ISSN:2149-1909

THE JOURNAL OF NEUROBEHAVIORAL SCIENCES

Year: 2016 Vol:3 No:1

NÖRODAVRANIŞ BİLİMLERİ DERGİSİ

JNBS Published by Üsküdar University

JNBS

THE JOURNAL OF NEUROBEHAVIORAL SCIENCES
NÖRODAVRANIŞ BİLİMLERİ DERGİSİ

Volume: 3
Issue Number: 1
Year: 2016

Owner/Sahibi
Üsküdar University/Üsküdar Üniversitesi

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IT/Teknik Servis
Gürkan Karadere, Baybars Tolgahan Yılmaz

Period/Periyot
4 ayda 1 yayınlanır, ücretsiz dağıtılır.

Yönetim Yeri/Administrative Adress
Altunizade Mah. Haluk Türksoy Sokak No: 14, 34662
Üsküdar/İstanbul
Bilgi Hattı/Contact: +90 216 400 22 22
Web: www.jnbs.org www.uskudar.edu.tr
e-mail: jnbs@uskudar.edu.tr

Graphic Design/Grafik Tasarım
Koro Reklam Aklı Advertising Agency
Kuzguncuk Mah. Yapraklı Çınar Sok. No:9
Kuzguncuk/Üsküdar/İstanbul
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Printing office/Matbaa
G.M. Matbaacılık ve Tic. A.Ş.
100 Yıl Mah. MASSİT 1. Cad. No:88 Bağcılar / İstanbul
Phone: +90 212 629 00 24
Print Date/Baskı Tarihi: January 2016

JNBS 2016 Published by Üsküdar University www.jnbs.org

**The Journal of Neurobehavioral Sciences (JNBS) is a peer-reviewed open-access neuroscience journal without any publication fees.

**JNBS is published electronically and in the printed form 3 times a year by Uskudar University.

ISSN:2149-1909

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JOURNAL OF NEUROBEHAVIORAL SCIENCES ADVISORY COMMITTEE

NÖRODAVRANIŞ BİLİMLERİ DERGİSİ DANIŞMA KURULU ÜYELERİ

JNBS 2016 Published by Üsküdar University www.jnbs.org

ABOUT THIS JOURNAL

The Journal of Neurobehavioral Sciences (JNBS) is a peer-reviewed open-access neuroscience journal without any publication fees. All editorial costs are sponsored by the Üsküdar University Publications and the Foundation of Human Values and Mental Health. Each issue of the Journal of Neurobehavioral Sciences is specially commissioned, and provides an overview of important areas of neuroscience from the molecular to the behavioral levels, delivering original articles, editorials, reviews and communications from leading researchers in that field.

JNBS is published electronically and in the printed form 3 times a year by Uskudar University.

The language of JNBS is in English. However, our editorial office provide Turkish abstracts in addition to English for each article.

Aims & Scope

The scope of the journal is broad. It covers many disciplines and spans molecules (e.g., molecular neuroscience, biochemistry) through systems (e.g., neurophysiology, systems neuroscience) to behavior (e.g. cognitive neuroscience) and clinical aspects (e.g. psychopharmacology). The journal covers all aspects of neuroscience with an emphasis on translational psychiatry and psychology, as long as the goal is to delineate the neural mechanisms underlying normal or pathological behavior.

Preclinical and clinical studies are equally considered for publication. We also invite manuscripts on the methods of computational modeling of psychiatric and neurological disorders, and treatment outcome.

The journal has a special emphasis on psychiatric and neurological disorders.

However studies on normal human behavior are also considered. Studies on animals and technical notes must have clear relevance and applicability to human disease.

Case Reports that includes recent neuroscientific treatment or diagnosis methods are generally within the scope of JNBS.

Please see our editorial board section for information on specific sections.

In addition, the following two categories are further featured in JNBS:

- Mini-reviews that succinctly survey appropriate areas of current research or theory
- Commentaries that serve as vehicles for brief presentations of new theories, hypotheses, points of view, or critiques of current research

Papers will be selected on the basis of their methodology and negative results are strongly considered for publication.

The average time from submission to first decision is less than 30 days. Accepted articles are published online ahead of print in an average of 40 workdays, and articles are published in print 3-6 months after acceptance.

Please see our Guide for Authors for information on article submission. If you require any further information or help, please email us (jnbs@uskudar.edu.tr)

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INTRUCTIONS FOR AUTHORS

Instructions for Authors

Prior to submission, please carefully read and follow the submission guidelines entailed below. Manuscripts that do not conform to the submission guidelines may be returned without review.

Submission

Submit manuscripts electronically (.doc format with including all figures inside) via the online submission system of our website (www.jnbs.org or www.scopemed.org/?sec=gfa&jid=34).

Cumhur Taş, MD PhD
Co-Editor, Journal of Neurobehavioral Sciences
Department of Psychology

Üsküdar University
Altunizade Mh., Haluk Türksoy Sk No: 14,
İstanbul-Turkey

General correspondence may be directed to the Editor's Office.

In addition to postal addresses and telephone numbers, please supply electronic mail addresses and fax numbers, if available, for potential use by the editorial and production offices.

Masked Reviews

Masked reviews are optional and must be specifically requested in the cover letter accompanying the submission. For masked reviews, the manuscript must include a separate title page with the authors' names and affiliations, and these ought not to appear anywhere else in the manuscript.

Footnotes that identify the authors must be typed on a separate page.

Make every effort to see that the manuscript itself contains no clues to authors' identities. If your manuscript was mask reviewed, please ensure that the final version for production includes a byline and full author note for typesetting.

Types of Articles

Brief Reports, commentaries, case reports and mini-reviews must not exceed 4000 words in overall length. This limit includes all aspects of the manuscript (title page, abstract, text, references, tables, author notes and footnotes, appendices, figure captions) except figures. Brief Reports also may include a maximum of two figures.

For Brief Reports, the length limits are exact and must be strictly followed.

Regular Articles typically should not exceed 6000 words in overall length (excluding figures).

Reviews are published within regular issues of the JNBS and typically should not exceed.

10000 words (excluding figures)

Cover Letters

All cover letters must contain the following:

A statement that the material is original —if findings from the dataset have been previously published or are in other submitted articles, please include the following information:

*Is the present study a new analysis of previously analyzed data? If yes, please describe differences in analytic approach.

*Are some of the data used in the present study being analyzed for the first time? If yes, please identify data (constructs) that were not included in previously published or submitted manuscripts.

*Are there published or submitted papers from this data set that address related questions? If yes, please provide the citations, and describe the degree of overlap and the unique contributions of your submitted manuscript.

*The full postal and email address of the corresponding author;

*The complete telephone and fax numbers of the same;

*The proposed category under which the manuscript was submitted;

*A statement that the authors complied with APA ethical standards in the treatment of their participants and that the work was approved by the relevant Institutional

Review Board(s).
*Whether or not the manuscript has been or is posted on a web site;

*That APA style (Publication Manual, 6th edition) has been followed;

*The disclosure of any conflicts of interest with regard to the submitted work;

*A request for masked review, if desired, along with a statement ensuring that the manuscript was prepared in accordance with the guidelines above.

*Authors should also specify the overall word length of the manuscript (including all aspects of the manuscript, except figures) and indicate the number of tables, figures, and supplemental materials that are included.

INTRUCTIONS FOR AUTHORS

Manuscript Preparation

Prepare manuscripts according to the Publication Manual of the American Psychological Association (6th edition).

Review APA's Checklist for Manuscript Submission before submitting your article. Double-space all copy. Other formatting instructions, as well as instructions on preparing tables, figures, references, metrics, and abstracts, appear in the Manual.

Below are additional instructions regarding the preparation of display equations and tables.

Display Equations

We strongly encourage you to use MathType (third-party software) or Equation

Editor 3.0 (built into pre-2007 versions of word) to construct your equations, rather than the equation support that is built into Word 2007 and Word 2010. Equations composed with the built-in Word 2007/Word 2010 equation support are converted to low-resolution graphics when they enter the production process and must be rekeyed by the typesetter, which may introduce errors.

To construct your equations with MathType or Equation Editor 3.0:

Go to the Text section of the Insert tab and select Object.

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If you have an equation that has already been produced using Microsoft Word 2007 or 2010 and you have access to the full version of MathType 6.5 or later, you can convert this equation to MathType by clicking on MathType Insert Equation. Copy the equation from Microsoft Word and paste it into the MathType box. Verify that your equation is correct, click File, and then click Update. Your equation has now been inserted into your Word file as a MathType Equation.

Use Equation Editor 3.0 or MathType only for equations or for formulas that cannot be produced as word text using the Times or Symbol font.

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Use Word's Insert Table function when you create tables. Using spaces or tabs in your table will create problems when the table is typeset and may result in errors.

Abstract and Keywords

All manuscripts must include an English abstract containing a maximum of 250 words typed on a separate page. After the abstract, please supply up to five keywords or brief phrases. For the Turkish native speakers JNBS also requires a Turkish version of the abstract and keywords. However this rule does not apply to non-native speakers and our translation office will include the Turkish abstract free of charge.

References

List references in alphabetical order. Each listed reference should be cited in text (Name, year style), and each text citation should be listed in the References section.

In-text Citations

• For two or fewer authors, list all author names (e.g. Brown & Taş, 2013). For three or more authors, abbreviate with 'first author' et al. (e.g. Uzbay et al., 2005).

• Multiple references to the same item should be separated with a semicolon (;) and ordered chronologically. References by the same author in the same year should be differentiated by letters (Smith, 2001a; Smith, 2001b).

• Cite articles that have been accepted for publication as 'in press', include in the reference list.

• Cite unpublished work, work in preparation, or work under review as 'unpublished data' using the author's initials and surname in the text only; do not include in the reference section

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• Journal Article:

Hughes, G., Desantis, A., & Waszak, F. (2013). Mechanisms of intentional binding and sensory attenuation: The role of temporal prediction, temporal control, identity prediction, and motor prediction. Psychological Bulletin, 139, 133–151. http://dx.doi.org/10.1037/a0028566

• Authored Book:

Rogers, T. T., & McClelland, J. L. (2004). Semantic cognition: A parallel distributed processing approach. Cambridge, MA: MIT Press.

• Chapter in an Edited Book:

Gill, M. J. & Sypher, B. D. (2009). Workplace incivility and organizational trust.

In P. Lutgen-Sandvik & B. D. Sypher (Eds.), Destructive organizational communication: Processes, consequences, and constructive ways of organizing (pp. 53–73). New York, NY: Taylor & Francis.

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Graphics files are welcome if supplied as Tiff, EPS, or PowerPoint files. Multipanel figures (i.e., figures with parts labeled a, b, c, d, etc.) should be assembled into one file.

The minimum line weight for line art is 0.5 point for optimal printing.

JNBS 2016 Published by Üsküdar University www.jnbs.org

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PUBLICATION ETHICS AND PUBLICATION MALPRACTICE STATEMENT (ETHICAL GUIDELINES FOR PUBLICATION)

The publication of an article in the peer-reviewed journal JNBS is an essential building block in the development of a coherent and respected network of knowledge. It is a direct reflection of the quality of the work of the authors and the institutions that support them. Peer-reviewed articles support and embody the scientific method. It is therefore important to agree upon standards of expected ethical behaviour for all parties involved in the act of publishing: the author, the journal editor, the peer reviewer, the publisher and the society of society-owned or sponsored journals.

Uskudar University, as publisher of the journal, takes its duties of guardianship over all stages of publishing extremely seriously and we recognise our ethical and other responsibilities.

We are committed to ensuring that advertising, reprint or other commercial revenue has no impact or influence on editorial decisions. In addition, Editorial Board will assist in communications with other journals and/or publishers where this is useful to editors. Finally, we are working closely with other publishers and industry associations to set standards for best practices on ethical matters, errors and retractions - and are prepared to provide specialized legal review and counsel if necessary.

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(These guidelines are based on existing COPE's Best Practice Guidelines for Journal Editors.)

Reporting standards

Authors of reports of original research should present an accurate account of the work performed as well as an objective discussion of its significance. Underlying data should be represented accurately in the paper. A paper should contain sufficient detail and references to permit others to replicate the work. Fraudulent or knowingly inaccurate statements constitute unethical behavior and are unacceptable. Review and professional publication articles should also be accurate and objective, and editorial 'opinion' works should be clearly identified as such.

Authors are required to state in writing that they have complied with the Declaration of Helsinki Research Ethics in the treatment of their sample, human or animal, or to describe the details of treatment.

Data access and retention

Authors may be asked to provide the raw data in connection with a paper for editorial review, and should be prepared to provide public access to such data (consistent with the ALPSP-STM Statement on Data and Databases), if practicable, and should in any event be prepared to retain such data for a reasonable time after publication.

Originality and plagiarism

The authors should ensure that they have written entirely original works, and if the authors have used the work and/or words of others, that this has been appropriately cited or quoted.

Plagiarism takes many forms, from 'passing off' another's paper as the author's own paper, to copying or paraphrasing substantial parts of another's paper (without attribution), to claiming results from research conducted by others. Plagiarism in all its forms constitutes unethical publishing behavior and is unacceptable.

Multiple, redundant or concurrent publication

An author should not in general publish manuscripts describing essentially the same research in more than one journal or primary publication. Submitting the same manuscript to more than one journal concurrently constitutes unethical publishing behavior and is unacceptable.

In general, an author should not submit for consideration in another journal a previously published paper. Publication of some kinds of articles (e.g. clinical guidelines, translations) in more than one journal is sometimes justifiable, provided certain conditions are met. The authors and editors of the journals concerned must agree to the secondary publication, which must reflect the same data and interpretation of the primary document. The primary reference must be cited in the secondary publication. Further detail on acceptable forms of secondary publication can be found at www.icmje.org.

Acknowledgement of sources

Proper acknowledgment of the work of others must always be given. Authors should cite publications that have been influential in determining the nature of the reported work. Information obtained privately, as in conversation, correspondence, or discussion with third parties, must not be used or reported without explicit, written permission from the source. Information obtained in the course of confidential services, such as refereeing manuscripts or grant applications, must not be used without the explicit written permission of the author of the work involved in these services.

Authorship of the paper

Authorship should be limited to those who have made a significant contribution to the conception, design, execution, or interpretation of the reported study. All those who have made significant contributions should be listed as co-authors. Where there are others who have participated in certain substantive aspects of the research project, they should be acknowledged or listed as contributors.

The corresponding author should ensure that all appropriate co-authors and no inappropriate co-authors are included on the paper, and that all co-authors have seen and approved the final version of the paper and have agreed to its submission for publication.

Hazards and human or animal subjects

If the work involves chemicals, procedures or equipment that have any unusual hazards inherent in their use, the author must clearly identify these in the manuscript. If the work involves the use of animal or human subjects, the author should ensure that the manuscript contains a statement that all procedures were performed in compliance with relevant laws and institutional guidelines and that the appropriate institutional committee(s) has approved them. Authors should include a statement in the manuscript that informed consent was obtained for experimentation with human subjects. The privacy rights of human subjects must always be observed.

Disclosure and conflicts of interest

All authors should disclose in their manuscript any financial or other substantive conflict of interest that might be construed to influence the results or interpretation of their manuscript. All sources of financial support for the project should be disclosed.

Examples of potential conflicts of interest which should be disclosed include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding. Potential conflicts of interest should be disclosed at the earliest stage possible.

Fundamental errors in published works

When an author discovers a significant error or inaccuracy in his/her own published work, it is the author's obligation to promptly notify the journal editor or publisher and cooperate with the editor to retract or correct the paper. If the editor or the publisher learns from a third party that a published work contains a significant error, it is the obligation of the author to promptly retract or correct the paper or provide evidence to the editor of the correctness of the original paper.

Duties of editors

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The editor of a peer-reviewed journal is responsible for deciding which of the articles submitted to the journal should be published, often working in conjunction with the relevant society (for society-owned or sponsored journals). The validation of the work in question and its importance to researchers and readers must always drive such decisions. The editor may be guided by the policies of the journal's editorial board and constrained by such legal requirements as shall then be in force regarding libel, copyright infringement and plagiarism. The editor may confer with other editors or reviewers (or society officers) in making this decision.

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The editor and any editorial staff must not disclose any information about a submitted manuscript to anyone other than the corresponding author, reviewers, potential reviewers, other editorial advisers, and the publisher, as appropriate.

Disclosure and conflicts of interest

Unpublished materials disclosed in a submitted manuscript must not be used in an editor's own research without the express written consent of the author.

Privileged information or ideas obtained through peer review must be kept confidential and not used for personal advantage.

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Editors should require all contributors to disclose relevant competing interests and publish corrections if competing interests are revealed after publication. If needed, other appropriate action should be taken, such as the publication of a retraction or expression of concern.

It should be ensured that the peer-review process for sponsored supplements is the same as that used for the main journal. Items in sponsored supplements should be accepted solely on the basis of academic merit and interest to readers and not be influenced by commercial considerations.

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An editor should take reasonably responsive measures when ethical complaints have been presented concerning a submitted manuscript or published paper, in conjunction with the publisher (or society). Such measures will generally include contacting the author of the manuscript or paper and giving due consideration of the respective complaint or claims made, but may also include further communications to the relevant institutions and research bodies, and if the complaint is upheld, the publication of a correction, retraction, expression of concern, or other note, as may be relevant. Every reported act of unethical publishing behavior must be looked into, even if it is discovered years after publication.

Duties of reviewers

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Contribution to editorial decisions

Peer review assists the editor in making editorial decisions and through the editorial communications with the author may also assist the author in improving the paper. Peer review is an essential component of formal scholarly communication, and lies at the heart of the scientific method. JNBS shares the view of many that all scholars who wish to contribute to publications have an obligation to do a fair share of reviewing.

Promptness

Any selected referee who feels unqualified to review the research reported in a manuscript or knows that its prompt review will be impossible should notify the editor and excuse himself from the review process.

Confidentiality

Any manuscripts received for review must be treated as confidential documents. They must not be shown to or discussed with others except as authorized by the editor.

Standards of objectivity

Reviews should be conducted objectively. Personal criticism of the author is inappropriate. Referees should express their views clearly with supporting arguments.

Acknowledgement of sources

Reviewers should identify relevant published work that has not been cited by the authors. Any statement that an observation, derivation, or argument had been previously reported should be accompanied by the relevant citation. A reviewer should also call to the editor's attention any substantial similarity or overlap between the manuscript under consideration and any other published paper of which they have personal knowledge.

Disclosure and conflict of interest

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JNBS 2016 Published by Üsküdar University www.jnbs.org

PREFACE

Dear colleagues;

Üsküdar University proudly presents the first issue of JNBS in 2016. Since 2014, JNBS has published more than 70 articles tapping into various fields of neuroscience and has gained a nation-wide high reputation as well as an increased worldwide recognition. We would like to thank all the authors and reviewers for their great efforts who helped us to sustain our quality and do hope to receive their support in the future.

In this issue of JNBS, Hizli-Sayar wrote out an editorial about the clinicians' hesitation in using clozapine. In addition, Flora et al. defined the effects of anaerobic and aerobic exercise on serotonin levels in rat brain tissues and Abdu et al. contributed with another behaviour neuroscience study that they have conducted in adult Wistar rats with two research articles. Review articles of this issue have been written by Toker et al., Natarajan et al., Akpinaroğlu et al., Fard et al., and Antikacioğlu have taken place in the current issue. In addition to the above mentioned articles, two interesting case reports which were about the effects of rTMS for treating auditory hallucinations in schizophrenia and swallow outcome in three female siblings with Huntington's disease and chorea were presented by respectful authors. Lastly, we do hope that Dr. Evrensel's clinical case and Dr. Ulucan's commentary in the use of BDNF as a biomarker for athletic performance would be of interest to the readers of JNBS.

On behalf of our editorial board, I would like to thank for all your support and do hope to receive more to keep up and improve our success.

Kind Regards,

Cumhur Tas, MD, PhD

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JNBS 2016 Published by Üsküdar University www.jnbs.org

Year : 2016
Volume : 3
Issue Number : 1
Doi Number : 10.5455/JNBS.1457524476

Article history:
Received 09 March 2016
Received in revised form 13 March 2016
Accepted 14 March 2016

CLINICIANS' HESITATION IN USING CLOZAPINE

KLİNİSYENLERİN KLOZAPİN KULLANIMINDAKİ TEREDDÜTLERİ

Gökben Hızlı Sayar*[1]

Dear Editor;

Clozapine has a central role in the treatment of several serious psychiatric disorders. The efficacy of clozapine has been examined in a large number of studies since it was first introduced. Both positive and negative symptoms of schizophrenia improve with clozapine treatment. It is the particular antipsychotic medication that has been shown to be superior to other drugs in patients with treatment-resistant schizophrenia (Kane & Correll, 2010). Clozapine has also been shown to diminish the rate of hospitalization (Tiihonen et al., 2009). It significantly decreases the comorbid use of alcohol and substance in patients with schizophrenia, probably by reducing the craving (Green, 1999). Evidence suggests that clozapine is efficacious also in decreasing suicidality in schizophrenia (Meltzer, 1999)

Despite evidence-based treatment guidelines, long delays observed in clozapine initiation. Antipsychotic polypharmacy and high doses are also commonly used before initiation of clozapine treatment. There is evidence that clozapine is underused, and clinicians' doubts related to clozapine must be reevaluated (Çetin, 2014).

