels, TSH) were within normal ranges; serologies for HIV, HCV and HBV were negative; C-reactive protein 1.1 mg/l; chest CT with no data of pulmonary interstitial infiltrates. Lumbar puncture was performed, which reported 243 mg/dL of protein, 0 cells, 80 mg/dL of glucose. Nerve conduction studies of 4 limbs revealed the AIDP variant, according Hadden criteria[7] (Figure 1 and Table 1). Using the Brighton criteria, GBS was concluded,[3] for which the patient received treatment with human immunoglobulin G at a dosage of 2 g/kg, divided into 5 days. She remained hospitalized for 6 days, without in-hospital complications or dysautonomia, with improved recovery of functionality, and she was discharged home having a Hughes scale score of 3.

Revision

Both the vaccine against the influenza virus and the SARS-CoV2 virus have been related to the increase in GBS cases in the last decades, which has been controversial. Recently, the vaccine against the SARS-CoV2 virus was added to the vaccination schemes already implemented in the population, as well as the application of the seasonal influenza vaccine in the winter period.

Guillain-Barré syndrome (GBS) is the most common cause of acute flaccid paralysis in the world, with an incidence of 0.81 to 1.91 cases per 100,000 inhabitants.[1] In its classic form, GBS is a post-infectious autoimmune disease, in two thirds of cases symptomatic respiratory or gastrointestinal infections precede the onset of GBS symptoms; other triggering factors that have been described are vaccines.[1] The AIDP electrophysiological variant is the most frequently reported in some populations, and has been related to symptomatic infections by certain viruses, for example: cytomegalovirus, Epstein-Bar, Influenza A virus, Hepatitis B. The lack of a serological study for these viruses in our patient is a shortcoming of our report.[1]

Since 1976, an increase in cases of Guillain Barre syndrome has been reported linked to vaccination against the seasonal influenza virus, notably increasing the risk during the vaccination period of that year. During these vaccination campaigns, GBS cases peaks have been reported that reached high incidences, of 1 per 100,000 vaccinated.[8]

Figure 1. Nerve conduction recordings of motor nerves: A) left median nerve presents prolonged distal latency (arrow); B) Tibial nerve (left and right), in both nerves there is prolongation of the distal latencies (arrows).

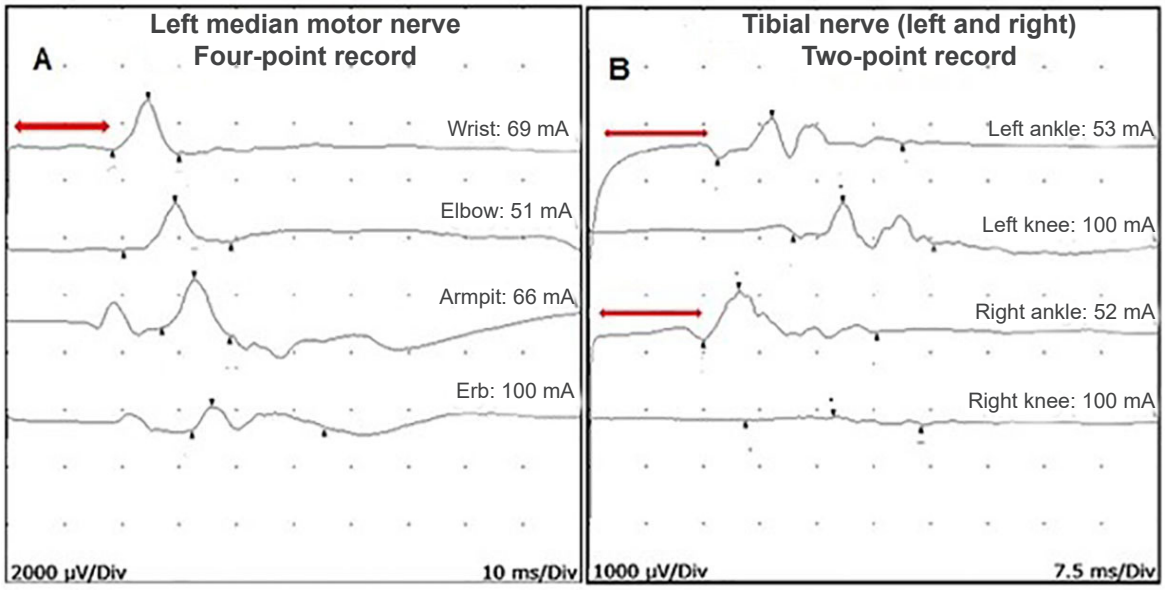

Table 1. Nerve conduction recordings of motor nerves.