Clozapine is known to have low extrapyramidal side effects and low tendency to elevate prolactin. However, it has some uncommon but life-threatening side effects such as agranulocytosis, myocarditis, and cardiomyopathy. Overestimation of side effects, clinicians' perception of them and lack of knowledge on how to manage them has been hypothesized as underlying reasons for clinicians' hesitation in using clozapine (Raja, 2011). The incidence of agranulocytosis was approximately 0.8 % in 12,760 patients receiving clozapine; leukopenia occurred in almost 3 percent of cases (Munro et al., 1999). The peak risks for both occurred early in treatment, between 6 to 18 weeks from initiation. Regular white blood cell count monitoring over a five-year period has been determined to decrease the risk of agranulocytosis from 1-2% to 0.38%. With adequate resources and control, a significant number of them can be identified early on, and appropriate measures are taken to minimize their impact. However, the burden of monitoring may further prevent psychiatrists from prescribing clozapine. Reasons of clinicians for limited use of clozapine are listed as reluctance to have blood test, side effects, metabolic problems, lack of experience, patient/family reluctance to use clozapine, clinicians concerns about poor compliance, need to admit/bed shortage, tendency to try other antipsychotics first, delayed diagnosis/not sure about diagnosis, negative views of others (Gee, 2014). In contrast, the evidence suggests that patients receiving clozapine are more satisfied with the medication when compared to other antipsychotics (Hodge & Jespersen, 2008).

Given the high burden and costs of inadequate treatments for schizophrenia, the underutilization of clozapine is remarkable. The effectiveness of clozapine in treatment-resistant cases, worthinesses for increased efforts to encourage greater use in appropriate patients. More should be done to initiate clozapine treatment and to prevent delay of a potentially life-saving treatment.

*[1]Corresponding author: Uskudar University, NPİstanbul Hospital, Departent of Psychiatry, Istanbul, Turkey. E-mail: gokben.hizlisayar@uskudar.edu.tr
Phone: +90 216 633 06 33 Mobile: 0530 244 13 16

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JNBS 2016 Published by Üsküdar University www.jnbs.org

Year : 2016
Volume : 3
Issue Number : 1
Doi Number : 10.5455/JNBS.1442221850

Article history:
Received 16 September 2015
Received in revised form 1 December 2015
Accepted 14 December 2015

EFFECT OF ANAEROBIC AND AEROBIC EXERCISE TOWARD SEROTONIN IN RAT BRAIN TISSUE

SIÇAN BEYİN DOKUSUNDAKİ SEROTONİNE YÖNELİK OKSİJENLİ VE OKSİJENSİZ ÇALIŞMA ETKİSİ

Rostika Flora[*1], Theodorus[2], Muhammad Zulkarnain[2], Rahmad Aswin Juliansyah[3], Syokumawena[3]

Abstract

Physical exercise plays a substantial role in maintaining our heath. In the molecular level, physical exercise induces the release of neurotransmitter, such as serotonin. Lack of serotonin could lead to stress or depression condition. We assumed that physical exercise could increase serotonin level in the brain. Therefore, this study aimed to investigate the effect of anaerobic and aerobic exercise toward serotonin level in male Wistar rat brain tissue. Twenty-eight male Wistar rats were divided into seven groups consist of control; 1x, 3x, 7x of aerobic exercise; and 1x, 3x, 7x of anaerobic exercise which conducted in a week. A rat treadmill was used at speed 35 m/min during 20 min for anaerobic exercise, and it was used at speed 20 m/min during 30 min for aerobic exercise. Serotonin level was measured using ST/5-HT (Serotonin/5-Hydroxytryptamine) ELISA Kit. Significant differences between treatments were tested by ANOVA (α = 5%). In contrast, both of anaerobic and aerobic exercise had lower serotonin level than the control.

Keywords: serotonin/5-hydroxytryptamine, anaerobic, anaerobic, physical exercise

Özet

Fiziksel egzersiz sağlığımızı korumamızda hayati bir rol oynar. Moleküler seviyede fiziksel egzersiz serotonin gibi sinir ileticilerinin salgılanmasına neden olur. Serotonin eksikliği stres ya da depresyon durumuna sebep olabilir. Fiziksel egzersizin beyindeki serotonin seviyesini artırdığını varsaydık. Bu nedenle, bu çalışmada erkek Wistar sıçanları beyin dokusundaki serotonine yönelik oksijenli ve oksijensiz çalışma etkisini araştırmayı amaçladık. 28 adet erkek Wistar sıçanı, bir haftada gerçekleştirilen 1x, 3x, 7x'li oksijenli ve oksijensiz çalışma grupları olmak üzere 7 adet kontrol grubuna ayrılmıştır. Sıçan çarkı, oksijensiz çalışma için 20 dakika boyunca 35 m/min hızda kullanılırken oksijenli çalışma için 30 dakika boyunca 20 m/min hızda kullanılmıştır. Serotonin seviyesi ST/5-HT (Serotonin/5- Hidroksitriptamin) ELISA Kit kullanılarak ölçülmüştür. Tedaviler arasında önemli farklılıklar ANOVA (= 5%) ile test edilmiştir. Varsayımımızın aksine, hem oksijenli ve hem oksijensiz çalışma gruplarının kontrol grubundan daha düşük bir serotonin seviyesine sahip olduğu ortaya çıktı.

Anahtar Kelimeler: *Serotonin/5- Hidroksitriptamin, oksijenli, oksijensiz, fiziksel egzersiz*

[*1]Corresponding author: Study Program Biomedical Science, Faculty of Medicine, University of Sriwijaya, Palembang, Indonesia.
E-mail: rostikaflora@gmail.com
[2]Faculty of Medicine, University of Sriwijaya
[3]Postgraduate Student of Biomedical Science, Faculty of Medicine, University of Sriwijaya

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1.Introduction

Lack of physical activity leads to increase many health problems. The World Health Organization noted that lack of physical activity is the fourth death factor (6% of deaths worldwide) (WHO, 2010). Based on its metabolism, there are two types of physical activity, aerobic and anaerobic. Aerobic exercise is a physical activity that uses ATP from the oxidative phosphorylation of glycogen and free fatty acids which depends on the availability of oxygen. In contrast, anaerobic exercise uses ATP from glycolysis which no need of oxygen (Astrand et al., 2003).

Physical activity could induce the release of serotonin (Klempin et al., 2013) (Lin & Kuo, 2013) (Meeusen & De Meirleir, 1995). Serotonin (5-hydroxytryptamine), a monoamine scattered in the human body, acts as a neurotransmitter in the synapse of nerve cells (Charnay & Leger, 2010) (Pytliak et al., 2011). Serotonin has substantial roles in the physiological function of the human body, including thermoregulation, regulation of cardiovascular, locomotion, pain, reproduction, sleep-wake cycle, memory, cognition, aggression, responses to stressors, emotions and mood (Charnay & Léger, 2010). Serotonin dysfunction leads to illness, such as depression, schizophrenia, anxiety and panic, migraine, hypertension, pulmonary hypertension, eating disorders, vomiting and irritable stomach syndrome (Pytliak et al., 2011).

According to Lin and Kuo (2013), an increase in synthesis and secretion of serotonin in the serum and in the central nervous system is affected by the intensity of physical activity. Physical exercise by increasing serotonin can affect emotional improvement in patients with major depression (Ahmad et al., 2007). Research conducted by Chaouloff et al., (1985) showed that Wistar rats treated on a treadmill for 60 and 120 minutes, 20 m/min, during 4-5 times exercise in a week revealed an increase of serotonin level. Physical exercise could improve the cognitive function and mental health. Light physical exercise raises the neuronal activity of hippocampus by increasing the neurotrophic factor and neurogenesis factor (Okamoto & Soya, 2012). The study conducted by Wang et al., (2013) showed an increase of serotonin level in the Wistar rat hippocampus after treated in the running wheels for 2 km in 4 weeks. The hypothesis was that both exercises (anaerobic and aerobic) could increase the serotonin level in the rat brain.

Study about the effect of frequency of the exercise toward the serotonin was limited. Prior study in rats revealed that intense frequency of anaerobic and aerobic exercise (seven times in a week) generated a heart infraction, while once and three times exercise in a week were safe (Flora et al., 2012). That indicates that intense physical exercise, such as seven times in a week, damage the heart muscles. However, the effect of the exercise in moderate or intense frequency toward serotonin level in brain tissue was unknown. Therefore, this study aimed to observe the effect of once, three, and seven times anaerobic and aerobic exercise in a week toward serotonin level in Wistar rat brain.

2.Material and Method

2.1.Experimental Design

This study was in vivo experimental study in posttest-only control design (Brink et al., 2005). This study was conducted in February 2015 at animal house laborator, Pharmacology and Therapy, Faculty of Medicine, Padjajaran University, Bandung. This study was approved by the Ethic Committee of the Faculty of Medicine Universitas Sriwijaya and Ethic Committee of the Mohammad Hoesin General Hospital Centre, Palembang, Indonesia.

2.2.Animal Preparation

Twenty-eight healthy and adult male rats, 6-8 weeks old, 140-250 g (*Rattus norvegicus* strain Wistar) were used. The amount of sample was determined using Federer's formula (Federer, 1991): $(n-1)\ (t-1) \geq 15$

The seven groups of treatment were conducted ($t = 7$) including control, 1x, 3x and 7x exercise in a week of anaerobic and aerobic treatment and each group was consist of four healthy and adult male rats ($n = 4$). All rats were obtained from Institut Teknologi Bandung, Bandung, Indonesia.

2.3.Treatment

Treatments were divided into control with no exercises, anaerobic exercise and aerobic exercise. A rat treadmill was used for both of anaerobic and aerobic treatment. The frequencies of anaerobic and aerobic exercise were the same. Both of anaerobic and aerobic exercise were conducted in once (1x), three times (3x), and seven times (7x) in a week (Flora et al, 2012). However, aerobic exercise was set at speed 20 m/min for 30 min, while anaerobic exercise was set at speed 35 m/min for 20 min (Soya et al., 2007; Fahrenia et al., 2009, and Flora et al., 2012). Acclimatization of lab condition was conducted in a week for all groups while treadmill acclimatization was conducted for the anaerobic and aerobic group (Kregel, 2006). All rats body weight was measured before and after the treatment.

2.4.Brain Preparation

Rat brain tissues were cleaned with PBS (0.01 M, pH = 7.4), then all of them were homogenized by MagNa Lyser Green Beads (5.000 x g, 60 seconds). All samples were centrifuged at 5.000 x g for 5

minutes. Then, the supernatant was collected and stored at -70oC.

2.5. Serotonin Measurement

50 µL supernatant of each sample was used for Serotonin assay. Serotonin level was measured based on competitive ELISA (Enzyme-linked Immunosorbent Assay) using ST/5-HT (Serotonin/5-Hydroxytryptamine) ELISA kit & its protocol (E-EL-0033, Elabscience).

2.6. Statistical Analysis

The data were analyzed using SPSS 19 for windows and were presented as means ± standard error. Analysis of variance (ANOVA) followed by Tukey HSD post-Hoc test was used to compare mean of serotonin level from the control, anaerobic, and aerobic exercise. Independent T-test was used to compare the mean of serotonin level between each frequency in aerobic and anaerobic exercise. α = 0.05 was considered as the significant difference level.

3. Result

Measurement data of rat weight, before and after treatment, was conducted to observe the effect of aerobic and anaerobic exercise to the rat weight. The result showed that anaerobic exercise revealed a higher reduction of rat weight (1.5 – 2.75 g) than the aerobic exercise.

Serotonin level of the aerobic and anaerobic group was lower than serotonin level of the control. The lowest serotonin was observed in 1x aerobic exercise (0.006 ±0.003 ng/ml) and the highest was observed in the control (0.709±0.063 ng/ml). ANOVA showed an insignificant difference between 1x, 3x, and 7x of anaerobic or aerobic exercise (Table 1). Independent t-test showed an insignificant difference in 3x (p=0.5) and 7x (p=0.151) of the anaerobic and the aerobic exercise, whereas a significant difference (p=0.000) only occurred between anaerobic and anaerobic exercise in 1x exercise (Table 1).

Table 1: The Serotonin level is numbers before (left side) "±" symbol, all numbers after (right side) "±" are the standard error in male Wistar rat brain tissue from all treatments

Treatment Group	Level (ng/ml)	
	Anaerobic	Aerobic
Control	0.709±0.063 a	0.709±0.063 a
1x	0.074±0.004 bA	0.006±0.003 bB
3x	0.084±0.003 bA	0.065±0.025 bA
7x	0.099±0.034 bA	0.034±0.007 bA

Note. Data each group (n=4) were presented as mean ± standard error. Different lower case letters (a,b) in the same column show a significant difference between control, 1x, 3x, and 7x treatment ($p<0.05$, Tukey HSD post hoc test). Difference upper case letters (A,B) in the same row show a significant difference between the anaerobic and the anaerobic exercise in each frequency ($p<0.05$, t-test 2-tailed).

4. Discussion

Serotonin, a derivative of tryptophan, has substantial roles in human physiology function, such as thermo regulator, nutrition control, cardiovascular, reproduction function, pain, aggressiveness, sleeping cycle, memories, cognition, mood, emotion and stress response (Charnay & Leger, 2010). Regular and continuous physical exercise could increase the serotonin level by relaxing the body and increasing the serotonin expression and secretion in serum or in central neuron system (Hassan & Amin, 2011) (Lin & Kuo, 2013). Study result of observing human as object showed that 3 times Pilates exercise during 12 weeks increased the serotonin level and reduced the stress (Hassan & Amin, 2011). Particular time, approximately 8 to 12 weeks after continuous exercise or training is needed by the body to be adapted and make any positive effects (Willmore & Costill, 1999; Astrand et al., 2003). The prior study revealed that physical exercise would give positive effect after 10 weeks of training (Fiatarone, et al, 1994). Otherwise, Wilson and Marsden (1996) research showed that serotonin level increased in rat's ventral hippocampus after the rats were treated with 60 minutes treadmill exercise for 20 m/min/day during 4-5 weeks. Another research showed that serotonin level increased when treated animals were treated in aerobic exercise for 3 times a week during 20 weeks (Valim et al., 2013).

A significant difference of serotonin level between 1x aerobic and 1x anaerobic exercise group was observed. Among aerobic and anaerobic treatment the lowest serotonin level was observed at 1x aerobic exercise (0.006±0.003 ng/ml), and the highest serotonin level was observed at the control followed by the 7x anaerobic exercise. However, this study showed that the exercises done just in a week had lower serotonin level than serotonin level in the control. According to the result, the short duration of exercise did not induce the increase of serotonin secretion. One week of treatment made the given exercises presented early as a stressor rather than as a stimulus to increase serotonin level in brain tissue. Physical exercise done intensively without rest is an acute exercise could induce a stress to the body and decrease the serotonin level in the brain. The study by Chen et al., (2008) showed that Sprague–Dawley rat treated by running 9 m/minute for 60 minutes every day during four weeks revealed a decrease of serotonin level in its hippocampus.

The main limitation of this study was the duration of the treatment. One week of exercise was not long enough to see a positive effect of the exercises. We suggest for measuring the serotonin in a specific place of serotonin (hippocampus) rather than in whole brain tissue. Moreover, duration of the treatment and histopathology of the brain tissue should be prolonged and observed to know clearly about the effect of anaerobic and aerobic

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exercises toward the serotonin level. In conclusion, both of physical exercise done during a week in three different frequencies could not increase the serotonin level in rat brain. Besides, a short time of anaerobic and aerobic exercise led to decrease the serotonin level in rat brain.

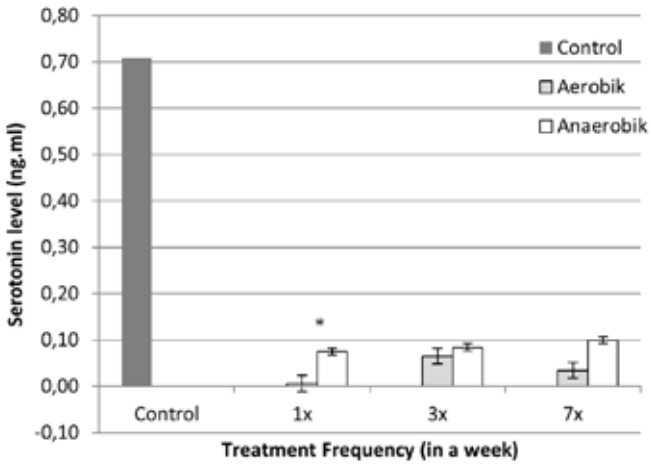

Fig. 1: Column chart of serotonin level in control, aerobic and anaerobic treatment. The (*) shows a significant different of serotonin level between 1x anaerobic and 1x aerobic treatment.

Acknowledgement

This study was financially supported by Hibah Fundamental 2015 from Ministry of Research, Technology and Higher Education of the Republic of Indonesia and the University of Indonesia.

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Year : 2016
Volume : 3
Issue Number : 1
Doi Number : 10.5455/JNBS.1444218339

Article history:
Received 08 October 2015
Received in revised form 20October 2015
Accepted 02 February 2015

EFFECT OF DICHLORVOS ON HISTOARCHITECTURE OF THE CEREBRAL BLOOD VESSELS IN ADULT WISTAR RATS

YETİŞKİN WISTAR SIÇANLARINDA SEREBRAL KAN DAMARLARININ HİSTOMİMARİSİ ÜZERİNDEKİ DİKLORVOS ETKİSİ

IdrisTela Abdu*[1], Lawan Hassan Adamu[2], Musa Habibu Modibbo[2], AbdullahiAsuku Yusuf[2]

Abstract

Cerebral blood vessels are vital in supplying brain in both human and animals. Any anomaly by rupture or interruption of blood flow may lead to fatal consequences. Dichlorvos is a volatile organophosphate that forms the active ingredient of locally formulated insecticide and pesticide known as Otapiapia or Madararpiapia. It is an anti-acetylcholinestrase that binds irreversibly to acetylcholinesterase and leads to its inhibition. The study aims to determine the effects of dichlorvos on the histology of the cerebral vessels in adult wistar rats. Twenty five apparently healthy adult wistar rats were randomly selected and divided into five groups. The first two groups were used as control while the last three groups were exposed to graded doses of dichlorvos in ethanol solution and experimented for twenty eight days. Twenty four hours after the last exposure the animals were sacrificed and the brain tissues were collected for routine histological technique. The relative brain weights of all the animals were determined and one – way ANOVA was conducted to compare the mean of the control with the treated groups. There was no statistically significant difference [F = 0.88, p = 0.49] in the mean brain weights of the controls and the treated groups. The H&E stain of the treated groups showed variable degrees of perivascular oedema, pyknosis and apoptosis. Prolong use of dichlorvos could cause cerebral vascular changes in the histoarchitecture such as perivascular oedema and apoptosis, may not affect the brain weight.

Keywords: Dichlorvos, Histoarchitecture, Cerebral blood vessels

Özet

Serebral kan damarları insanların ve hayvanların beyinleri için çok önemlidir. Kan akışının kesilmesi ya da durması nedeniyle oluşan herhangi bir anomali ölümcül sonuçlara sebep olabilir. Diklorvis, Otapiapia ya da Madarar piapia olarak bilinen bölgesel olarak formüle edilmiş sinek ve böcek ilaçlarının aktif maddeleriyle oluşan uçucu bir organofosfattır. Diklorvis, geri dönülemez bir şekilde asetilkolinesteraza bağlanan ve inhibisyonuna sebep olan bir anti- asetilkolinesterazdır. Bu çalışma yetişkin wistar sıçanlarının serebral damar histolojisindeki diklorvos etkilerini saptamayı amaçlar. Sağlıklı görünen 25 adet wistar sıçanı rastgele seçilmiş ve beş gruba ayrılmıştır. İlk iki grup kontrol grubu olarak kullanılırken son üç grup etanol çözeltisinde aşırı dozda diklorvosa maruz bırakılmış ve 28 gün boyunca deney uygulanmıştır. Son dozdan 24 saat sonra hayvanlar öldürülmüş ve beyin dokuları rutin histolojik teknikler için alınmıştır. Bütün hayvanların nisbi beyin ağırlıkları saptanmış ve tedavi edilen gruplarla kontrol grubunun ortalamasını kıyaslamak için ANOVA uygulanmıştır. Kontrol gruplarıyla tedavi edilen grupların ortalama beyin ağırlıklarında istatiksel olarak önemli bir fark [F = 0.88, p = 0.49] saptanmamıştır. Tedavi edilen grupların H&E kimyasal maddeleri(kalıntıları) perivasküler ödem, piknoz ve apoptozun farklı derecelerini göstermiştir. Diklorvosun aşırı kullanımı perivasküler ödem ve apoptoz gibi histomimaride serebral vasküler değişikliklere sebep olabilir fakat beyin ağırlığını etkilemeyebilir.

Anahtar Kelimeler: *Diklorvos, Histomimari, Serebral kan damarları*

*1Corresponding author: Department of Anatomy, Faculty of Basic Medical Sciences, College of Health Sciences, Bayero University Kano, Kano State, Nigeria E-mail: gwtel4u@gmail.com Phone: +(234)7068608199

[2]Department of Anatomy, Faculty of Basic Medical Sciences, College of Health Sciences, Bayero University Kano, Kano State, Nigeria

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1. Introduction

Blood vascular networks constitute a major component of the structure of the brain in addition to neurons, glia, and the extracellular milieu. The neurovascular unit is comprised of the endothelial cells which make up the vessels as well as several other associated cell-types including astrocytes and perivascular cells such as pericytes and smooth muscle cells (Ramos et al., 2008). Pericytes wrap around vessels and are in direct contact with endothelial cells via gap junctions (Bergers and Song, 2005). Blood vessels in the brain are also surrounded by the endfeet of astrocytes. Thus, astrocytes constitute a cellular bridge between neurons and blood vessels. Astrocyte endfeet located on vessels interact directly with endothelial cells and are capable of up-take and/or release of a number of molecules such as amino acids, growth factors (Abbott, 2002; Abbot et al., 2006).

The use of dichlorvos has long been in practice. In addition to its use as control for insects on crops, household, and stored products, dichlorvos is also use to treat external parasitic infections in farmed fish, livestock, and domestic animals (Erdogan et al., 2007). In Nigeria it is hawked around and used for agricultural and domestic purposes to kill various forms of insects and to protect stored products from insects. Dichlorvos is a volatile organophosphate which is preponderantly active pesticide ingredient in the locally formulated Ota-piapia (Musa et al., 2010). This is because of solely to its cheap production, efficacy, accessibility, and affordability (Essiet, 2009). Dichlorvos is rapidly absorbed through the gastrointestinal and respiratory tracts and skin, it enters human system via inhalation, dermal or oral routes, and it is metabolized by the liver and excreted by the kidney (Durkin & Follansbee, 2004; CERI, 2007).

The mechanism of action for the dichlorvos is mainly by blocking of acetylcholinesterase – an enzyme which in turn decomposes acetylcholine (Lewalter&Korallus, 1986; Harlin& Dellinger, 1993). Overdose of this OP leads to symptoms which include weakness, headache, tightness in chest, blurred vision, salivation, sweating, nausea, vomiting, diarrhea, respiratory failure, and abdominal cramps being an acetylcholinesterase inhibitor, (CEPA, 1996). It is mainly metabolized by esterase to dimethylphosphate and dichloroacetaldehyde. Dimethylphosphate is excreted in the urine, while dichloroacetaldehyde is rapidly metabolized via two pathways to dichloroethanolglucuronide, hippuric acid, urea and carbon dioxide, and excreted in the urine and expiration (CERI, 2007). The mechanisms underlying these effects are not known, and the role of acetylcholinestrase (AChE) inhibition is controversial (Kamel and Hoppin, 2004; Abou-Donia, 2003) and may vary depending on the exposure parameters. Chronic neurotoxicity subsequent to a single acute exposure to dichlorvos may be triggered by AChE inhibition. Acute and sub lethal doses of dichlorvos were shown to have long-term effects in humans (Ohbuet al., 1997; Proctor et al., 2006). Oral administration of dichlorvos to rat (70 mg/kg) inhibited not only AChE but also hexokinase, phosphofructokinase, lactate dehydrogenase and glutamate dehydrogenase. Dichlorvos administration also caused significant depletion in the brain glycogen content along with increased glycogen phosphorylaseactivitity (Sarin and Gill, 1998). Repeated administration of 50% of LD50 (i.e., 40 mg/kg body wt per day for 10 - 21 days) of dichlorvos caused myelin pallor and micro-vacuolation of the white matter. This may also leads to primary degeneration of axons and secondary myelin sheath abnormalities caused the spongy tissue loosening when observed under the electron microscope (Zelman, 1977; Zelman and Majdeckt, 1979).

Dichlorvosor Madararpiapia in Hausa parlance is one of the organophosphates that are used for eradicating pests and insects especially among low income countries. This was because of its low price and availability. Because of the quest for greater efficiency, dichlorvos is often used beyond the recommended quantity not mindful about the health consequences. Many researches were conducted regarding the use of dichlorvos, however less attentions was paid to its effects on the cerebral vasculature, therefore this study aims at determining the effects of this chemical on histoarchitecture of the cerebral blood vessels in adult wistar rats.

2 Materials andMethod

2.1 Animals

Twenty five apparently healthy adult wistar rats consisted of both sexes and weighed about 195 – 400g were purchased from the Pharmacology Department, Aminu Kano Teaching Hospital (AKTH) Kano, Nigeria and allowed to acclimatize for two weeks in laboratory condition before subjected to experimentation. The animals were housed in a well-ventilated rectangular aluminium cages (290 × 320 × 390 mm) bedded with soft saw dust and maintained under standard laboratory conditions with proper illumination of 12:12-h light/dark cycle in a temperature (210C ± 20C) and humidity (55 ± 5%) and humidity controlled room. The animals had free access to food (vital feed) and water ad libitum. The animals' sanitation and husbandry were in accordance with "Guide for the Care and Use of Laboratory Animals". The animals were then divided into five groups (i.e. I, II, III, IV& V) with each group containing at least one of the congeners.

2.2 Chemical and doses Preparation

A stock concentration of 1000 g/l of dichlorvos

(Delvap Super ®) was purchased from the vendors of insecticides, pesticides and other Agro allied Chemicals at Sabongari market, Kano, Nigeria. The lethal concentration LC50 of dichlorvos which was reported as15mg/m3 (Lewis, 1996) was taken as a reference value. The present study was carried out with sublethal doses equivalent to 75% (11.25mg/m3), 50% (7.50mg/m3) and 25% (3.75mg/m3) of the reference LC50dose.

2.3 Experimental Design

Five poorly ventilated 1m x 1m cubed wooden boxes labelled A, B, C, D and E, each with a rectangular sliding glass pane measured about 0.2m x 0.1m for entrance at the top was constructed for the exposure of the animals.About 2 mls each of the graded solutions were drawn separately using 4 mls hypodermic syringes and then sprayed thoroughly into the boxes every day before the animals were exposed. The animals in groups I and II were exposed into ambient air and 2 mls of 2.5 mg/m3ethanol as positive and negative controls respectively whereas those in groups III, IV and V were exposed into the boxes sprayed with 11.25 mg/m3, 7.50 mg/m3, and 3.75 mg/m3 concentrations of the standard solution in ethanol respectively. The exposure lasted for 2 hours in all the groups every day for twenty eight days. Twenty four hours after the last exposure, each of the animals was sacrificed by cervical dislocation.

2.4 Samples Collection and tissue preparation

Each of the animals was weighed on digital balance (AWS, USA) before brains were quickly dissected out and the tissues immediately collected also weighed on a digital scale and finally fixed in a Bouin's fluid. After overnight fixation, the tissues werethoroughly washed, dehydrated, cleared in xylol, and processed for paraffinembedding. Therefore relative brain weights were expressed and recorded as percentage of their body weights using the formula below.

$$\text{Relative brain weight} = \frac{\text{Brain weight}}{\text{Body weight}} \times 100$$

2.5 Histopathology of the Brain Tissues

Paraffin blocks of the brain tissues were cut at 2 - 3µm thickness and stretched on glass slides. Afterdeparaffinization, the sections were stained with hematoxylin-eosin andobserved under light microscope.

2.6 Statistical Analysis

All values were represented as means ± SEM. Statistical significance between the control and experimental data was subjected to ANOVA together with Tukey's test ($p < 0.05$). All analyses were conducted using Minitab (version 16) statistical software.

2.7 Slides Preparation and Interpretation

The sections of the brain tissues were stained using hematoxylin and eosin and viewed underMotic photomicroscope to which fitted Celestron© digital microscope imager (USA) with an inbuilt 15x magnifying lens at 150 and 600 magnifications respectively.

3. Results

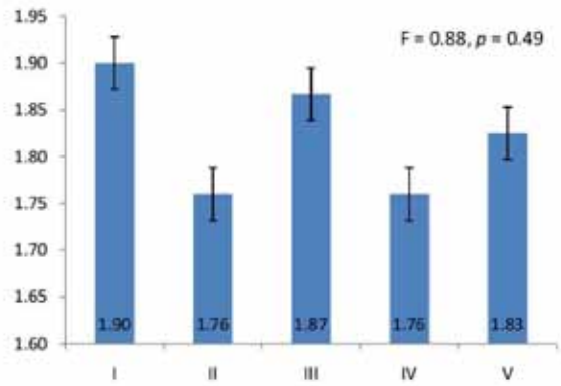

Fig. 1: Mean Brain Weights of Control and Dichlorvos Treated Groups

Figure 1, shows bar chart of the ANOVA test comparison of the mean brain weights of the control and treated groups. The mean ± SEM distribution showed 1.90±0.09, 1.87±0.03, 1.83±0.09, 1.76±0.04 and 1.76±0.05 for groups I, III, V, II&IV respectively. The inferential statistic showed there was no statistically significant difference in mean [F= 0.88, p = 0.49] between the control and treated groups.

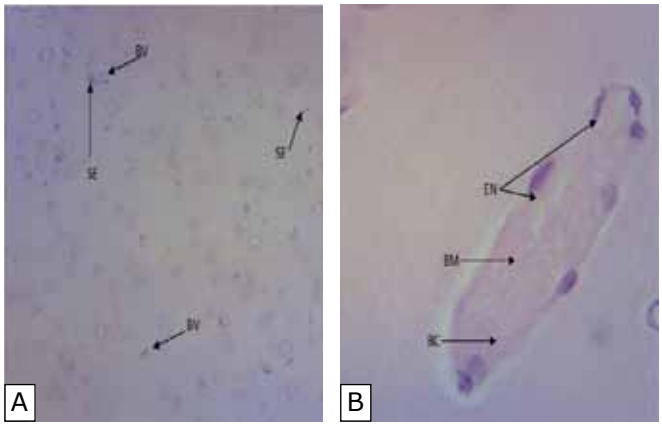

Plate IA&B: H&E normal photomicrograph of cerebral vascular architecture exposed to ambient air as control in Adult Wistar Rat at (A) x150 and (B) x600 magnifications respectively.
BC= Blood Clots; **EN**= Endotheliocytes; **PVE**= Perivascular oedema; **pEN**: Polymorphic Endotheliocytes; **Lu**= Lumen

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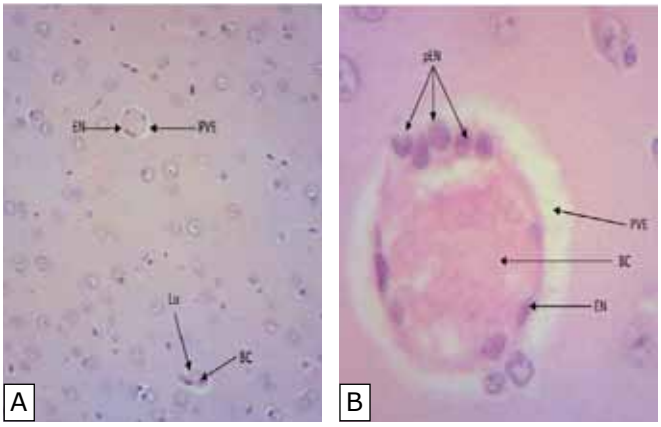

Plate IIA&B: H &E photomicrograph of cerebral vascular architecture exposed to 2.5 mg/m3 ethanol in Adult Wistar Rat at (A) x150 and (B) x600 magnifications respectively.
BC= Blood Clots; **EN**= Endotheliocytes; **PVE**= Perivascular oedema; **pEN**: Polymorphic Endotheliocytes; **Lu**= Lumen

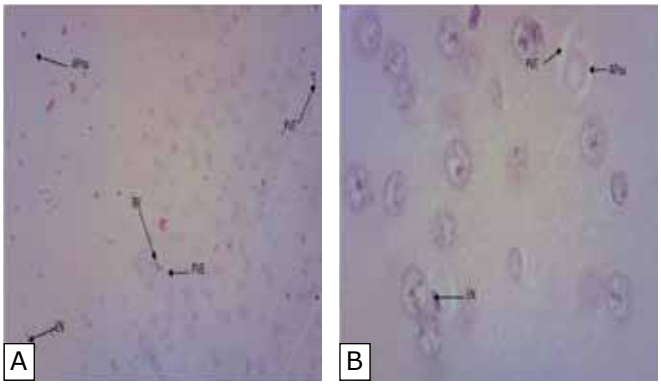

Plate III A&B: H&E photomicrograph of cerebral vascular architecture exposed to 11.25mg/m3 in Adult Wistar Rat at x150 and x600 magnification respectively.
BV= Blood vessel **PVE**= Perivascular oedema;
EN= Endotheliocytes; **APnu**= Apoptotic nuclei; **Lu**= Lumen

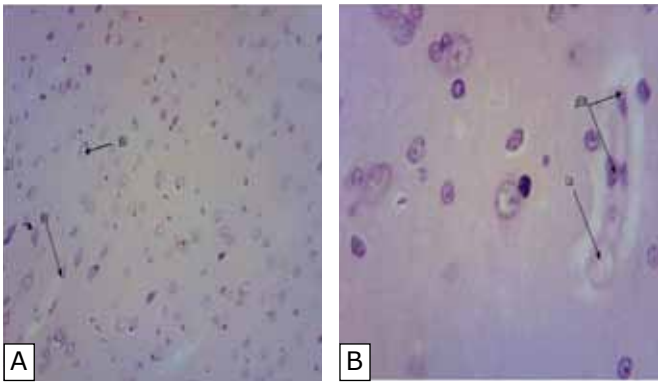

Plate IV A&B: H&E photomicrographs cerebral vascular architecture exposed to 7.50mg/m3 dichlorvos at (A) x150 and (B) x600 magnifications respectively.
BV= Blood Vessel; **pEN**= Polymorphic Endotheliocytes;
Lu= Lumen

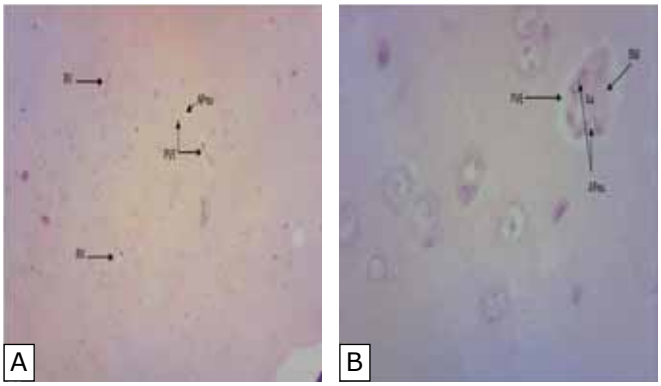

Plate VA&B: H&E photomicrograph of cerebral vascular architecture exposed to 3.75 mg/m3 dichlorvos in Adult Wistar Rat at (A) x150 and (B) x600 magnifications respectively.
BM= Basement Membrane; **BV**= Blood Vessel; **PVE**= Perivascular oedema; **EN**= Endotheliocytes; **APnu**= Apoptotic nuclei;
Lu= Lumen

The results in plate IA showed normal photomicrograph of cerebral vascular architecture exposed to ambient air as control. The cerebral blood vessel (BV) in this group featured squamous endotheliocytes (SE) at lower (150x) magnification lying peripherally on intact basement membrane (BM). At higher magnification (600x) in plate 1B, the normal blood vessels showed vascular lumen consisting of the remains of the blood clots (BC). The basement membrane (BM) was circumferentially lined with the squamous endotheliocytes (SE) providing lumen (Lu) studded with blood clots (BC). The photomicrograph of cerebral vessels in plate IIA was a histoarchitecture of the animals exposed to 2.5 mg/m3 ethanol as negative control group. The plate showed a highly circumscribed perivascular oedematous zone (PVE) around the blood vessels with the squamous endotheliocytes (EN) located peripherally on the circular basement membrane (BM) which formed the lumen (Lu) of the capillaries at lower magnification. At higher resolution (plate IIB), the photomicrograph showed the high circumferentially perivascular edematous (PVE) zone around the blood vessels. The lumen was however studded with the remnant of blood clots while basement membrane (BM) was lined by polymorphic endotheliocytes (pEN). In plate IIIA the photomicrograph of 11.25 mg/m3dichlorvos tested group at lower magnification showed mildly surrounded perivascular oedematous (PVE) zone with the endotheliocytes (EN) of some vessels bearing mild apoptotic (APnu) tendencies. The endotheliocytes were generally scanty. At higher magnification (plate IIIB), the blood vessels featured pronounced PVE with the basement membranes bearing very scanty or no endotheliocytes. The photomicrograph of the endotheliocytes exposed to 7.5 mg/m3dichlorvos at lower magnification was presented in plate IVA. The plate showed

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the vessels containing scanty endotheliocytes surrounded by mild perivascular edema (PVE) on the basement membrane (BM). At higher resolution (plate IVB), the endotheliocytes were virtually absent in the lining of the basement membrane. Plate VA was a photomicrograph of cerebral blood vessels of adult wistar rat exposed to 3.75 mg/m3 at lower magnification. The endotheliocytes were absent in some of the blood vessels whereas others contain scanty and were surrounded by perivascular edematous zone (PVE). At higher magnification VB, the blood vessels still showed perivascular oedematous zone around the blood vessels with collapsed basement membrane (BM) bearing apoptotic endotheliocytes.

4. Discussion

The results in table 1, showed variable degrees in the distribution of the brain weights following treatment with graded doses of dichlorvos solutions in exposure chambers. It is evident that the control groups had the highest mean±SEM of 1.90±0.09 while groups II & IV had the least distributions of 1.76±0.04 and 1.76±0.05 respectively. The ANOVA test however showed no statistically significant difference in the mean brain weights [F= 0.88, p = 0.49]. These findings contradicted Sarin and Gill (1998) and Zelman (1977) in related dichlorvos neurotoxicity study following oral treatment where it found significant inhibition of metabolic enzymes were such as hexokinase, phosphofructokinase, lactate dehydrogenase and glutamate dehydrogenase which depleted brain glycogen – essential ingredient necessary for myelination and regeneration of axons. This variation could probably be due to difference in the route of exposure, concentration and setting of the experiments.

The photomicrograph of group I animals that were exposed to ambient air as control showed normal histology of cerebral blood vessels cerebral (BV) indicating squamous endothelicytes (EN) arranged peripherally on basement membrane (BM). It also showed a central vascular lumen containing the remains of the blood clots (BC). There were noticeable histologic changes of the vascular endotheliocytes in group II the ethanol exposed (negative control) group, in which the endotheliocytes on the blood vessels (BV) presented marked perivascular oedematous zone (PVE) around the blood vessels. The vascular endotheliocytes were also surrounded by polymorphic (pEN) endotheliocytes with some of them knocked out of the basement membrane (BM) lining thereby distorting the arrangements. This result contradicted the finding of Phillips (1986) which observed that the endothelial cells of brain blood vessels in rats breathing after continuous ethanol vapor during 3 weeks were normal, which in accordance to the present study, there was histopathological alterations in the endothelium when compared to controls.The photomicrograph of the VB in group III was presented in plate 3. The histoarchitechture showed perivascular edematous zone around the blood vessels (PVE). The basement membrane (BM) also collapsed with the lumen surrounded by haphazard squamous endotheliocytes that partly blocked it. The endotheliocytes also showed mild apoptotic tendencies. Similar results were obtained in group IV and V except that in group IV the lumen was circumferentially collapsed with partly ruptured basement membrane surrounded by scanty amorphous endotheliocytes in a perivascular edema. However in group V the blood vessels maintained the lumen of the blood vessel devoid of the endotheliocytes on the basement membrane surrounded by slight a perivascular edema. In a similar study conducted by Muthuviveganandavelet al., (2011) found that perivascular oedema and congestion of cerebral blood vessels in Albino rats following oral exposure to pyrethroids organophosphates. In a similar studies conducted by Owoeyeet al., (2014) and Sharma and Singh (2012) reported presence of apoptotic changes in pyramidal neurons of the CA1 and CA3 subfields and blood vessels caused by oxidative damage induced by dichlorvos. Similarly, Binukumar and Gill (2010) also indicated that decreased mitochondrial electron transfer activities of cytochrome oxidase (complex IV) along with altered mitochondrial complex I, and complex II activity, which might have resulted from elevated mitochondria calcium uptake might have caused an increase in malondialdehyde, protein carbonyl and 8-hydoxydeoxyguanosine formation which as a result enhances lipid peroxidation as well as protein and mitochondrial DNA oxidation that could lead to DNA fragmentation and cellular apoptosis.