	Distal latency (ms)	Conduction velocity (m/s)	Distal CMAP (mIV)
Motor nerves			
Medium	18.4	33	0.9
Ulnar	4.6	34	2.9
Tibial	15	59	0.7
Peroneal	11.1	40	0.4
Sensory nerves			PANS (µV)
Medium	NR	NR	NR
Sural	3.4	41	11.8

CMAP: compound muscle action potential; SNAP: sensory nerve action potential; NR: no record; mIV: millivolts; µV: microvolts

Due to the SARS-CoV2 virus pandemic, mass vaccination systems were established. Currently, several cases of GBS have been reported related to vaccination against SARS-CoV2, particularly with vaccines designed with adenovirus vectors,[9] consequently, the mechanisms of association have been investigated, without finding conclusive evidence.[9] During 2021, a total of 833 GBS cases were reported worldwide in patients who were vaccinated with AstraZeneca, out of a total of 592 million vaccinated.[7] In the Mexican population, a study reported 8 cases of GBS after vaccination against SARS- CoV2, 2 of which were linked to the application of the AztraZeneca vaccine.[4]

Within the different case series published on the GBS association related to vaccination against SARS-CoV2, and the seasonal influenza vaccine, it is mentioned that the majority of cases present the classic sensory-motor clinical variant of GBS and the electrophysiological variant of AIDP, as in the case of our patient.[4,10]

Despite the fact that previous studies indicate problems with the safety of the vaccines, there is still no conclusive evidence on the association between SARS-CoV2 vaccines and GBS. The risk of developing GBS after vaccination is low compared to other vaccines, such as influenza, suggesting that SARS-CoV2 vaccines are safe. On the other hand, the benefit its application outweighs the risk of contracting the infection.[5,11]

Analyzing the case of the influenza vaccine, during the swine influenza pandemic in 1976, a massive vaccination program was carried out in the United States of America, reporting an increased risk of presenting GBS after receiving the vaccine.[12] Since then, studies have been published assessing the risk of GBS after vaccination, finding an increased relative risk of up to 1.7 (95% CI, 1.0 - 2.8).[13] However, over time, it was documented that the risk of presenting GBS after influenza infection is higher compared to the application of the vaccine.[14]

According to the Brighton criteria —created by a panel of experts to classify patients with GBS into certainty levels—, our patient classified into certainty level 1. In addition, these criteria establish a time frame of 6 weeks to relate a case of GBS with a history of vaccination.[3] In the case of our patient, both vaccines were applied in a period of 22 days.

Due to the current SARS-CoV2 pandemic, mass vaccination against this virus was implemented using different types of vaccines, jointly with the reinforcement of the vaccination against the seasonal influenza virus in the winter season. These modifications in the vaccination schedules cause a modification in the population characteristics, consequently, it will be more common for monophasic autoimmune disease models such as GBS to develop in patients with a history of applying both vaccines, even with a temporal period of up to 6 weeks from the vaccine application and the onset of symptoms, without implying an association. In addition, as mentioned previously, we consider that there is a higher risk of GBS in the population not vaccinated against seasonal influenza. Regarding the SARS-CoV2 vaccine, we believe that epidemiological studies of large populations are necessary to establish a correlation with the increase of GBS cases.[14]

Conclusion

Currently, the global population is being vaccinated as a consequence of the SARS-CoV2 pandemic, in parallel, vaccination schemes against the seasonal influenza virus are being reinforced in the winter season, which causes certain population to have a particular clinical history. We report the case of a patient with AIDP variant GBS, with a history of vaccine application for the SARS-CoV2 virus and for seasonal influenza.

Conflicts of interest

The authors of this study have no conflicts of interest to disclose.

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Mind and Brain: From the Egyptians to Cajal and the Neuromyths

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Since the "Father of philosophy", Socrates, and his disciple Plato speculated on the nature of the human mind in the 5th century BC, numerous thinkers such as Descartes (1596–1650), Willis (1621-1675), Locke (1632–1704), Kant (1724–1804), and Freud (1856–1939) have sought to understand human behavior through their observations.[1-3] For René Descartes, the pineal gland, an unpaired structure in the brain, was the physical seat from which the mind could exercise control over the body; the "I think, therefore I am" philosopher thus inaugurated the contemporary mind-body dilemma in the 17th century, pioneering a topic that concerns both physiology and psychology.[2,4] The 17th century English anatomist, Thomas Willis, considered that the corpus callosum was the area where ideas were generated.[3] Willis believed that it was necessary for the rational soul to be accessible to observation and addressed this subject through comparative anatomy of humans and animals, finding that there are many similarities between the brain of man and mammals.[5] Later, well into the 20th century, cognitive psychology and neuroscience merged to give rise to the biological science of the mind, cognitive neuroscience, named after George Miller and Michael Gazzaniga. Miller, cognitive psychologist, first described the limited capacity of human working memory in 7 ± 2 information units; Gazzaniga, neuroscientist, studied the functional lateralization of the brain through the surgical section of the corpus callosum of patients with refractory epilepsy.[1,6,7] As a result, neuroimaging techniques, such as functional magnetic resonance imaging, made possible for the first time to observe mental activity and thus discover what is inside the human brain, making the dream of so many philosophers of yesteryear come true.