5. Conclusion

Dichlorvos is the active ingredient of the locally formulated pesticide-cum-insecticide popularly known as Madararpiapia or Ota piapia. Prolong use of this chemical by constant exposure through inhalation caused change in the histoarchitecture of the cerebral blood vessels through the formation perivascular oedema and apoptosis of the endotheliocytes. Many diluents were available for use in preparation of local dichlorvos preparation; care has to be taken in the right choice of the diluents to avoid harmful agents that can affect the histology of the cerebral blood vessels. It is therefore recommendable that the National Agency for Food Drug Administration and Control (NAFDAC) should ensure strict obedience in the use of dichlorvos.

Acknowledgement

The researchers wish to sincerely appreciate the Department of Pathology, Aminu Kano Teaching Hospital, Bayero University Kano for all the assistance provided in the course of this research.

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JNBS 2016 Published by Üsküdar University www.jnbs.org

Year : 2016
Volume : 3
Issue Number : 1
Doi Number : 10.5455/JNBS.1443509530

Article history:
Received 29 September 2015
Received in revised form 11 November 2015
Accepted 18 January 2016

ASSESSMENT OF PAIN SYMPTOMS IN TERMS OF CULTURE

KÜLTÜREL AÇIDAN AĞRI SEMPTOMLARININ ELE ALINIŞI

Sinem Gönenli Toker*[1], Burcu Göksan Yavuz[2], Oğuz K. Karamustafalıoğlu[3]

Abstract

The common feature of somatoform disorders is the presence of somatic symptoms that cannot be explained by a general medical condition. Pain disorder is also among the somatoform disorders. Pain is defined as an unpleasant sensation occurring as a consequence of a disease, injury or an organic pathology. Breuer and Freud, in their studies on hysteria, suggested that pain could be a manifestation of a psychological problem. The lifetime prevalence is not precisely known. In the Turkish mental health study 12 month incidence of pain disorder is found to be % 11.3 among women, % 4.8 among men and % 8.4 in the general population. The cultural diversity of the mental illnesses particularly somatic symptoms is noticed. Traditions and belief systems influence the formation, presentation and the managemant of dissociative and somatoform symptoms. Types of somatic symptoms differ across the cultures. Higher rates of somatic complaints are found in South America, Asia, particularly in developing countries. The seperation between physical and emotional experience occurs precisely in Western countires. Thus somatic symptoms are rarely seen in Western culture.

Keywords: pain, culture

Özet

Amaç: Ağrı, hastalık, bedensel yaralanma veya organik bozukluğa bağlı rahatsızlık verici bir duygu olarak tanımlanır. Bu gözden geçirmede ağrı semptomlarının ortaya çıkışı ve seyrinde kültürel faktörlerin etkileri incelenmiştir. Yöntem: Ağrı ve diğer somatik semptomların farklı kültürlerdeki görünümleri irdelenmiştir. Bulgular ve sonuç: Psikiyatrik hastalıklarda özellikle somatik semptomların kültüre özgü çeşitliliği dikkat çekmektedir. Gelenekler ve inanç sistemleri, disosiatif ve somatoform semptomların oluşması, ortaya konması ve bunlarla başa çıkılmasını büyük oranda etkiler. Somatik hastalardaki semptom tipi kültüre göre değişmektedir. Güney Amerika ve Asya'da, özellikle gelişmekte olan ülkelerde somatik yakınmaların sıklığı daha yüksek oranda bulunmuştur. Batı kültüründe fiziksel ve duygusal deneyimler daha kesin olarak birbirinden ayrılır. Bu sebeple somatik şikayetler batı toplumlarında daha az görülüyor olabilir.

Anahtar Kelimeler: *Acı, Kültür*

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*1Corresponding author: Psychiatry Department, Medipol University school of medicine, Istanbul. E-mail: sgonenli@hotmail.com
Mobile: +90 05325072520
[2]Psychiatry Department, Acıbademm University school of medicine, Istanbul. E-mail: bgoksan@yahoo.com
[3]Psychology Department, Uskudar University, Istanbul. E-mail: oguzkaramustafa@gmail.com

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Common features of somatoform disorders are the existence of physical symptoms that act like general medical situations that cannot be explained by another mental disorder or direct effects of a substance. These symptoms cause a clinically significant distress or impairment in social, occupational, or other important areas of functioning[1] (American Psychiatric Association, 1994; 2013). Somatoform disorders have 7 subgroups in DSM IV; Somatisation disorder, Undifferentiated somatoform disorder, Conversion disorder, Pain disorder (table 1), Hypochondriasis, Body dysmorphic disorder and somatoform disorder not otherwise specified. In DSM-V, somatoform disorders and pain disorders are classified as "Somatic Symptom Disorders and Related Disorders". (table 2)

Pain, which is related to the Latin word poena (punishment, revenge, torture), is described as "a disturbing feeling due to illness, physical injury or an organic disorder"[2] (Evlice & Uğuz, 1999). In their research about hysteria, Breuer and Freud predicted that pain might be a sign of a psychological problem. On the other hand, International Association for the Study of Pain (IASP) describes pain as an unpleasant emotional situation that originates from a specific area that might be caused by a tissue damage and related to individuals past experiences. In DSM-IV, pain requires to be the predominant focus of the clinical presentation for pain disorder.

Table 1: DSM-IV Diagnostic Criteria of Pain Disorder

A. Pain in one or more anatomical sites is the predominant focus of the clinical presentation and is of sufficient severity to warrant clinical attention.
B. The pain causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
C. Psychological factors are judged to have an important role in the onset, severity, exacerbation, or maintenance of the pain.
D. The symptom or deficit is not intentionally produced or feigned.
E. The pain is not better accounted for by a mood, anxiety, or psychotic disorder and does not meet criteria for Dyspareunia.

Table 2: DSM-V Somatic Symptom and Related Disorders

a. Including: requires at least one disturbing somatic sign
b. Including: requires at least one of the thoughts, feelings or behaviours below for 6 months: i. Non-proportional thoughts ii. Continuous high level of anxiety iii. Overinvestment
c. Qualifiers i. Determinants • The pain as predominant • Continuous ii. Severity • Mild: 1 of B diagnosis criteria • Moderate: 2 or more of B diagnosis criteria • Severe: 2 or more of B diagnosis criteria with multiple somatic signs

The prevalence of the pain disorder is not well known. However, it is considered frequent in general medical practice. It is two times more frequent in women than men. There is no familial predisposition reported. It is frequent between the ages of 30-50. Recent researches report its 6 months and life time prevalence between 5-12%. Psychiatric disorders, especially affective signs are frequent almost in 1/3 of the cases. 12 months pain disorder frequency is reported as 11.3% in women, 4.8% in men and 8.4% in all population in Turkey mental health profile study[3] (Kılıç, 1988). In a study of Sağduyu et. al. with 262 patients, the most frequent symptom was head ache (68.5%) and it was reported that lumbar/back pain was more frequent in women than men (45.7% and 18.8%, respectively)[4] (Sağduyu et al.,1999).

It is common in whole world to physically express the general distress. Several physical systems are used to find the source of the distress and to form the required answer. Psychiatric disorders are linked with the increase of bodily perception, successful treatment of illnesses like anxiety and mood disorders mostly results with disappearance of somatic complaints as well. It is known that adverse experiences in early periods of life might cause psychobiological changes and objectively and perceptively poor health features might be observed on these people. It is observed that learning mechanisms have a significant role on bodily expression of mental distress and children might apply with pain symptoms that are similar to their parents' way of expressing their distress.

While emotional factors and psychic needs of the individual play a role in perceiving pain, in some patients, especially in patients with chronic pain, suffering extent is also added. Suffering is an adverse emotional response to pain and depression and anxiety might be considered in this regard[2] (Evlice & Uğuz, 1999). Occasionally, people express their tension (stresses like loss of somebody, not beeing able to reach a goal) and guilt with pain, unintentionally ease the weight of their problems that bother them and move them away from their own thoughts. The significance given to pain might be intended to avoid a subliminal difficulty and conflict and this situation is described as primary gain. Thus, the intolerable inner conflict is transformed into more acceptable pain complaints that might have support, help, attention and understanding of people. This way, individuals might have their social environment in their hands, get away from responsibilities. This is described as secondary gain. Chronic pain is a process including stationary and maladaptive behaviour processes that cannot be explained with existing physical pathology in which the main issue is the reaction patient gives to pain, not the damage or pain themselves. In chronic pain, which the pain cannot be explained with somatic and physiopathologic disorders; maintaining the patient role might be observed due to frequent treatment applications, overresponsibility adscription towards the physicians, impairments and avoidings in social and vocational functionality due to health concerns, oversensitiveness against beeing abandoned, fear of loosing the secondary gains that provided by the patient role.

Pain behaviour as refuging in illness is a process that develops with the responses (consolidation) of social environment (physicians, family, society) to the pain and the perception of pain of the patient. The significance of psychosocial factors in patients with chronic pain has been remarked[5,6] (Fields et al.,1994; Livigston, 1998).

George Engel identified the risk factors of chronic pain as existence of defeat, guilt, aggressive impulses and fear of loss[7] (Engel, 1959).

The importance given to pain by patients, patients' way of explicating the pain and their behaviour against the pain is closely related to their former experiences and personalities. Depression incidence is significantly higher in patients with chronic pain compared to normal population. In the study of Sağduyu et al. (1999), 54.8% of the patients stated that they feel depressed, 58.1% of them stated that they feel anxious. The main signs of chronic pain syndrome are; pain, anxiety, depression and insomnia. Neurovegetative signs of depression are also observed in these patients. Besides, (functional) pain complaint is rather frequent in depressive patients. Some clinicians tend to evaluate chronic pain as an equivalent of depression (masked depression)[2] (Evlice & Uğuz, 1999).

Features like dramatic demonstration of complaints, occurrence of pain beeing related to life events, exposure of multiple systems, history of chronic illnesses or violence in family, using of denegation, consolidation of pain behaviour by social environment are considered as leads towards signs beeing psychogenic[2] (Evlice & Uğuz, 1999).

In psychiatric diseases, diversity of particularly somatic symptoms due to culture is remarkable. Traditions, belief systems and expectations substantially effect the occurrence, demonstration and handling of dissociative and somatoform symptoms. Most patients develop medical symptoms that clinicians can understand because these symptoms are less stigmatizing than psychological symptoms[8] (Escobar, 2004). Patients with painful symptoms apply to psychiatrists after frequently going through general medical examinations and using several medications. As Kleinman indicated, not only culture forms the disease, it also determines the way individuals perceive the disease. Transformation of personal or social stress to somatic complaints is accepted as "norm" in most cultures. Symptom type of somatic patients vary according to culture. For example, while heath, hot flash, tingling, burning in hands and feet, insensibility, burning sensation in head symptoms are frequent in Nigeria and India, these symptoms are rare in western contries[8] (Escobar, 2004). Cross-cultural studies with depressive patients show that depressive patients in Asia and Latin America have more somatic complaints compared to United States of America (USA)[10,11] (Escobar et al., 1983; Kleinman, 1982). Epidemiological field surveys have shown that the most frequent medically unexplained symptoms in USA are gynaecological symptoms, followed by gastrointestinal and cardiovascular symptoms. Several studies in USA have reported that somatisation is very frequent in Latin race, particularly in Puerto Rican patients[12,13,14] (Canino et al., 1992; Escobar, 1995; Escobar et al., 1992). In a 15 centered study of Gureje that consists of 14 countries including Turkey, prevalence of somatoform disorders was determined high in two centers in South America (Rio de Janerio and Santiago). In the same study, incidence of chronic pain was the highest in Ankara (79.1%) and Verona (72.2%) and the lowest in Athens (16.7%) and Shanghai (22.2%). Another remarkable result is that somatisation symptoms are related to female gender but independent from poor education level[15] (Gureje, 2004). In a study of Faroog et al that consist of 195 patients between the ages of 16-65 in 1994, it was reported that somatic and depressive symptoms were significantly more frequent in Asians compared to white race. Turkey is also a country that maintains cultural specialities. Somatic complaints that vary according to geographical regions are mentioned. Hafırgan, which is reported particularly around Şanlıurfa is one of them. This issue is described as palpitation in stomach and distress, it is frequently reported among local people and considered as a syndrome specific to culture[16] (Hafirgan,2003). High frequency of similar complaints show that demonstration of distress with body is also very common in our country. Thus, Turkey Mental Health Profile study suggested that psychogenic pain is the most common psychiatric diagnosis[3] (Kılıç, 1988).

According to researches, incidence of somatic complaints was found higher in South America and Asia, particularly in developing countries. Physical and emotional experiences are differentiated more rigorously in western culture. Therefore, somatic complaints might be less frequent in western societies.

Patients that have a difficulty demonstrating their memories of sexuality, aggregation and childhood verbally in the society they live in might use their body as a communication way. Consequently, bodily symptoms show repressed emotions and conflicts that patients avoid to verbalise. Patients that have painful symptoms without physical reasons might be demonstrating their inner conflicts via their bodies symbolically.

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JNBS 2016 Published by Üsküdar University www.jnbs.org

Year : 2016
Volume : 3
Issue Number : 1
Doi Number : 10.5455/JNBS.1452575043

Article history:
Received 11 January 2016
Received in revised form 29 January 2016
Accepted 22 February 2016

NEUROPROTECTIVE BENEFITS OF ATORVASTATIN IN DEMENTIA AND STROKE

ATORVASTATİN'İN DEMANS VE FELÇ DURUMLARINDA SİNİR KORUYUCU YARARLARI

Pushpa Natarajan[1], Sampath Kumar[2], Sinu Sahl[3], Vijaya Anand[*3]

Abstract

Dementia and stroke are the major health problem often occurs in older individuals aged 65 or more. There are many studies confirm that cholesterol might be involved in the pathogenesis of dementia and stroke. Atorvastatin, broadly used to lower cholesterol in coronary heart disease, are viable medications in decreasing the danger of dementia and stroke. Use of atorvastatin for prolonged period seems to be effective for the prevention of dementia and stroke. The objective of this review is to focuses the pharmacological benefit of atorvastatin in dementia and stroke.

Keywords: Dementia; Stroke; Atorvastatin

Özet

Demans ve felç 65 ya da daha yaşlı bireylerde sıkça görülen büyük bir sağlık problemidir. Kolesterolün demans ve felç patojeninizde yer aldığını doğrulayan pek çok çalışma vardır. Genel olarak koroner kalp hastalığında kolesterolü düşürmek için kullanılan Atorvastatin demans ve felç tehlikesini azaltmada uygulanabilir bir tedavidir. Atrovastatin'in uzun süreli kullanımının demans ve felci önlemede etkili olduğu görünmektedir. Bu çalışmanın amacı demans ve felç durumlarında atorvastatinin farmakolojik yararına odaklanmaktır.

Anahtar Kelimeler: *Demans; Felç; Atorvastatin*

[1]Department of Microbiology, Cauvery College for Women, Tiruchirappalli, Tamilnadu, India
[2]Department of Chemistry and Biosciences. SASTRA Universty, Kumbaknonam, Tamil Nadu, India.
[*3]Corresponding author: Department of Human Genetics & Molecular Biology, Bharathiar University, Coimbatore, Tamilnadu, India. Mobile: 9842525830

THE JOURNAL OF NEUROBEHAVIORAL SCIENCES
NÖRODAVRANIŞ BİLİMLERİ DERGİSİ

1. Introduction

Dementia is a most important public health problem because of its high occurrence in elderly individuals, mainly in the category of older subjects aged 65 or more (Barone et al., 2011). Dementia can be induced by a variety of conditions and the most common is Alzheimer's disease and in other clinical conditions, primarily or secondarily affecting the brain (Corrao et al., 2013). There is accumulating evidence that elevated serum cholesterol may be implicated in the pathogenesis of dementia.

Stroke is the rapidly raise the loss of brain functions due to a loss of blood flow in the brain. The Framingham Heart Study (FHS) and the Multiple Risk Factor Intervention Trial (MRFIT) confirmed a significant relationship between ischemic stroke and cholesterol levels (Kannel et al., 1971). High levels of cholesterol have decreased considerably after atorvastatin treatment in cerebrovascular disease. Atorvastatin is a lipid lowering agent; additionally it exerts an anti-inflammatory property which is important for prediction and treatment for dementia and stroke (Vijaya Anand et al., 2009). This review focuses the pharmacological benefit of atorvastatin on dementia and stroke.

2. Atorvastatin and Dementia

A group case control study based in the United Kingdom-based General Practice Research Database established that among the individuals with 50 years and older who taken atorvastatin therapy, the risk for developing dementia was considerably reduced, independent of their lipid status (Jick et al., 2000). In addition, there is no influence on the risk of developing dementia in this population who received other lipid-lowering agents. The systemic vascular protective effects of atorvastatin treatment are expected to add their beneficial effects, mainly on vascular forms of the dementia syndrome. Certainly, the results of the Heart Protection Study (HPS) and Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trials do not show the efficacy of statins in slowing cognitive refuse and dementia (Shepherd et al., 2002).

A de novo pharmacological effect of atorvastatin mediated by decreasing oxidative damage may be single mechanism which has the underlying benefits of atorvastatin in Alzheimer disease (Barone et al., 2011). Current evidence recommends that treatment of mild-to-moderate Alzheimer's disease with atorvastatin (80 mg/day) provide major benefit on the Alzheimer Disease Assessment Scale-Cognitive (ADAS-cog) following 6 months. An important positive effect on ADAS-cog performance occurred, followed by 6 months of atorvastatin therapy compared with placebo, but the level of benefit produced may be predicated on prior treatment, a person's apolipoprotein E genotype or whether the patient shows high cholesterol levels (Sparks et al., 2006) .

Based on a population, group case-control trial was conducted with 152,729 patients from Lombardy (Italy) with 40 years of age or above who were recently treated with atorvastatin. Compared with patients who had a very low dose of statins coverage (less than 6 months), those of 7-24, 25-48 and>48 months of coverage correspondingly had a risk reduction of 15%, 28% and 25%. Simvastatin and atorvastatin were both related to a decreased risk of dementia, while no similar data was noted for fluvastatin and pravastatin. It is evident that the long-term use of atorvastatin seems efficient for the prevention of dementia (Corrao et al., 2013). Therefore, atorvastatin exert many positive effects through a variety of mechanisms in the presence of atherosclerotic risk factors.

3. Atorvastatin and Stroke

Large clinical trials with atorvastatin are the reduction in ischemic stroke (Crouse et al., 1998), for example, the HPS shows a 28% reduction in ischemic strokes in over 20,000 patients with cerebrovascular disease or other high-risk situation (Collins et al., 2004). As a result of the findings of these huge atorvastatin trials increase the interesting query of how a class of cholesterol-lowering agents can decrease ischemic stroke when the ischemic stroke is not associated with cholesterol levels.

Cerebrovascular tone and the flow of blood are regulated by endothelium-derived (nitric oxide) (Dalkara et al., 1994). Mutant mice lacking endothelial nitric oxide synthase (eNOS-/-) are fairly hypertensive and extend greater proliferative and inflammatory response to vascular injury (Huang et al., 1995). Certainly, eNOS-/-mice develop larger cerebral infarcts following cerebrovascular occlusion (Huang et al., 1996). Therefore, the valuable effects of atorvastatin in ischemic stroke may be due to their ability to up regulate the expression and activity of eNOS (Kureishi et al., 2000). Interestingly, statins treatment did not affect blood pressure or heart rate before, during and subsequent to cerebrovascular ischemia and did not modify levels of serum cholesterol in mice, consistent with neuroprotective properties of statins.

Additionally, to increase in cerebral blood flow, other beneficial effects of atorvastatin are possible to happen that can have a strong effect against on the severity of ischemic stroke. Atorvastatin lowers the P-selectin expression and leukocyte adhesion via increases in NO production in a model of cardiac ischemia and reperfusion (Lefer et al., 2001). Several other studies have reported that atorvastatin up regulate tissue-type tissue plasminogen activator (t-PA) and down regulate plasminogen activator inhibitor-1 (PAI-1) expression through a same mechanism involving inhibition of Rho (G-protein)

geranylation (Essig et al., 1998).