Ancient Egyptians placed great value on the preservation of the human body after death; they believed that it would accompany them in the afterlife.[8] In addition, they considered that the source of the emotions, the soul and the intelligence was not in the brain but in the heart, accordingly, when embalming their dead for mummification, the brain was removed through the nostrils and discarded, while other organs, such as the heart, were preserved.[8,9] Embalmers did not attempt to preserve the brain because they believed that it would be replaced by a new one in the afterlife.[8] The *Book of the Dead of ancient Egypt* describes how the deceased pharaoh would be assisted by Osiris, god of resurrection, to replace his head with that of god Atum, creator of the universe, which would be occupied by a new brain.[8,10] As far as is known, Egyptians did not have a real conception of brain function, however, descriptions compatible with neurological diseases such as epilepsy, dementia and cerebral infarction dating from that time are preserved.[9]

The functioning and structure of brain cells were described by Santiago Ramón y Cajal, an Spanish doctor who was the first to describe that the brain is comprised of cells that almost never touch and not by a contiguous network, as his predecessors stated (Figure 1).[11] Cajal, who had painting as his first vocation, perfected existing staining techniques and through a conventional microscope observed and sketched "neural landscapes" for the first time, describing principles whose validity endures to this day: the neuron as an independent cell, its extensions called dendrites that receive impulses, and the distal structure called axon that transmits those impulses to other neurons in order to communicate. Dr. Cajal's descriptions, which constitute the Neuron Doctrine, laid the groundwork to further describe the functioning of the brain.[11]

Figure 1. Bust of Dr. Santiago Ramón y Cajal. Faculty of Medicine of the Autonomous University of Yucatan in Mérida.

The brain of the golden eagle and the human work on these basic physiological principles, but where is the mind in all this? The mind is the virtual entity of the functioning of the brain, analogous to software being a virtual manifestation of the computer. The functioning of the mind is reflected in electrical impulses, neurotransmitters and hormones that neurons use to communicate with each other over small or large distances. Thus, the mind cannot be located in specific parts of our brain, however, it has been stablished that the cerebral cortex and the gray matter neurons inside the brain are necessary elements, although not sufficient, for its constitution.

The human brain weighs an average of 1,500 grams and contains 100,000 million neurons, these being more numerous than the stars in our galaxy.[12] This complex system is made up of multiple interconnected parts that — when self-organized into a single system — manifest one or more emergent properties strikingly different from any of the properties of the individual components.[6] Emergent properties are a common phenomenon accepted by many fields of knowledge, such as physics, biology, chemistry, and sociology.[6] In neuroscience, a clear example is consciousness, which arises from the collective activity of a large number of neurons:[13] focusing on the individual firing of a neuron at the cellular level may not tell us everything we need to know to understand it.[6]

Distinguished thinkers such as Eric Kandel, Nobel laureate in medicine, state that the 21st century will be marked by discoveries in the biology of the mind, just as the 20th century was by Watson and Crick's biology of the gene.[14] The discovery of the DNA helix laid the foundation for understanding how hereditary information was transmitted and combined between individuals; the milestone that crowned the investigation of the genetic code was the Human Genome Project, which consisted of identifying and locating the genes of the human species by analyzing the DNA of hundreds of people.[15] In 2003, it was possible to identify that human beings have between 20,000 and 22,500 different genes.[15,16] Similarly, the Neuron Doctrine of Santiago Ramón y Cajal established the basic principles of the International Human Connectome Project that aims to identify the structural and functional connections of neurons through methods such as functional magnetic resonance imaging and electroencephalography; it is evident that the study of the Human Connectome is more complex and gradual than the Human Genome Project.[17] Although the brain is the product of our genes and all human beings share 99% of our identical DNA, the particular experiences of each individual influence variations in brain networks; this is confirmed in identical twins who, even when they share 100% of genetic material, do not have the exact same brains.[17,18]

The popularization of neuroscience to the general public has its risks and can lead to misunderstandings, since it is often difficult to explain and convey all the subtleties of scientific discoveries. When brain science is linked to other areas such as education, misconceptions, called "neuromyths", may arise.[19,20] The most widespread neuromyth, among teachers, general population and people highly exposed to neuroscience, is the one of "learning styles", which states that people learn better when they receive information in their preferred learning style: auditory, visual or kinesthetic.[19-21] Although there are areas in the brain specific for auditory, visual and motor information processing, all are interconnected: studies have shown that there is no better learning with techniques focused on a particular style, but, on the contrary, learning is limited.[19,20] When working simultaneously with these three "styles" learning is more significant, that is, it is associated with more memories. This is just one example of a neuromyth — a false scientific belief about neuroscience applied to learning —, however, there are many more and all of them often have a misinterpreted scientific foundation.[19,20] Another popular neuromyth upholds that left or right hemispheric brain dominance helps to explain differences between students, establishing that some are more creative and others more analytical.[19-22] This theory posits that personality, behavior, and abilities in individuals are governed by a cerebral hemisphere.[19-22] Although it is true that the hemispheres are specialized in different tasks (lateralization), their connection through the corpus callosum makes them work together, in addition, neuroimaging data have not provided clear evidence of phenotypic differences in the strength of left-dominant or right-dominant networks.[22]