Early outcome measured by the National Institutes of Health Stroke Scale (NIHSS) and the modified Rankin Scale (mRS) was better in acute stroke patients treated with atorvastatin than in those treated with simvastatin. These variations may reveal a neuroprotective effect unique to atorvastatin (Lamp et al., 2010). The Stroke Prevention by Aggressive Reduction of Cholesterol Levels (SPARCL) trial exhibit daily treatment with 80 mg of atorvastatin in patients with a recent stroke or TIA reduced the occurrence of fatal or nonfatal stroke by 16% (Huisa et al., 2010). Compared with placebo, use of high dose atorvastatin (80 mg/day) for secondary stroke prevention is not only of important clinical benefit but it is also low cost therapy. It produces major benefits in health with an incremental cost within reasonable limits (Arrospida et al., 2010).

Atorvastatin (20 mg/day) may be useful in reducing ischemic stroke frequency in ischemic stroke patients with a history of intracranial hemorrhage and is not associated with an increased risk of intracranial hemorrhage recurrence (Jia et al., 2013). Recently Ouk et al., 2013 study evidenced that the anti-inflammatory action of atorvastatin is arbitrated, by proliferator-activated receptor alpha (PPARα). The reduction in interleukin-6 (IL-6) plasmatic levels were PPARα dependent. The expression of the adhesion molecule intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) molecule was decreased by the atorvastatin treatment and this outcome was PPARα subordinate in the cortex, however not in the striatum of treated animals. Atorvastatin also decreased the cerebral expression of inducible nitric oxide synthase (iNOS) in the cortex, but there is no effect in the striatum of treated animals, whatever the PPARα status.

4. Conclusion

The most important result of this review is that atorvastatin is an effective lipid lowering drug. Treatment with atorvastatin provide a way of preventing the progression of dementia and stroke.

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REVIEW ARTICLE

THE JOURNAL OF NEUROBEHAVIORAL SCIENCES
NÖRODAVRANIŞ BİLİMLERİ DERGİSİ

Year : 2016
Volume : 3
Issue Number : 1
Doi Number : 10.5455/JNBS.1452923860

Article history:
Received 24 January 2016
Received in revised form 02 March 2016
Accepted 14 March 2016

GENE THERAPY AND GENE DELIVERY TO THE BRAIN USING VIRAL VECTORS

GEN TERAPİSİ VE VİRAL VEKTÖRLERİN KULLANIMI İLE BEYNE GEN NAKLİ

Can Akpınaroğlu*[1], Gökben Hızlı Sayar[2]

Abstract

Treating monogenic disorders via gene therapy although still considered experimental by some, has becoming a more accepted method lately especially in these last 10 years with a number of recent clinical successes. Genetic modifications are becoming easier to perform with the progressing technology and discovery of new techniques such as the Clustered regularly interspaced short palindromic repeats (CRISPR)-CRISPR associated protein 9 (Cas9) methods which can modify DNA with great ease and accuracy. Gene therapy is a powerful technique with huge potential to treat psychiatric and neurodegenerative disorders including Alzheimer's and Parkinson's disease. Gene therapy is simple in principle, which is corrective genetic material is sent into cells and the disease is cured by ending the problem at its source. Viral and non-viral vectors which are used for the delivery of the desired genes to the targeted cells are briefly listed and explained. Unlike viral vectors, non-viral vectors don't cause an immune response but their pretty low transfer rate makes them rather less interesting for research. Viral vectors of adenoviruses, adeno-associated viruses, retroviruses with its subclass of lentiviruses and herpes viruses are compared with their advantages and disadvantages related to usage in brain and CNS treatment of our topic. Neurotrophic factors (NTFs) have important roles in brain and nervous tissue. Delivering NTFs via viral vectors for treating neurodegenerative diseases is a promising approach. Providing information about principles, methods, hurdles and clinical applications of gene therapy with its historic background to present it with its all basic details and therapeutic effects it can provide to problems related to brain are aimed in this writing.

Keywords: Gene Therapy, Viral Vectors, Brain

Özet

Tek bir gene bağlı hastalıkların gen terapisi ile tedavisi hala bir kısım tarafından deneysel olarak nitelendirilse de özellikle bu son 10 yıldaki en son klinik başarılar ile gittikçe daha fazla kabul gören bir yöntem haline gelmektedir. DNA'yı harika bir kolaylıkla ve hassasiyetle modifiye edebildiğimiz clustered regularly interspaced short palindromic repeats (CRISPR)-CRISPR associated protein 9 (Cas9) metodu gibi yeni tekniklerin keşfi ve ilerleyen teknoloji ile genetik modifikasyonları uygulamak daha kolay bir hale gelmektedir. Gen terapisi psikiyatrik ve Alzheimer ya da Parkinson hastalığı gibi nörodejeneratif rahatsızlıkları tedavi edebilecek güçlü ve büyük bir potansiyeli olan bir yöntemdir. İyileştirecek olacak genetik malzemenin doğrudan hücrelere yollanması ve rahatsızlığın direkt olarak kaynağından çözümlenmesi, gen terapisinin basit prensipidir. İstenilen genlerin hedef hücrelere taşınması için kullanılan viral ve viral olmayan vektörler listelenmiş ve kısaca açıklanmışlardır. Viral vektörlerin aksine viral olmayan vektörler bağışıklık sistemini tetiklemezler fakat düşük transfer seviyeleri onları araştırmalar için daha az ilgi çekici yapmaktadır. Adenovirüsler, adeno ilişkili virüsler, alt kategorileri olan lentivirüslerle birlikte retrovirüsler ve herpes virüsleri konumuz olan, beyinde ve merkezi sinir sisteminde tedavi amaçlı kullanımlarına ilişkin avantajları ve dezavantajları ile karşılaştırılmıştır. Nörotrofik faktörlerin beyinde ve sinir dokusunda önemli rolleri vardır. Nörodejeneratif rahatsızlıkları tedavi etmek için nörotrofik faktörleri viral vektörler kullanarak iletmek, umut vadeden bir yaklaşım yoludur.

Bu yazıda, bütün temel ayrıntıları ve beyine dair sunabileceği tedavi edici etkileri ile tarihsel arkaplanı da dahil edilerek gen terapisinin prensipleri, metodları, zorlukları ve klinik uygulamaları hakkında bilgi vermek amaçlanmıştır.

Anahtar Kelimeler: *Gen Terapisi, Viral Vektörler, Beyin*

*[1]Corresponding author: Yeditepe University, Department of Genetics and Bioengineering, Istanbul, Turkey E-mail: akpinaroglucan@gmail.com
[2]Uskudar University, NPİstanbul Hospital, Departent of Psychiatry, Istanbul, Turkey.. E-mail: gokben.hizlisayar@uskudar.edu.tr Phone: +90 216 633 06 33 Mobile: 0530 244 13 16

1. Introduction

Technology is developing with an increasing acceleration and thus enabling scientific progress and increment in our scientific knowledge. With scientific progress our knowledge about the universe is deepening. Biology managed to set its roots and appear as a scientific discipline later than others mainly because it's highly dependent on technology. Biology and its field genetics is one of the most advancing study since 1900 and the start of 21st century.

Genes are the hereditary molecular units in DNA which make up a specific portion of a nucleotide and they encode instructions for making up proteins or RNA (Alberts et al., 2002). Their place in the genome can be located, they can be transcriptased and may have functional regions (Pearson, 2006).

Gene therapy has a huge potential for curing lots of diseases even otherwise incurable psychological disorders related to host's genes as genes responsible for various psychological disorders and human brain's functions are being understood more clearly every day.

Gene therapy is the therapeutic method for treating hereditary or other disorders and diseases caused by some specific genes. Correcting these undesired traits caused by genes with using viral or non-viral vectors and introducing the desired genes are aimed. Faulty genes can also be silenced to turn them off instead of correcting them (La Spada, 2009). Gene therapy seems like an effective alternative for CNS (central nervous system) disorders like Alzheimer's, Parkinson's and Huntington's diseases.

Although being simple in theory gene therapy has various difficulties making it quite hard to perform in practice. Transferring new genes to the host cell is quite hard and has its hurdles. The vectors that are used to transfer genes to the target cells must be efficient at gene delivery and there are various required traits a vector should have to be considered successful (Somia & Verma, 2000). Vectors should be easy to produce to obtain enough vectors for practical usage for the treatment of the patient and to be cost efficient. An ideal vector's side effects like toxic or immunological response should be minimal. Also a successful vector has to express the transgene for a long time to make it have a therapeutic effect. When an immune response is triggered the immune system might block the gene delivery vehicles and even destroy the cured cells as they have been modified with new foreign genes (Verma & Somia, 1997). Immunogenic viruses however may be modified to prevent an immune response. Gene delivery vehicles have to target the right cells to be considered efficient. Being efficient at transferring genes to the attached target cells and having a sustained period of production is desired (Verma & Weitzman, 2005).

Viral vectors are favored as they are far more efficient at attaching to the target cells and transferring their genome to the attached cell than non-viral vectors. Viral vectors however have a capacity of the length of the genome they can carry. Effects of adenoviruses and herpes simplex viruses are not permanent as their genome might be discarded after cell division since they don't integrate their DNA to the host cell's genome. Retroviruses and adeno-associated viruses however, integrate their genome to the host cell's genome.

Genes that are used for transfer might lack the information for splicing variants of the transcript and the critical regulatory sequences for the initiation of transcription. Several regulatory elements such as polyadenylation site for the mRNA that is transcribed or signal sequences are necessary for the transgene to be functional. Regulatory elements like promoters are located on the upstream of the gene that is transcribed. Contrary to constitutive promoters which are always active in the cell in all circumstances, such as viral long terminal repeats (LTR), regulatory elements which are tissue selective confer cell-restricted activity such that the transferred gene is transcribed only in distinct glial cells or neurons. Appropriate transgenes are required to function with the cell type-selective promoters. Promoters can also be modified to regulate the expression of the transferred gene. Some different physiologic factors, like hormones, also effect the expression of the genes. Formation of secondary structure of DNA is facilitated or inhibited by ions so manipulation of ions also can help with regulation of the transgene.

Gene therapy is being used for sicknesses that are caused by single gene mutations like hemophilia or cystic fibrosis. Disorders caused by multiple genes are quite complicated to cure as of now. Clinical trials have been undergone for cystic fibrosis however they were not successful (Crystal, 1995). Two methods of gene therapy exist: somatic cell gene therapy (SCGT) and germline gene therapy (GGT). In SCGT genetic changes that happen in the patient are not passed on to its offspring since all the genetic modifications occur in body cells and not in germ cells (eggs and sperm), gametocytes, gametes or undifferentiated stem cells.

First attempt of gene therapy happened in 1980 by Martin Cline from University of California, Los Angeles (UCLA) who used recombinant DNA (Wade, 1981). Two patients who had β-thalassemia blood disorder which causes serious anemia due to low levels of hemoglobin since beta-globulin gene of the person is faulty or non-existent, underwent the operation. Cline isolated and transformed the β-thalassemia which he extracted from the patients' bone marrow cells (Wirth et al, 2013). Cline, with the intention of increasing the transformed cells' replication ability, included a viral thymidine kinase gene in the viral vector he used. Cline's experiment wasn't successful and he was withdrawn from his

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NÖRODAVRANIŞ BİLİMLERİ DERGİSİ

position at the university and his funding was cut since he didn't take permission from UCLA and he breached National Institutes of Health (NIH) guidelines (Mak, Choma & Green, 2010).

The first successful gene therapy happened in 1990 (Blaese et al., 1995). Lots of unsuccessful trials in its early years made gene therapy seem like an unviable method but successes later achieved gained scientists' attention again (Richards, 2012). Gene therapy became approved for the treatment of lipoprotein lipase deficiency in Europe with the medicine Glybera in 2012 (Ylä-Herttuala, 2012).

1.1. Non-viral vectors

Non-viral vectors are easier to produce and immune response is usually not triggered. Any toxic, if it is caused, is low. Another upside of using non-viral vectors is they can target any type of cell and they do not have a maximum length of genetic material that they can carry however they are less efficient in gene transduction than viral vectors (Nayerossadat et al., 2012).

Naked DNA delivery: Delivery of naked plasmids is the most basic non-viral method. Electroporation or gene gun (Yang et al., 1990) is used to increase the efficiency of naked DNA transfer (Li & Huang, 2000). With electroporation pores on the cell membrane is opened with an electrical pulse and genes are transferred via these pores (Rols et al., 1998). Sonoporation, photoporation and magnetofection are other physical naked DNA transfer methods.

Other than direct physical naked DNA transfer, cationic lipids are used as non-viral vectors. These synthetic vectors made from liposomes don't have a limit to the length of genes they can carry however they might sometimes cause toxic. They are more efficient than naked plasmid transfer still but far less efficient than viruses.

1.2. Viral-vectors

Viral vectors are basically genetically modified viruses to transfer desired genes to the host cell. Usually retroviruses, adenoviruses, adeno-associated viruses, herpes viruses, pox viruses, human foamy viruses and lentiviruses are chosen. Viral vectors have higher chances of causing immune response. Viruses have a limited capacity for carrying genes so they can't transfer DNA with long gene sequences.

Retrovirus vectors: Also known as RNA viruses since they only carry RNA, retroviruses are unable to infect post-mitotic cells like some kidney, brain and liver cells. Retroviruses also carry a reverse transcriptase along with their single stranded RNA. They can only infect still dividing cells (Miller et al., 1990). Maximum length of genes they can carry is 8000 bases. Via membrane fusion the viral capsid with the RNA genome enters the cell after binding to its receptor. By using its reverse transcriptase the retrovirus creates a DNA model of its RNA for the host cell to produce.

Adenovirus vectors: Adenoviruses are the most commonly used gene therapy vectors and they are not highly pathogenic. Maximum length of DNA they can carry is 7500 bases. Changes made by adenoviruses take a long time to take effect as they enter lysogenic cycle and thus those changes on cells might be discarded.

Adeno-associated viruses: Adeno-associated viruses usually don't cause any immune response or sicknesses (Atchison et al., 1965). They can carry up to 5000 base containing DNA. The CFTR gene which is responsible for the disease is 4443 base pairs long so it can fit into adeno-associated viruses and since it doesn't cause harmful side effects it is considered a safe and viable vector for treatment of cystic fibrosis (Colledge & Evans, 1995).

Herpesvirus vectors: Herpes simplex viruses (HSV) which are a member of herpes viruses carry their genetic material as double-stranded DNA. They can carry up to 15000 bases of foreign DNA.

Lentivirus: Lentiviruses are actually a subclass of retroviruses which, unlike other retroviruses, can infect post-mitotic cells meaning that they can infect non-dividing cells. HIV is also a lentivirus.

2. Advantages and Disadvantages of different viral vectors

Compared to other viral vectors, adeno-associated viruses (AAV) are good candidates for CNS gene therapy. AAV vectors are able to target a variety of tissues which are astrocytes, neurons, glial and ependymal cells. Duration of their transgene expression in brain is 6 months long and 6 years long in other tissues of primates. Pathogenesis is minimal as there are no associated pathologies. They are ideal for scalable production as highly pure vector can be produced on large scale (Grieger et al., 2006). Advantages of AAV are that they are nonpathogenic and their expressions are relatively persistent. Their disadvantage is that they can accommodate only 4700 bases of foreign DNA which is rather short.

Retrovirus vectors target neurons and astroglial cells. Their transgene expression's duration is 3 months in brain and 9 months in other tissues of murines. They have some potential pathologies associated with their integration. Retrovirus vectors are moderately scalable production of highly pure vector.

Lentivirus vectors have the advantages of having a persistent expression and being able integrate into host chromosome. Disadvantages of lentivirus vectors are that they can accommodate only 6000-8000 bases of foreign DNA, they are potent human

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pathogens and they are produced in low titers.

Adenovirus vectors' targeted tissues for transduction is neural, astroglial and glioma cells. Duration of their transgene expression is 2 years long in non-brain tissues of primates. Pathogenesis is evident as there is immune response to vector and helper-virus contamination. Helper-virus contamination can be large scale produced. Advantages of adenovirus vectors are that they are episomal, meaning there is no possibility of insertional activation of host genes, they can be grown to high titers (-1010 /mL), they have high levels of expression of the foreign genes and their expression is relatively persistent. Disadvantages of adenovirus vectors are that their genetic manipulation is unwieldy and elicits host immune response.

Herpes-simplex virus (HSV) vectors can target only neurons for transduction and their transgene expression which is 7 months in brain of murine and also unstable, has the shortest duration compared to other vectors. Helper-virus contamination presents pathologies and their scalable production has not achieved yet. Advantages of herpes virus vectors are that they can accommodate up to 15000 bases of foreign DNA, they have high level of expression of foreign genes within hours, they can be concentrated to high titers and they are also episomal.

3. Clinical Applications of Viral Vectors

With the developing vector design technology using gene therapy as treatment for psychological disorders becomes more of a possible option. As our knowledge about the complicated mechanisms of genes such as promoters expands, it seems more possible to manipulate these seemingly modular structures to treat psychiatric disorders (Lesch, 1990). Such treatments can cure rather resistant disorders and cause fewer side effects meaning that the improvements in technology in future will help us applying the modulated version of genes as a therapeutic method.

Adeno-associated virus vectors are a feasible option for targeting central nervous system (Gray, 2012) and they are also considered safe vectors for transferring glutamic acid decarboxylase gene to treat Parkinson's disease as they are not toxic or no other adverse effects were observed later, showing them to be safe for brain (Kaplitt et al., 2007).

Viral vectors however have issues of causing inflammatory and immune response (Cichon et al., 1999). Non-viral, non-immunogenic vectors can be used however, gene delivery using electroporation (Haas et al., 2001) or gene gun (Lo et al., 1994) in vitro, gave poor results of gene transfer. Other non-viral methods such as cationic lipids (Wang et al., 2000) or calcium phosphate (Watanabe et al., 1999) were also not efficient in gene delivery with some toxic caused.

4. Neurotrophic Factors (NTF's)

Multiple aspects of neuronal development including axonal growth, neuronal maintenance, survival and synaptic plasticity are maintained by a range of proteins called Neurotrophic factors. NTFs can slow down or prevent disease process by promoting growth, metabolism and function of neurons in addition of being capable of regrowing damaged neurons (Deister & Schmidt, 2006). There are various neurotrophic factors such as nerve growth factor (NGF), neurotrophin-3 (NT-3), brain-derived neurotrophic factor (BDNF) and NT-4/5 which are neurotrophins, a family of secreted proteins and neurturin (NRTN) and glial cell line-derived neurotrophic factor which belong in superfamily of transforming growth factor beta (TGF-β).

5. Viral Vector Mediated Delivery of NTF's

Viral vectors can be used to supply neurotrophic factors to desired cells via viral-vector mediated gene therapy. Diseased neurons will be supplied with viral vectors which will transduce the diseased neuron for secretion of the therapeutic NTF. For the viral vector mediated delivery of NTFs to be successful early diagnosis of neuronal dysfunction and loss is necessary. Retarding or preventing the progression of the disease has to be the first goal of a gene therapy. Secondly, gene therapy of NTFs should aim enhancing the regeneration of neuronal connections and lost neurons.

For the viral vector mediated delivery of NTFs to have a therapeutic effect for neurodegeneration, cells have to be healthy enough to support the production and release of NTFs at the targeted region. Also signaling and expressions of the related NTFs have to be supported at the targeted region as well.

6. Conclusion

Treating mental disorders which are caused by chemical disruptions of molecular mechanisms of brain or other problems caused by monogenic or even multiple gene errors, is about to become a reality with gene therapy. Delivery of genes into the brain is becoming possible as scientific breakthroughs are happening spontaneously around the world, such as the discovery of the method clustered regularly interspaced short palindromic repeats (CRISPR)-CRISPR associated 9 (Cas9) which revolutionized the study of gene editing by increasing the efficiency, speed and pricing of genetic modifying which will also help with improvement of gene therapy (Gori et al., 2015), (Daneshvar, 2015). However before stepping into the complex

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mechanisms and structure of the human brain in order to transfer genes for treatment, there are some steps of precautions and scientific progress that we should not skip in order to be successful. Perhaps achieving a stable transgene expression would be the foremost. Regulation of the transgene along with its induction is important as amount of transgene products are crucial too. Our vector technology has to develop in order to prevent an immune response or toxic upon delivery of vectors into the host and to be able to transfer longer base sequence containing genes. Although cause of some mental disorders such as schizophrenia, bipolar disorder or depression seem to be related to genetics, involvement of other various factors make gene therapy a non-certain treatment for them. However as the effects of various genes in many psychiatric and neurodegenerative disorders is undeniable, sometimes being the sole cause of it, gene therapy is certainly a possible solution which will be applied frequently in future.

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REVIEW ARTICLE

Year : 2016
Volume : 3
Issue Number : 1
Doi Number : 10.5455/JNBS.1456158664

Article history:
Received 22 February 2016
Received in revised form 01 March 2016
Accepted 14 March 2016

A NEUROANATOMOPHYSIOLOGICAL APPROACH TO THE "FORMATION & EXPRESSION" OF PERSONALITY & PSYCHOPATOLOGY

KİŞİLİK VE PSİKOPATOLOJİNİN "FORMASYONU & EKSPRESYONU"NA NÖROANATOMOFİZYOLOJİK BİR YAKLAŞIM

Levón Antikacioglu[*1], Nevzat Tarhan[1]

Abstract

Despite the advancements in neurosciences, there are still, only a few Personality Theories, making use of neuropsychology. In the present paper, we tried to propose a NeuroAnatomoPhysiological approach to the "Formation and Expression" of Personality and Pschopatology and discussed the possibility of formation of a new study area.

Keywords: Neuro-Anatomo-Physiological Basis of Personality-Psychopatology, functional connectomes, neuroimaging technologies, personality traits and disorders, cultural background and biases.

Özet

Bu makalede, nörobilimdeki tüm gelişmelere karşın, nöropsikoloji temelli Şahsiyet Teorileri'nin henüz çok az olduğuna dikkat çekilmiştir. Bu durumu dikkate alan yazarlar, yeni bir NöroAnatomoFizyolojik temelli "Şahsiyetin ve Psikopatoloinin oluşumu ve ekspresyonu" ile ilgili bir yaklaşım önermişlerdir. Ayrıca yeni bir çalışma alanının oluşabilme ihtimalini tartışmışlardır.

Anahtar Kelimeler: *Şahsiyetin ve psikopatoloinin Nöro-Anatomo-Fizyolojik Temelleri, fonksiyonel konnektomlar, nörogörüntüleme teknolojileri, Şahsiyet vasıfları ve bozuklukları, kültürel arkaplan ve peşin hükümler.*

JNBS 2016 Published by Üsküdar University www.jnbs.org

[*1]Corresponding author: Faculty of Humanities and Social Sciences, Uskudar University, Turkey E-mail: levon.antikacioglu@uskudar.edu.tr
Phone: +90 (216) 400 2222 Sponsored by Uskudar University

THE JOURNAL OF NEUROBEHAVIORAL SCIENCES
NÖRODAVRANIŞ BİLİMLERİ DERGİSİ

1. Introduction

Centuries ago Galenus (Galen, 1938), related the personality, to bodily humors like "sanguine", "choleric", "melancholic" and "phlegmatic".

Since then several others, like Ernest Kretschmer (Kretschmer, E. 1925), linked personality to body forms like, Pyknic – Asthenic – Athletic – Dysplastic.

William Sheldon attempted to connect to Endomorph – Ectomorph – Mesomorph (somatic) types (Sheldon, W. H. 1940).

In modern times emerged more comprehensive Personality Theories based on biology.

Hans Eysenck began to study psychological traits and based them on biology. He based his Personality Theory, on the activation of the limbic system and reticular formation. Gave importance to the level of conditionability, and, distinguished the well-known extroversion-introversion, neuroticism and psychoticism dimensions (Eysenck, H. J. 1952).

Jeffery Alan Gray, based his bio-physiological theory of personality on three hypothetical brain systems: "behavioral inhibition", "behavioral activation" and "fight/flight system" and, emphasized the importance of their sensitivity to reinforcement (Gray, J. A. 2003; Corr, P. 2008).

C. R. Cloninger`s one instead, is a psychobiological theory. It is a "traits'" theory, which he extensively based on genetic, neurobiology, and neuropharmacology (Cloninger, C. R. at al. 1994).

The "Big Five Personality Traits Theory" (FFM: Five Factor Model) instead, partially is based on neurology. To test it, researchers conducted studies by neuroimaging techniques: In a study, they reported; "a personality trait of less openness have an accelerated loss of gray matter volume in the right inferior parietal lobule, compared with subjects with a personality trait of more openness" (Taki, Y. 2013).

In another one, researchers have tried to associate each of the five traits of FFM, with the volume of different brain regions and, they found supporting data, thus outlined the potential of "personality neuroscience" (De Young, C. G. 2010).

Even if they are not related to the FFM theory, there are several similar other studies also. But interestingly, it is remarkably striking that, almost all of the studies done to link MRI findings to personality traits, are connecting the findings, to very specific cerebral locations and/or to their activities.

For instance Davidson and Irwin, "emphasized the importance of PFC, its ventromedial and dorsolateral sector, in negative / positive emotions, and, amygdala in the perception of negative clues"(Davidson, R. J., & Irwin, W. 1999).

Canli, T. at al., trough a study which he conducted by fMRI, concluded that probably emotional experiences involve a complex network of interacting brain regions (Canli, T. 1999).

Canli, T. again, in another study that he made by fMRI, in which he tried to relate extroversion-introversion to cerebral specific locations, concluded that "This study provides direct evidence that personality is associated with brain reactivity to emotional stimuli, and, identifies both common and distinct brain regions, where such modulation takes place" (Canlı at. al. 2001).

Yet in another study Canlı (Canli, T. at al. 2002) by fMRI, measured amygdalas' response to happy faces. They noticed that "the specificity of the relation between extraversion and amygdala activation to happy expressions was supported in three ways: (i) Extraversion did not correlate significantly with activation to other emotional (angry, fearful, and sad) expressions; (ii) neuroticism did not correlate significantly with activation to any expression; and (iii) this correlation was the largest of all possible correlations among the "big 5" major personality traits factors (extraversion, neuroticism, openness, agreeableness, and conscientiousness) and all four facial expressions." (Canli, T. at al. 2002).

Völlm at al. in a study in which they made on Borderline and Antisocial Personality patients, said "active regions in the patient group showed a more bilateral and extended pattern of activation across the medial, superior and inferior frontal gyrus extending to the anterior cingulate" (Völlm, B. et al. 2004).

Again Canlı found that "E (Extraversion) and N (Neuroticism) scores are correlated with individual differences in the activation of the brain during cognitive affective tasks" (Canli, T. 2004).

In another one, the researchers sustained that the human orbitofrontal cortex is important for processing reward and punishment (Kringelbach, M. L., & Rolls, E. T. 2004).

Yang and Raine, " proposed that the emotional deficits are associated with impairments in the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), amygdala–hippocampus complex, and the insula, whereas antisocial behavior may be linked to deficits in the OFC, ACC, dorsolateral prefrontal cortex, and superior temporal gyrus." (Yang, Y., & Raine, A. 2008)

2. Discussion

As we have seen in the above mentioned ones and, in several other researches, scientists have attempted to relate the personality, or traits, or emotions etc. to specific cerebral locations' activities, and to some extent, also to their interaction.

Nevertheless we would rather assert that our traits or emotions or other personality components, "shouldn't be handled as made of some specific

isolated compartmental neuroanatomical modules only". Because intracerebral associative, short associative, commissural, projection fibers are all, secrets known by everybody (Luria, A.R. 1973). So, if in a given time, a certain personality trait's, attitude's, emotion's expression, is detected to be correlated with any cerebro-electrical discharge, we have to take for granted that, that focal point "must of course have simultaneous and/or consequential, and/or reciprocal interactions with other areas too, even if by our actual devices, they can pass unnoticed".

None of the above mentioned behaviors are reflexes; instead, they are learned expressions. And learning and performing cannot happen independently from the "entire CNS"; every single learning, and its performance, is proposed to be "strictly a systemic CNS issue" (Antikacioglu, L. 2015).

Therefore probably while the Hebbian theory is in action: " When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased" (Hebb, D.O. 1949), when it is time to detect those metabolically changed and/or grown -bulked up- cells, by our actually used neuroimaging devices, in reality we are capable to detect "just the focuses" of those relatively more active connections. In the while, "the dispersed neurons, which are linked to those easily noticeable focal ones, which have already been established by metabolic changes / connections, are passing unnoticed". For the simple reason that, "their ramifications are too spread over a wide area and, are too tinny". This is perhaps the only simple reason of why, while we are presently detecting the active neural bunches easily and plainly, we are not yet capable of tracing neither the single neurons' activities, nor their endlessly ramified weak connections.

Another argument that should be taken in consideration is the "non-existing relation, between the variety of our psychological/ psychopathological/psychiatric terminologies, and the neurophysiological functioning principles": In other terms, the only truth is that, "what we describe through psychological, psychopathological and/or similar other concepts, jargons and terminologies, not surprisingly, do not have any corresponding, counterpart in neurophysiology": Because from the standpoint of the CNS, any word / attitude / cultural information / bias / maladaptive habit / emotional state or performance, "are just materials, converted (traduced) into electrical impulses and neurotransmitters, and executed, within the well-known neurophysiological principles". If the information surpasses the excitability threshold, the neurons get excited, neurotransmitters can be released, and, the information can be stored / transmitted / inhibited. Otherwise, the communication between neurons cannot occur. For neurophysiological principles, these are all that count. Thus, any concept in any sub-discipline of psychology, which is related to learning / forgetting / amnesia / symptom / syndrome, psychopathology, and psychiatry or similar, by our CNS, is handled by the "same neurophysiological principles".

So we propose that, if we were able to detect, through a new technology, while our organism is in "full action" oriented to some task or problem solving activity (not simply lied down as actually is done in present neuroimaging or EEG techniques), we would have seen in the skull, a "fabulously sparkling pathways, almost changing direction, speed, intensity and volume, at speeds of lightening". The image of such a continuously changing dynamic view, would be sufficient enough to confirm the fact that our substantial behaviors are part of an "entire CNS" and cannot be originated from, solely limited neuroanatomical regions, like Amygdala or Hypothalamus or Hippocampus or Cingular gyrus. Or perhaps what we need is not a new technology but simply, some better software, to better decode what the actual devices are detecting. In fact, it seems that news of implementing attempts, of different perspectives of analysis, are on the way (Dodero, L. at al. 2015).

By this way probably we would be able to identify endless "patterns of Functional Connectomes" corresponding to different "Psychological, Psychopathological, Psychiatric States, Personalities and Traits etc.". And perhaps it would even be possible, the emergency of a promising new discipline: "Psycho Connectomics or Psycho Connectomology", embracing several sub disciplines.

If the above mentioned hypothesis goes demonstrated, we can arrive to a neat result: "What we call personalities, traits, emotional, psychopathological states etc. are, nothing more than dynamically changing, but at the same time remaining within determined patterns and borders of, functional connectomes made of different intensity, volume, type and directions. This assertion in turn is also a hypothesis that can be verified or falsified, by the more sensitive forms of our present technology.

2.1. How Personality, Traits, Emotional States, Diseases are formed?

For some reason or another, from the very beginning of our conception, our genetic code begins to work. Simultaneously, a nature-nurture combination in a still unknown way to us, shapes our learning and CNS, and then donates "a sui generis" way of operation, to it.

So every individual acquires, either at his preparedness to perceive the external world, or

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in reacting to it, his / her "sui-generis functional connectomal pattern" [These should probably correspond to some extent, what Aaron T. Beck, (Beck, T. A., 1979.) describes, as "automatic thoughts", "main beliefs", dysfunctional thoughts" or all of them, as the targets in CBT.]. And any person, for instance, categorized as introverted, exposes "functional connectomal patterns" common to introverts, or if the person has a Narcissistic Personality disorder, shares common patters with other Narcissist Personalities. The same will be valid for obsessives or histrionics etc. Each individual belonging to a category, of course forms also his / her "proper personal differences".

Thus, we propose to assume that, "the persistence of a personality, and/or formations, manifestations of any psychological, psychopathological state, are no more than the manifestation of the tridimensional expression of its functional connectomes, in a more or less steady way, although varying in integrity, quantity, quality and intensity from each other's".

Thus, perhaps it is time to consider "each personality type or personality treat or personality disorder or psychopathological, emotional state etc., as a merely different functional connectomal pattern", which in turn can entirely be studied, under an embracing discipline, which can be named as "Psycho Connectomics or Psycho Connectomology".

3. Conclusion

It looks that it is time to propose a NeuroAnatomoPhysiological Personality Approach, which merely relies on our "Functional Connectomes": What we call personality, personality traits, attitudes, biases, cultural equipment, psychopathological symptoms, syndromes, by allegedly differentiated disciplines, are nothing more than the, dynamic but consistent, total sum of "functional connectomal (electrical) patterns", differing slightly from each others' in intensity, quality, quantity and volume, either at our preparedness to perceive the external world or, in reacting to it. Therewith it will probably be very handy, the foundation of a discipline called "Psycho Connectomics". And this assertion/s will be proved or disproved by future mapping techniques, or by new softwares, extracting the appropriate information, from the existing ones.

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REVIEW ARTICLE

Year : 2016
Volume : 3
Issue Number : 1
Doi Number : 10.5455/JNBS.1449860617

Article history:
Received 11 December 2015
Received in revised form 26 February 2016
Accepted 14 March 2016

RESECTION OF DEEP BRAIN STEM LESION: EVOLUTION OF MODERN SURGICAL TECHNIQUES

DERİN BEYİN SAPI LEZYONUNUN ÇIKARILMASI: MODERN AMELİYET TEKNİKLERİNİN GELİŞİMİ

Salman Abbasi Fard[1], Nimer Adeeb[1], Mona Rezaei[1], Babak Kateb[2], Martin M. Mortazavi[*3]

Abstract

Deep brain stem lesions have previously been considered unresectable. With the development of tailored skull base approaches, detailed knowledge of topographical anatomy, utilization of intra-operative mapping, identification of safe entry zones, extensive arachnoid dissection, cautious handling of neurovascular structures, modern surgical techniques with minimal compression of brain stem and retractor-less surgery, the resection of these previously unresectable lesions, has become possible. Herewithin, an overall review is provided and illustrative cases are presented with detailed discussion of the technical perspective of each approach and resection.

Keywords: Brain Stem, Technical Note, Brain Lesion, Surgical Resection

Özet

Derin beyin sapı lezyonlarının daha önceden cerrahi müdahaleyle çıkartılmasının mümkün olmadığı düşünülüyordu. Kişiye göre özelleştirilmiş kafa iskeleti yaklaşımlarının gelişimiyle, detaylı topografik anotomi bilgisiyle, intraoperatif haritalamanın kullanılmasıyla, güvenli giriş alanlarının belirlenmesiyle, gelişmiş araknoid teşhisiyle, nörovasküler yapıların dikkatli müdahalesiyle, minimal beyin sapı kompresyonu ve daha az rektartör kullanılan ameliyatlarda kullanılan modern cerrahi tekniklerle birlikte, daha önceden cerrahi müdahale ile çıkartılması mümkün olmayan lezyonların çıkartılması mümkün hale gelmiştir. Sonuç olarak, bu çalışmada genel bir bakış ele alınmış ve her yaklaşımın ve müdahalenin teknik perspektifi detaylı bir şekilde ele alınarak örnekleyen vakalar ortaya konulmuştur.

Anahtar Kelimeler: *beyin sapı, teknik not, beyin lezyonu, cerrahi rezeksiyon*

[1]California Neurosurgical Institute, 333 South Moorpark Road, Thousand Oaks, CA, 91361 USA.
[2]Society of Brain Mapping and Therapeutics, 8159 Santa Monica Blvd. Suite 200, West Hollywood, CA 90046 USA.
[*3]Corresponding Author: California Neurosurgical Institute, 333 South Moorpark Road, Thousand Oaks, CA, 91361 USA E-mail: m_mortazavi@hotmail.com Phone: +1 - (805) 795-7656

THE JOURNAL OF NEUROBEHAVIORAL SCIENCES
NÖRODAVRANIŞ BİLİMLERİ DERGİSİ

1.Introduction

Deep intra-axial brain stem lesions, had long been considered unresectable due to high morbidity and mortality risk (Bailey P, 1939; Matson DD, 1969).

Tumors and vascular malformations such as cavernous malformations are among these lesions (Cantore G, 1999).

Brain stem houses neurons and nerve tracts that control vital functions such as breathing, blood pressure and heart rate control, swallowing and the ability to make sounds, as well as the ability for movement and sensation of the face, mouth, tongue, body and extremities.

Lesions within the brain stem therefore, affect some of these vital functions. As the brain stem, at its largest diameter is about 4 cm, one can understand how tightly these neurons and tracts are impacted together. Any growing lesion would therefore, not only disturb these vital functions, but also, the very approach for resecting these lesions, would put these normal vital structures into danger.

In the beginning of the 1970's, some neurosurgeons started reporting data on surgical resection of these, with less grave outcome (Lassiter KR, 1971). This change of attitude came along with research outlining better understanding of the micro anatomy of the brain stem, development of modern neuro-monitoring techniques for mapping of these eloquent brain structures, and further development of micro neurosurgery. Development of better microscopes with better illumination was also crucial.

2. Technical Report

As the brain stem houses these very important functions, it is protected well within the bony skull base. This fact led to development of further skull base approaches allowing the surgeon to reach the brain stem.

The brain is compacted within the thin arachnoid membrane.

The vessels of the brain, as well as important cranial nerves are either within the folds of this arachnoid membrane; the so called arachnoid cisterns, or under this membrane; the so-called subarachnoid space. Understanding the micro-anatomy of these structures and the skill set needed to dissection and opening of these arachnoid membranes, will allow the brain to relax (Ono M, 1984; Lü J, 2005; Adeeb N, 2013; Párraga RG, 2015). Additional diversion of the cerebrospinal fluid (CSF) though ventriculostomy or lumbar drain will give further brain relaxation.

Once the skull base approach is performed, meaning adequate bone of the skull has been resected, the dura mater is then opened and the subarachnoid space and cisterns are widely dissected. At this point, the neurosurgeon can reach deep structures by dissecting in between normal folds of the brain without injuring the brain structures (Párraga RG, 2015). Relaxation of the brain will not necessitate use of retractors and therefore a retractor-less surgery can be performed with no pressure on the brain.

This dissection is especially sensitive at the brain stem. In order to enter the brain stem, some safer entry zones exist, through which, the risk of morbidity is less than other areas. Although these areas are called 'safe entry zones'. in reality, there is no complete 'safe' entry zone. However, these entry zones are 'safer' in relation to entering brain stem at other locations (Brown AP, 1996; Mai JC, 2013; Cavalcanti DD, 2015).

Beside good knowledge of the topographic anatomy of these safe entry zones, the development of mapping has become an important tool.

During mapping, certain neurological functions of interest for the regions involved, are continuously monitored during the surgery and any change is being observed. Once the dissection to the area of interest is performed, the brain stem is stimulated with low current, in order to delineate where the most important functions reside. Safe entry zones, usually does not show any activity on mapping upon electrical stimulation. The result of the mapping, along with knowledge of the surgical anatomy of the brain stem, allows surgeon to enter the brain stem (Morota N, 1995).

Entrance to the brain stem follows the natural direction of the tracts, meaning, entrance needs to be done perpendicular to the tracts. These tracts have a rostral to caudal direction, so that the tracts are rather cautiously 'opened' away from each other, than cut. This maneuver continues until the lesion is reached (Brown AP, 1996; Mai JC, 2013; Cavalcanti DD, 2015).

At this point, the surgeon cautiously starts to make an interface between the brain stem and the lesion. Obviously, some lesions, such has high-grade gliomas, are spread within the brain and a good interface can not be achieved. On the other hand, lesions such as cavernous malformations, with a somehow identifiable interface, can with patience, safe and stable technique, be dissected off of the brain stem. Often, these vascular malformations, have previously caused multiple bleedings. Once the lesion is entered, the mere entrance of the some lesions such as cavernous malformations, allows some remaining blood or blood products to exit the lesion and relax the brain stem off of the compression caused by previous bleedings (Mai JC, 2013; Abla AA, 2014).

As the dissection between the brain stem and the lesion continues, the brain stem side of the interface, is covered by micro-cottonoids and the lesions is dissected away from the brain stem into a

central cavity. The dissection continues around the lesion. Once the whole lesion is dissected off the brain stem, it can be resected.

Cavernous malformations are associated with deep venous anomalies (DVA) in about 50% of the cases. These DVA's, although anomalous, drain venous blood from normal brain stem and need to be preserved at any cost, although often closely attached to the cavernous malformation (Garcia RM, 2015).

Herewithin, two illustrative cases, were presented; one in the upper brain stem (Midbrain, Mesencephalon) and one in the mid brain stem (Pons). The mesencephalic lesion is approached through a subtemporal craniotomy. The pontine lesion is approached through a Telovelar approach via a suboccipital craniectomy.

3.Conclusion

With the combination of good understanding of the topographical anatomy of the brain stem, intra-operative mapping, CSF-diversion, and modern retractorless neurosurgical techniques, previously unresectable lesions, can now be resected with reasonable morbidity.