These 1,500 grams of brain matter is all we are, because without memory we would not be ourselves: everything we love is in the brain, everyone we know is there, our joys and sorrows, science and art, all our knowledge. Since ancient times, every philosopher, every hunter and gatherer, every king and commoner who ever lived has seen the world and the universe through their brain. Nothing that is human is alien to us through neuroscience.

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Ventral view of rat brain

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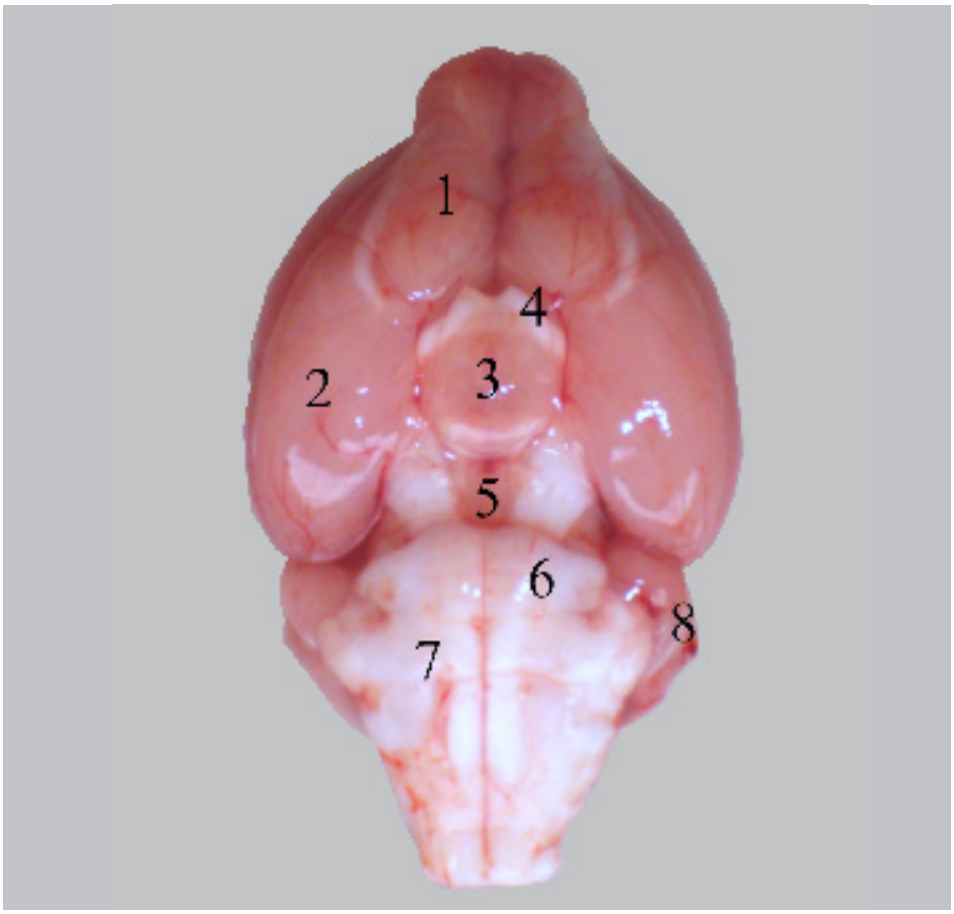
I.P.N. contributed the original idea, the obtaining of the image, the execution of the procedure, as well as the preparation of the image and the manuscript for publication.



The image shows the brain of an adult male Wistar rat (250-300 g) as viewed from its base. The rat was sacrificed by decapitation during the execution of an experimental procedure. Both the skull bones and the meninges were sectioned to allow visualization of the brain and facilitate its removal. The ophthalmic nerves were sectioned during the procedure. Various anatomical structures can be identified, such as: **1**) olfactory bulb, **2**) temporal lobe, **3**) hypothalamus, **4**) optic chiasm, **5**) thalamus, **6**) pons, **7**) medulla oblongata, **8**) cerebellum. The prominent size of the olfactory bulbs is notable, which is related to the olfactory sensitivity of these rodents.

Keywords: *Neuroanatomy, Rodents, Basic Science*