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CASE REPORT

THE JOURNAL OF NEUROBEHAVIORAL SCIENCES
NÖRODAVRANIŞ BİLİMLERİ DERGİSİ

Year : 2016
Volume : 3
Issue Number : 1
Doi Number : 10.5455/JNBS.1449305089

Article history:
Received 05 December 2015
Received in revised form 11 December 2015
Accepted 20 December 2015

USE OF REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION FOR TREATMENT OF AUDITORY HALLUCINATIONS: A CASE REPORT AND BRIEF REVIEW

İŞİTSEL VARSANILARIN TEDAVİSİNDE TRANSKARANİAL MANYETİK UYARIM KULLANIMI: BİR OLGU SUNUMU VE KISA GÖZDEN GEÇİRME

Gökber Hızlı Sayar[*1], Hüseyin Bulut[2], Nevzat Tarhan[1]

Abstract

In this case we report the efficacy of repetitive transcranial magnetic stimulation for treatment resistant auditory verbal hallucinations. The majority of protocols have utilized low-frequency suppressive repetitive transcranial magnetic stimulation over the left temporoparietal cortex with some therapeutic benefits in ameliorating auditory hallucinations. Normalizing the functional connectivity between the temporoparietal and frontal brain regions may underlie the therapeutic effect of repetitive transcranial magnetic stimulation on auditory hallucinations in schizophrenia. Regarding side effects, the rTMS intervention was well tolerated in this case. Future research must focus on the optimum stimulation site and parameters.

Keywords: transcranial magnetic stimulation, rTMS, schizophrenia, auditory hallucinations

Özet

Bu olgu sunumunda tekrarlayan transkranial manyetik uyarımın tedaviye dirençli işitsel varsanılarda etkinliği bildirilmektedir. Literatürde işitme varsanılarında tedavisel etkinliği oldığu bildirilen protokollerin çoğunda sol temporoparietal bölgeye baskılayıcı düşük frekanslı transkraniyal manyetik uyarım kullanılmıştır. Temporoparietal ve frontal beyin bölgeleri arasındaki işlevsel bağlantının düzeltilmesi, şizofrenide işitsel varsanılarda transkranial manyetik uyarımın etkinliğinin altında yatan mekanizma olabilir. transkranial manyetik uyarım bu olguda bildirilen hasta tarafından iyi tolere edilmiştir. Gelecekteki çalışmalar optimum uyarım bölgesi ve parametreleri üzerine yoğunlaşmalıdır.

Anahtar Kelimeler: *transkranial manyetik uyarım, rTMS, şizofreni, işitsel varsanılar*

[*1]Corresponding author: Uskudar University E-mail: ghizli@npistanbul.com Phone: +90 216 633 06 33 Mobile: 0530 244 13 16
[2]Büyükçekmece Government Hospital, Department of Psychiatry, Istanbul, Turkey. E-mail: hubulut@yahoo.com

1.Introduction

Schizophrenia is a debilitating psychiatric disorder with unknown etiology. Genetics and early environment appear to be relevant contributory factors. The symptomology of schizophrenia is typically divided into two categories: positive symptoms (hallucinations, delusions, etc.) and negative symptoms such as avolition, alogia, blunted affect, anhedonia. Although positive symptoms respond well to medication, the response of negative symptoms to medication is often limited.

Neuromodulation techniques like repetitive transcranial magnetic stimulation (rTMS) have been a promising option in schizophrenia. rTMS is a neurostimulation method permitting brain neuronal metabolism modulation in a non-invasive way. It has repeatedly been demonstrated that high-frequency rTMS (10-25 Hz) enhances brain excitability, and low-frequency rTMS (1 Hz and low) reduces it. It has also been found that high-frequency rTMS applied over the left prefrontal cortex (PFC) increases brain perfusion, while low-frequency rTMS has the opposite effect (Kole et al., 1999).

2.Case:

Mr. M is a 43-year-old, right handed male who was diagnosed with schizophrenia 20 years ago. He was on haloperidol 10 mg/day and clozapine 300 mg/day oral antipsychotic treatment. He had a history of treatment resistance to several typical and atypical antipsychotics and also to their combinations. For the last 2 years he was on a stable regimen which leaded to a significant decline in his persecution delusions, however, commenting hallucinations and non-verbal auditory hallucinations persisted. He reported that the auditory hallucinations produce severe distress and respond poorly to antipsychotic medication and electroconvulsive treatment. A detailed assessment did not reveal any other disease or TMS contraindications. Auditory hallucinations were assessed by using the Auditory Hallucination Rating Scale (AHRS) and the patient had a score of 33 at baseline (range of the scale: 2-40). The patient gave informed consent and was included in a rTMS protocol. His current dose of antipsychotic medication was maintained during treatment. 1 Hz TMS applied over the left TPC by figure-of-eight air-cooled coil using the Magstim Superrapid Stimulator (Magstim Company, Whitland, England) for 5 daily sessions per week (1000 pulses per session) for 4weeks. The location of stimulation was given halfway between the left temporal (T3) and left parietal (P3) electroencephalogram electrode sites on the basis of the international 10-20 placement system.

After a week of treatment, AH were improved with a 30% reduction in AHRS score and the improvement was 60% compared to baseline at the end of 4 weeks. This effect continued during the 2 months that followed the acute response. This protocol was well tolerated by the patient

3.Discussion:

About 60–80% of schizophrenic patients experience auditory hallucinations [AH]. There are four commonly recognized types of auditory hallucinations: commanding or commenting hallucinations, voices of one's thought, thought broadcasting auditory hallucinations and non-verbal auditory hallucinations. AH often produce severe distress and disability. In about 25% of patients, auditory hallucinations respond poorly to antipsychotic medication (Gromann et al., 2012). The fMRI studies suggest a direct involvement of speech perception neurocircuitry. Support for this view derived from the observation that patients with auditory hallucinations, compared with healthy control subjects, are more likely to experience perceptual illusions of words or word phrases when listening to acoustic noise (Alpert, 1985). These early findings suggest excessive sensitivity or reactivity of speech perception systems.

Neuroimaging studies show activation of brain areas during auditory hallucinations that are active during speech perception (Dierks et al., 1999). fMRI studies have detected activation in TPC during auditory hallucinations which is nearby the Wernicke's area and is also active during perception of speech (Benson et al., 2001). It is hypothesized that 1-Hz rTMS delivered to areas of the brain dedicated to speech perception might reduce auditory hallucinations (Hoffman et al., 2000). Various studies have been conducted recently investigating the effects of rTMS on AH. As AH is linked to cortical hyperexcitability, the majority of protocols have utilized low-frequency suppressive TMS over the left temporoparietal cortex (TPC). Typical parameters are 1 Hz frequency (inhibitory), to left TPC, with subthreshold intensity.

Several studies have been reported the efficacy of 1 Hz rTMS treatment, but results were inconsistent. Slotema et al. performed a literature search from 1966 through October 2008 for trials of rTMS mental disorders. They obtained data from randomized, sham-controlled studies of rTMS treatment for AH (7 studies) and negative symptoms in schizophrenia (7 studies) The mean weighted effect size for rTMS versus sham in the treatment of negative symptoms of schizophrenia was found to be 0.39 and 0.54 in the treatment of AH. With these results, rTMS was superior to sham treatment. Side effects were reported to be mild. They concluded that rTMS is a promising treatment option for depression, for auditory verbal hallucinations, and possibly for negative symptoms (Slotema et al., 2010).

Aleman et al. observed a significant mean weighted effect size for rTMS versus sham across the 10 studies, involving 212 patients. When only

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studies that used continuous stimulation (9 studies) were included, the mean effect size increased even more. In this meta-analysis, authors did not report any significant effect of rTMS on a composite index of general psychotic symptoms. They concluded that rTMS does not appear to be an efficacious treatment for positive symptoms beyond auditory hallucinations (Aleman et al., 2007).

Tranulis et al. applied a meta-analysis to explore the efficacy of rTMS in treating medication-resistant AH. They searched the electronic databases for studies comparing the effect of low-frequency rTMS over the left TPC to sham stimulation in patients suffering from AH. From 265 available abstracts, 6 parallel-arm, double-blind placebo-controlled and 4 crossover controlled trials, they found that low-frequency rTMS over the left TPC has a medium effect size action on medication-resistant AH (Tranulis et al., 2008). Similarly, Freitas et al. conducted meta-analyses in 2009 which includes the all prospective studies of the rTMS in schizophrenia evaluating the effects of high-frequency rTMS to the left dorsolateral prefrontal cortex (DLPFC) to treat negative symptoms, and 1 Hz rTMS to the left TPC to treat auditory hallucinations and overall positive symptoms. When analyzing controlled and uncontrolled studies together, the effect sizes showed significant and moderate effects of rTMS on negative and positive symptoms. However, the analysis of the sham-controlled studies revealed a small non-significant effect size for negative (0.27, p=0.42) and positive symptoms (0.17, p=0.13). When specifically analyzing auditory hallucinations, the effect size for the sham-controlled studies was large and significant (1.04; p=0.002). The authors decided that there was a need for additional controlled, extended trials to evaluate the efficacy of rTMS on positive and negative symptoms of schizophrenia. They also suggested the need for exploration for alternative stimulation protocols (Freitas et al., 2009).

Although low-frequency stimulation over left TPC seems to be effective in relieving AH symptoms, it does not appear to have any impact on other positive symptoms of schizophrenia. Although Freitas and colleagues were able to find a significant impact in their meta-analysis for AH, when all non-sham studies were eliminated from the analysis, all therapeutic effects of TMS on other positive symptoms disappeared. Further research examining the stimulation of different cortical areas using different stimulatory paradigms is recommended.

In a study reported by Geller et al. 10 patients with schizophrenia and 10 patients with depression were examined to determine if mood changes could be induced and whether different effects could be obtained in various patient groups (Geller et al., 1997). Very-low-frequency (once per 30 seconds) rTMS was administered on each side of the brain, 15 pulses each. Two of 10 patients with schizophrenia appeared to improve, at least transiently. Feinsod et al. (Feinsod et al., 1998) reported a non-blind study in which 7 of 10 patients with schizophrenia experienced decreased anxiety and restlessness in response to low-frequency frontal rTMS. On the other hand, a later double-blind study examining the effects of low frequency rTMS delivered to right DLPFC did not report any improvement following active stimulation relative to sham stimulation (Klein et al., 1999).

Bagati et al. (Bagati et al., 2009) conducted a study in 2009 that included 40 patients with schizophrenia who were randomized to either an rTMS group or a control group. Both groups were treated with standard antipsychotics following a 10-day preliminary phase in which the experimental group received low-frequency TMS over the left TPC. AH was significantly reduced in the rTMS group of patients. Similarly, Vercammen et al. (Vercammen et al., 2009) reported a significant reduction in hallucination frequency in patients with schizophrenia who received TMS to the left TPC, as well as a decrease in self-reported affective responsiveness in patients who received TMS to bilateral TPC. Self-mutilation is one of the most perilous complications confronted in psychiatric patients and is often related to AH. A case report presented the successful treatment of AH with 20 sessions of 1 Hz targeting areas of elevated metabolic activity in the TPC (Schulz et al., 2015).

Results vary across controlled and uncontrolled studies in the treatment of auditory hallucinations using low-frequency TMS to the left TPC. This could be attributed to the heterogeneity of study methodology. One out of three studies that used a dose of 80 % MT showed positive results (33%) in reducing AH while the positive result ratio is seven out of 12 studies that used 90 percent of MT dose (58%) and two out of two studies (100%) that used a dose of 100 % MT (Cole et al., 2015). However, further data are required to explain the relationship between the parameters of stimulation and efficacy in treating auditory hallucinations. Also, the other factors that are likely to impact the effectiveness of TMS include treatment-resistant symptoms, use of associated medication, such as anticonvulsants.

A sample of 50 patients who diagnosed with schizophrenia or schizoaffective disorder was studied by Hoffman et al. (Hoffman et al., 2003). Forty-two of the patients met criteria for medication resistance. Patients were randomly allocated to either active rTMS or sham stimulation. The length of time of unremitting auditory hallucinations was extended, with a mean of approximately 10 years in each group. Patients were classified as responders if hallucination severity was reduced by at least 50%. Using this criterion, they found that 14 of 27 patients [51.9%] achieved responder status in the active group, compared with 4 of 23 (17.4%) in the sham group. Those patients with more frequent

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auditory hallucinations demonstrated a greater differential effect when compared with patients receiving sham stimulation, whereas patients with lower hallucination frequency showed less robust differences between active and sham rTMS.

Clinical trials using rTMS successfully for treatment of auditory hallucinations have been reported by other groups (d'Alfonso et al., 2002; Poulet et al., 2005). Lee and colleagues (Lee et al., 2005) designated 39 patients with treatment-resistant AH to three groups: active rTMS to the left TPC, active rTMS to the right TPC and sham stimulation. Active rTMS delivered both to left and to right temporoparietal sites produced greater overall symptomatic improvements relative to sham stimulation. Chibbaro and colleagues (Chibbaro et al.,2005) studied 16 patients with schizophrenia and auditory hallucinations. rTMS at 1 Hz was administered at 90% of MT during four sessions on successive days. The duration of each stimulation session was 15 minutes. Half the patients received active rTMS, and half received sham stimulation. Both patient groups demonstrated a significant reduction in auditory hallucinations as well as in other positive symptoms after 7 sessions of rTMS. However, at later time points up to and including 8 weeks following the trial, improvements in the sham group disappeared, whereas improvement was retained for patients receiving active rTMS.

There have also been a number of negative studies on the use of TMS in patients with schizophrenia. Fitzgerald et al. (Fitzgerald et al., 2008) did not find a difference in therapeutic effect in domains such as frequency, duration, location, intensity, and disruption of voices between the active and sham groups of 20 patients with the diagnosis of either schizophrenia or schizoaffective disorder. However, authors reported a significant reduction in the loudness of hallucinations. In 2006, Saba et al. treated 18 patients with schizophrenia and refractory AH with TMS for 10 days (Saba et al., 2006). The patients received active or sham rTMS for 10 days over the left TPC. Psychopathological dimensions were measured with the positive and negative syndrome scale and clinical global impression at baseline and after 10 sessions of rTMS. Both groups were improved at the end of the trial, but there was not any statistically significant differences were found between groups. In that study authors concluded that active rTMS failed to show superiority over sham stimulation in the treatment of schizophrenic symptoms. Rosa et al. (Rosa et al., 2007) reported safe administration of TMS concurrently with clozapine in 11 patients with schizophrenia but did not reveal a significant reduction in auditory hallucinations. A large randomized trial (Slotema et al., 2011) in 2011 using fMRI to guide TMS treatment site failed to produce positive results in reducing the severity of auditory hallucinations. This study involved 63 patients who specifically suffered from treatment- resistant auditory/visual hallucinations. In 2011, a study by DeJesus et al. (de Jesus et al., 2011) was done using rTMS on 17 patients with refractory schizophrenia who suffered from auditory hallucinations and was being treated with clozapine. The authors reported no significant reduction in auditory hallucinations using r TMS. In a recent meta-analysis Cole et al., we found sixteen controlled studies and two open-label studies using low-frequency TMS (Cole et all., 2015). Of the randomized, controlled studies, 10 studies involving a total of 257 subjects with psychosis revealed positive results in treating auditory hallucinations with TMS, while eight studies involving a total of 284 subjects with psychosis did not show any efficacy using TMS.

A systematic review done by Slotema (Slotema et al., 2014) compared 25 randomized, control trials using the severity of the hallucinations or psychosis as the primary outcome measure. No differences were seen with the severity of psychosis. The severity of hallucinations was significantly reduced with the paradigm of left TPC rTMS at 1 Hz. Other models were measured and were unable to make a difference in hallucination severity.

McIntosh and colleagues (McIntosh et al., 2004), used the lower-dosed 4-day protocol and found no significant improvement in auditory hallucinations for active rTMS versus sham stimulation. Of note is that the stimulation was halted every minute for 15 seconds, which may have disrupted physiological effects of rTMS. Another study, reported by Fitzgerald et al. (Fitzgerald et al., 2005), studied 33 patients with treatment-resistant auditory hallucinations. rTMS was applied for 10 sessions for 15 minutes at 1 Hz and 90% of MT. Although active rTMS was found to be related to a significant reduction in the loudness of hallucination, the other measures related to general psychopathology did not result in a greater therapeutic effect.

4.Conclusion

Several studies recently investigated the effects of rTMS on schizophrenia. The majority of protocols have utilized low-frequency suppressive rTMS over the left TPC with some therapeutic benefits in ameliorating auditory hallucinations. Normalizing the functional connectivity between the temporoparietal and frontal brain regions may underlie the therapeutic effect of rTMS on auditory hallucinations in schizophrenia Given the often disabling nature of these symptoms, clinical use of this technique could be justified in certain cases. Regarding side effects, the active rTMS intervention was well tolerated.

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Year : 2016
Volume : 3
Issue Number : 1
Doi Number : 10.5455/JNBS.1444218339

Article history:
Received 17 December 2015
Received in revised form 02 February 2016
Accepted 22 February 2016

SWALLOW OUTCOME IN THREE FEMALE SIBLINGS WITH HUNTINGTON'S DISEASE AND CHOREA

HUNTINGTON VE KORA HASTALIĞI OLAN ÜÇ KIZ KARDEŞTEKI YUTKUNMA SONUÇLARI

Thejaswi Dodderi*[1], Chinju Micheal[2]

Abstract

The present study focuses on describing characteristics of swallow among Huntingtons Disease (HD) with Chorea before and after dysphagia therapy. Three female siblings of 21, 22 and 33 years having juvenile type onset of HD with chorea were included. The patients were evaluated comprehensively for swallowing using Manipal Manual for Swallowing Assessment. Each patient was subjected to ingestion of solid, thin liquid and thick liquid of 5ml and 10 ml quantified using a standard measurable cup. Descriptive statistics was administered on the data using statistical package SPSS (Version 17). On observation, all three patients presented with sensory and motor issues in addition to posture instability with abrupt body movements, food spillage, piece meal deglutition, intra bolus retention, wet voice and cough. Following which cognitive approach and behavioural approach based intervention was initiated. The symptoms of intra bolus retention and cough decreased post therapy with no change in sensory aspects. The present study evidences three female siblings with severe cognitive deficits and dysphagia secondary to HD. Despite rehabilitation being provided, they could not completely waiver off the symptoms. These evidences highlight the importance of identifying and addressing swallow based treatment outcomes in HD with chorea.

Keywords: Huntingtons disease, chorea, dysphagia, behavioural therapy

Özet

Bu çalışma, yutma zorluğu terapisinden önce ve sonra Koralı Huntingon Hastalığı(HD) arasındaki yutkunma özelliklerine odaklanmıştır. Çalışma, Koralı HD'nın ergenlik döneminde başlayan çeşidine sahip olan 21, 22 ve 33 yaşlarındaki üç kız kardeşten oluşmaktadır. Hastalar, Manipal Yutkunma Becerileri Kılavuzu kullanılarak yutkunmaları için kapsamlı bir şekilde değerlendirilmişlerdir. Her hasta, standart bir ölçme kabı kullanılarak katı, ince sıvı, 5ml ve 10ml'lik kalın sıvıları yutmaya maruz bırakılmışlardır. İstatistik programı olan SPSS (sürüm 17) kullanılarak betimleyici istatistikler elde edilmiştir. Gözlem sırasında, üç hasta da ani vücut hareketleriyle duruş dengesizliği, yiyecek dökme, kısmi yutma foksiyonu, intra kapsül retansiyonu, nemli ses ve öksürmenin yanı sıra duyusal ve motorsal bulgular ortaya koymuştur. Bilişsel ve davranışsal yaklaşıma dayanan müdahalelerin takibi başlatılmıştır. Öksürük ve intra kapsül retansiyonunun semptomları duyusal açılardan hiçbir değişlik olmadan tedavi sonrasında azalmıştır. Bu çalışma, yoğun bilişsel eksiklikleri ve Huntingon Hastalığı (HD)'na bağlı yutma zorluğu olan üç kız kardeşi inceler. Rehabilitasyon desteği almalarına rağmen, bu semptomlardan tam olarak kurtulamamışlardır. Bu bulgular, koralı Huntingon Hastalığı(HD)'nın yutkunmaya dayalı tedavi sonuçlarının tanımlanmasının ve gösterilmesinin önemini vurgulamaktadır.

Anahtar Kelimeler: *Huntingon Hastalığı, Kora, yutma zorluğu, davranışsal terapi*

*[1]Corresponding author: Nitte Institute of Speech & Hearing, Mangaluru, India. E-mail: thejaswi07@gmail.com
[2]Nitte Institute of Speech & Hearing, Mangaluru, India.

THE JOURNAL OF NEUROBEHAVIORAL SCIENCES
NÖRODAVRANIŞ BİLİMLERİ DERGİSİ

1. Introduction

HD is an autosomal dominant progressive neuro-degenetraive disorder, typically with an adult onset. Repetition of mutant protein HTT on the short arm Chromosome 4 leads to cerebellar atrophy, especially at the level of caudate nucleus and putamen. This in turn leads to progressive motor, emotional and cognitive decline with choreiform body movements (Rusz et al., 2013). In view of these facts, life expectancy of such individuals is significantly affected, with poor mortality and morbidity, due to untreated dysphagia (Sorenson & Fenger, 1992).

Swallowing issues begin right from the oral preparatory stages manifesting as postural instability, poor quantity of food intake, tachyphagia, in-complete mastication and reduced lingual control ending in premature swallow (Leopold & Kagel, 1985; Hunt & Walker, 1989; Hamakawa et al., 2004; Kagel & Leopold, 1992; Mochizuki et al., 1999). Oral stage has absent voluntary swallow, short oral transition time of 0.23 ms with greater quantity of intra bolus retention despite multiple swallows. These act as a barrier and impede safe pharyngeal stage swallow leading to irregular hyo-laryngeal movements, frequent coughing due to aspiration indicated in a wet voice quality. Despite these well defined HD characteristics till date there is no clinically apparent red flag that serves as a bio marker for early identification and prevention of dysphagia (Heemskerk & Ross, 2011).

Even though literature reports 30 years as the typical age of onset, the symptoms may be exhibited during early childhood and continue to late adulthood (Bates et al., 2002). Moreover, previous findings reported were questioned for lack of patients and poor method (Heemskerk & Ross, 2011). This calls in for more evidence in the era of evidence based practice for better understanding of the concept being investigated. Therefore, we hereby put forth swallowing related clinical findings of three female siblings diagnosed of having HD with chorea before and after dysphagia therapy.

2. Subjects and Methods

Three female siblings with complaint of involuntary body movements admitted for medical treatment in a multidisciplinary teaching hospital participated. The patients P1, P2 and P3 were of 21, 22 and 33 years of age (mean age of 25.33 years) respectively with history of juvenile onset of HD with chorea symptoms. The clinical diagnosis of HD with chorea was given based on previously established criteria of choreatic body movements, impaired motor control, social, behavioural and cognitive changes associated with positive family history (Huntingtons Study Group, 1994; Harper, 1991; Tabrizi et al., 2012). Following which details pertaining to onset of the problem were ascertained by asking the first onset of chorea, recurrent mood swings, poor social behaviour, memory issues, sleep disturbance, frequent falls. Based on this, age of onset was 17, 15 and 17 years of age (mean age of 16.33 years) respectively. Family history revealed non-consanguineous marriage with paternal history of similar symptoms in three members, who were deceased for same.

Cognitive status of the three siblings was determined using Mini Mental State Examination before initiating any further investigation (Folstein, Folstein, & McHugh, 1974). Manipal Manual for Swallowing Assessment was administered to assess the swallow abilities in the subjects (Balasubramanium & Bhat, 2012). This manual is proposed to comprehensively assess structure, function, phases and tolerance of swallowing across four sub-scales for Indian population.

Following the diagnostic evaluation, therapeutic regime was initiated keeping two domains into account, cognitive approach and behavioural approach (Nance, 2012). As all three patients presented with severe form of cognitive deficits, orientation therapy was initiated with focus on presentation of orientation information, like time, place and person oriented. We also counselled the mother with the aim to cut down her anxiety levels and understand the practicality of the condition, so as to provide better support services. In the behavioural approach, positional change, hydrating oral cavity, mixing sour liquids, consistency changes with quantity reduction, chin tuck manoeuvre, verbal prompt of /a:/ followed by spoon positioning was performed routinely. These measures taken were earlier reported as evidence for swallow rehabilitation in literature (Nance, 2012; Aubeeluck & Mokowitz, 2008). A Speech Language Pathologist provided therapy three sessions/day of 30 minutes each for five continuous days.

3. Results

Results of the swallow investigation revealed series of undesired ramified swallow outcomes across all three patients. We observed severe sensory-motor deficits associated with cognitive communication dysfunctions. Postural disturbance were also evidenced in the subjects, with P1 presenting with supine position while P2 and P3 sitting upright with back support. Scores of Mini Mental Status exhibited severe form of cognitive dysfunction with P1, P2 and P3 obtaining nil score. As a result, we placed them under the category of 24 hour compulsory assistance for everyday functioning. Results of the swallowing investigation carried out are represented in Table 1.

In assessment of structure, the first sub parameter of sensory aspect, none of the patients were able to

Table 1: : Scores of swallow assessment obtained pre and post-therapy across P1, P2 and P3.

	Assessment of Function				Phases of Swallowing		Total	
	Sensory		Motor					
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
P1	48	48	58	50	23	17	129	115
P2	48	48	63	63	29	26	140	137
P3	48	48	57	51	14	10	119	109

identify light vs. deep pressure when stimulated with the tongue depressor. Moreover, only awareness of the stimuli was observed behaviourally. Apparently in the second sub parameter of assessment of structure, the motor aspect, the three patients presented with persisting open mouth, drooling, lingual chorea, decreased tongue range, strength and absent voluntary cough. It was also observed that P3 presented with posterior tongue position at rest, while P1 and P2 had neutral tongue placement during rest. Results of phases of swallow provided evidences of oral and pharyngeal stage dysphagia. Series of intra bolus retention symptoms were noted at the level of lateral buccal cavity and tongue blade across the three subjects. In addition to these, poor lip seal, delayed onset of voluntary swallow, prolonged hyo-laryngeal elevation, lingual chorea with piece meal deglutition and aspiration cough was noted for thin and thick liquids. Comparatively, better intake of solids was observed with decreased symptoms of multiple swallows, intra bolus retention and cough. Overall, bolus preparation time was increased for solids. No nasal regurgitation was observed. Lastly, subjects were tolerant to textures across oral and pharyngeal phase.

Issues pertaining to identification of sensory stimuli did not change even after post-therapy. All three patients persisted with just awareness of sensory stimuli to be present. After three sessions of therapy, we observed decreased drooling and better tongue range in P1 and P3 subjects. No clinical differences were notable in P2 subject. On the continuum, we observed better swallow performance in terms of reduced quantity of intra bolus retention for thick liquids. This however did not change for thin liquids post-therapy and the patient presented with intra bolus retention and aspiration cough. No changes were noted in cognitive aspect post-therapy. In general, post-therapy swallow investigation revealed that only the degree of the oral and pharyngeal dysphagia could be reduced with more sessions of safe swallow for nutrition intake.

4. Discussion

The present study was undertaken to profile swallow skills in individuals diagnosed of having HD with chorea. On comprehensive swallow evaluation, in all three female siblings we documented oral and pharyngeal stage of swallow problems. We attribute progressive sensory-motor degeneration in the cerebellum, reported to be more severe in juvenile onset type of HD, as the root cause for presentation of these symptoms. These neurological deficits incapacitate the ability to control respiratory and bucco-lingual muscles compulsorily required for safe swallow (Hamakawa et al., 2004). The findings of the present study are similar to the reports evidenced in literature which characterises sensory-motor deficits with oro-pharyngeal dysphagia (Leopold & Kagel, 1985; Hunt & Walker, 1989; Hamakawa et al., 2004; Kagel & Leopold, 1992).

Co-ordination between swallowing and breathing is an essential element in protecting the airway tract during swallowing. Absence of this bio-mechanical physiology hinders co-ordinated initiation and propulsion of bolus consequently leading to series of premature swallow events, thereby causing progressive dysphagia (Sorenson & Fenger, 1992). Adverse affects of dysphagia are the common cause for individuals with HD to have aspiration pneumonia, respiratory issues and malnourishment that ultimately leads to cessation of life (Sorenson & Fenger, 1992).

Motor disturbances, such as chorea, are also accounted for impeding safe swallow in our study. Presence of choreatic or dance like movement hinders normal rhythmic, repetitive sequences of single motor movements (Willingham & Koroshetz, 1993). Evidences of lingual chorea in our patients must have dictated in-coordinated swallow, piece meal deglutition and intra bolus retention characteristics.

Functioning of tongue by means of rotation, thrust movements, bolus positioning and touch to palate are crucial aspects of normal swallow. Hence, impairment in the buccal-lingual muscles can affect individual's ability to pool out bolus trapped in the buccal cavity, specifically lateral sulci. Further on, complicating these motor movements is the lack of maintenance of posture (Reilman et al., 2012). In our all three patients we observed posture instability, one among various reasons that facilitates poor bolus preparation and delayed lingual movements in oral phase subsequently terminating as a pre-mature swallow.

In addition to these, sensory deficits are also a contributing factor. We attribute lack of sensory awareness as the possible reasons in our patients who presented with poor bolus preparation, bolus positioning and failure in pooling out intra-bolus residue. As per the swallowing manual, sensory deficits were assessed with two types of differential pressure being applied and the patient responding. Now due to poor cognition and lack of language skill we cannot accurately pin point degree of sensory deficits. Supportive of declining cognitive profile, evidences of language impairment have also been reported in HD patients (Azambuja et al., 2012).

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Strong evidences have been documented in literature which roots that brainstem regulates the central pattern generator for swallowing (Jean, 1990). Despite these viewpoints, several researchers have reported activation of cortical regions during voluntary swallow, in which few are suggestive of bilateral representations and some unilateral (Robbins et al., 1993; Smithard et al., 1997). Hence, intact cortical functions i.e., cognition is one of the basic pre-requisites for performing daily activities. This happens to be affected in HD with chorea, both initial and progressive stages (Cleret de Langavant, 2013). Studies draw focus upon impaired attention, short term memory deficits and executive function issues indicating a degenerative cognitive profile (Naarding, Kremer, & Zitman, 2001). Although we did not administer a detailed cognitive test battery, results of Mini Mental Status Examination helped us arrive at the conclusion of severe cognitive impairment in our patients. Literature reports Mini Mental Status Examination to be superior in sensing cognitive decline than other test battery like Montreal Cognitive Assessment thereby justifying adoption of present method (Gluhm et al., 2013)

Studies have suggested that manifestation of psychiatry issue in addition mood disorders hinders prognosis, while adding burden on the parents (Rickards et al., 2011). In all our patients, presence of suicidal tendencies, lack of sleep and depression was reported. These symptoms highlight what Paulson and colleagues report of stage II type of HD, which characterizes loss of independent functioning (Paulson et al., 2005). Severe cognitive impairment associated with stage II type of HD puts such individuals at greater risk of poor social life, dignity, safety, nutrition, bowel movements and functional competence. Presentation of these complex, multifaceted symptoms makes it very difficult for the family in providing care, as noted in the present study.

Having known the fatal consequence of HD with chorea it is alarming that very few clinical setups have focussed upon the principle 'there is never anything we can do for HD' (Nance, 2012). Despite these remarks there have been few initiatives, like palliative and hospice care, that addresses challenging deficits observed in later stages of HD (Dellefield & Ferroni, 2011). We state that, from the current case series observed, availing palliative and hospice care could provide them better quality of life in addition to receiving rehabilitation services. Apparently, initiating palliative and hospice care in terminal stages of progressive neurologic disease is mostly in developed countries, and in India it is still in primitive stages and lacks awareness for initiating implementation. This calls in for a more constructive approach in setting up institutes that primarily addresses and delivers ideologies of palliative and hospice care.

5. Conclusion

The present study was undertaken to profile swallow skills before and after intervention in individuals diagnosed of having HD with chorea. Results of swallow investigations revealed sensory-motor issues with oro-paryngeal dysphagia and cognitive communicative deficits. Post-therapy we observed lesser degree of dysphagia characteristics but with no improvement in cognitive skills. Presentation of these clinical case scenarios cues for accommodating compensatory strategies. Prognosis of HD in later stages is not so bright. However, therapeutic services must focus to facilitate quality of life by adopting palliative and hospice care based rehabilitation. Lastly, the present study calls in for more clinical evidence in early identification and rehabilitation of HD with chorea.

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JNBS 2016 Published by Üsküdar University www.jnbs.org

LETTER TO THE EDITOR

THE JOURNAL OF NEUROBEHAVIORAL SCIENCES
NÖRODAVRANIŞ BİLİMLERİ DERGİSİ

Year : 2016
Volume : 3
Issue Number : 1
Doi Number : 10.5455/JNBS.1456830409

Article history:
Received 01 March 2016
Received in revised form 06 March 2016
Accepted 14 March 2016

PERSISTENT LINGUAL DYSKINESIA AND PROTRUSION DUE TO CLOMIPRAMINE AND RISPERIDONE

KLOMİPRAMİN VE RİSPERİDON'A BAĞLI ISRARLI LİNGUAL DİSKİNEZİ VE PROTRÜZYON

Alper Evresel[*1], Celal Şalçini[2], Nevzat Tarhan[3], Barış Önen Ünsalver[3]

Tardive dyskinesia may develop with the long-term use of dopamine receptor blocker drugs such as antipsychotics. We herein report a case of persistent lingual dyskinesia and protrusion due to clomipramine and risperidone treatment.

A 41 year-old female patient presented to the psychiatry clinic with complaints of speaking difficulty and involuntary tongue movements (ITM). She was started on clomipramine 150 mg/day 13 years ago and added risperidone 1 mg/day 2 years ago treatment for obsessive compulsive disorder according to DSM-V. ITM and protrusion (Figure 1A-1B) was began 1 year ago. Therefore risperidone was discontinued. Despite ITM was not decrease. Diazepam, clonazepam, aripiprazole and clozapine was ineffective for ITM. She had no family history of movement disorder. Neurological and systemic examination was normal. Cranial magnetic resonance imaging (MRI) and quantitative electroencephalography (QEEG) were done. No paroxysmal activity was found in QEEG. Magnetic resonance imaging (MRI) was normal. Examination of eyes did not show Keyser-Fleisher rings. Based on these findings her condition was diagnosed as drug induced persistent lingual dyskinesia. ITM was decrease after tetrabenazine 25 mg/day treatment.

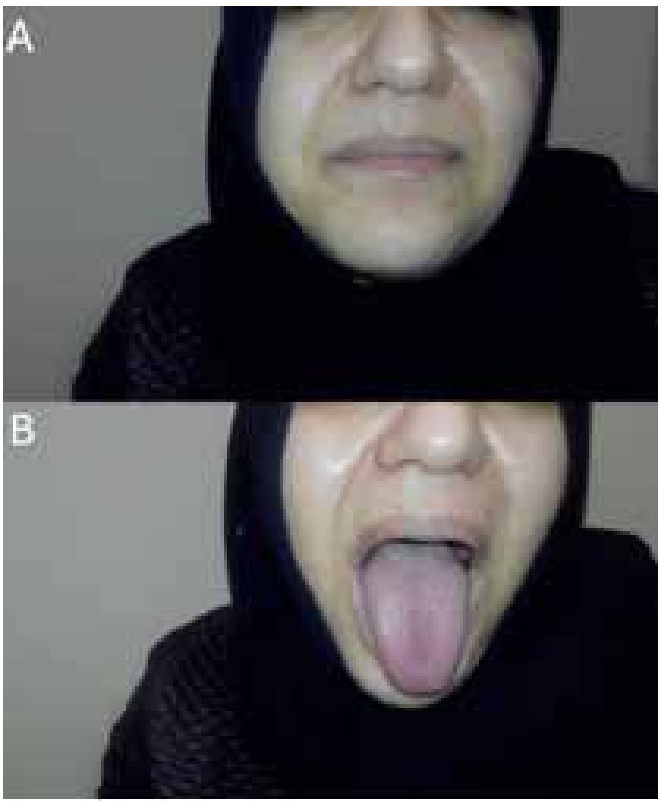

Figure 1: Clinical photograph showing tongue in the mouth (A) and involuntary protrusion (B).

Lingual dyskinesia has been associated with the use of antipsychotic drugs such as haloperidol. Dopamine receptors sensitization should be considered improvement of tardive dyskinesia by antipsychotic drugs (Lykouras et al. 1999, Aia et al. 2011). Dyskinesia may be local such as involuntary tongue movements and lingual protrusion (Aia et al. 2011). Clomipiramine is a tricyclic antidepressant.

[*1]Corresponding author: Uskudar University, Electroneurophisiology, Istanbul, Turkey. E-mail: alperevrensel@gmail.com
[2]Uskudar University, Department of Neurology, Istanbul, Turkey.
[3]Uskudar University, Department of Psychiatry, Istanbul, Turkey.

No case reports lingual dyskinesia and tongue protrusion due to clomipramine in the literature. Very few case reports risperidone induced lingual dystonia (Sharma and Biswas 2012). In the our case ITM began less than one year after starting risperidone treatment. The association of risperidone with tardive dyskinesia is rare. However particularly in patients exposed to long-term neuroleptic treatment this possibility should not be neglected.

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JNBS 2016 Published by Üsküdar University www.jnbs.org

LETTER TO THE EDITOR

THE JOURNAL OF NEUROBEHAVIORAL SCIENCES
NÖRODAVRANIŞ BİLİMLERİ DERGİSİ

Year : 2016
Volume : 3
Issue Number : 1
Doi Number : 10.5455/JNBS.1456905938

Article history:
Received 02 March 2016
Received in revised form 8 March 2016
Accepted 14 March 2016

BRAIN-DERIVED NEUROTROPHIC FACTOR AND EXERCISE, CAN IT BE A NEW BIOMARKER FOR ATHLETIC PERFORMANCE?

BEYİN TÜREVLİ NÖROTROFİK FAKTÖR VE EGZERSİZ, ACABA ATLETİK PERFORMANS İÇİN YENİ BİR BİYOMARKER OLABİLİR Mİ?

Korkut Ulucan*[1,2]

To editor,

Brain-derived neurotrophic factor, BDNF, is a member of the neurotrophin family, in humans, and has important roles on the survival of the neurons; also in growth and differentiation of newly produced neurons (Huang& Reichardt, 2001). In brain, BDNF is commonly active in hippocampus and cortex, where learning and memory areas are located (Yamada& Nabeshima, 2003), and also active in retina, saliva and prostate (Mandel et al. 2009 2009). BDNF is the gene responsible for coding BDNF protein, has 12 exons and located at 11p13. Alternative splicing gives rise to multiple transcripts, one of which encodes a preproprotein that is proteolytically processed to generate the functioning protein. Recent studies showed the reduced expression of this gene in Alzheimer's, Parkinson's, and Huntington's patients, and BDNF protein is believed to play a role in the biology of mood disorders, either alone or in contact with monoamins.

To improve brain health and function, including cognitive function and alleviating depression, one of the important behavioral habit is regular exercise. Exercise also increases adult neurogenesis in the dentate gyrus (DG), dendritic complexity of DG granule neurons, and synaptic plasticity (the cellular basis of learning) in the pathway connecting the entorhinal cortex to the DG (Xu, 2013). BDNF is known to show increased expression as a response to acute and chronic physical exercise, and this increased expression of the protein as a result of exercise may be the main benefit of exercise to brain health. Berchtold et al. (2005) showed also that exercise primes a molecular memory for BDNF induction after the exercise was ceased in rats. In addition, serum BDNF is known to increase under exercise conditions in humans, and the source of this BDNF is thought to be brain, under concrete conditions, BDNF can penetrate blood–brain barrier (BBB), although not all the studies says so (Maaike et al. 2011).

Although the effect of BDNF on brain health is a known fact, studies including sportsman, BDNF levels and polymorphism effecting BDNF expression are limited. Oztasyonar (2016) examined the BDNF levels of taekwondo fighters, boxers, and athletes before and after training, and compared the results to sedentary subjects. It was shown that all the trainers BDNF levels were higher than sedentary subjects, and also BDNF levels were higher after the exercise sessions. There are also some studies in humans, all implying the importance of BDNF levels and healthy mood conditions.

The effect of BDNF on sports performance is still unclear. The rise in BDNF levels after exercise may not show the athletic performance status. But new studies associating the average levels of serum BDNF and athletic performance will fulfill the importance of BDNF in athletic performance. Also the probability of administration of BDNF to athletes should be considered as a doping action although the molecular effect of BDNF on athletic performance is not clear. Besides, to date, it is thought that

*[1]Corresponding Author Marmara University, Faculty of Dentistry, Department of Medical Biology and Genetics, Istanbul, Turkey E-mail: korkutulucan@hotmail.com , korkut.ulucan@uskudar.edu.tr Phone: 0216 400 22 22- 2409
[2]Uskudar University, Faculty of Engineering and Natural Sciences, Department of Molecular Biology and Genetics, Istanbul, Turkey

serum BDNF is originated mainly from brain, in the case of penetrating from BBB. But the effect of administrated BDNF on athletic performance will be a topic of new research in sports science.

When we consider the healthy mood status of sportsman, one can speculate on the effect of healthy mood in athletic performance. In this case, BDNF will be one of the target molecules for success in sports. Studies on this topic will be needed to outline the link between psychological factors and athletic performance.

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JNBS 2016 Published by Üsküdar University www.jnbs.org

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