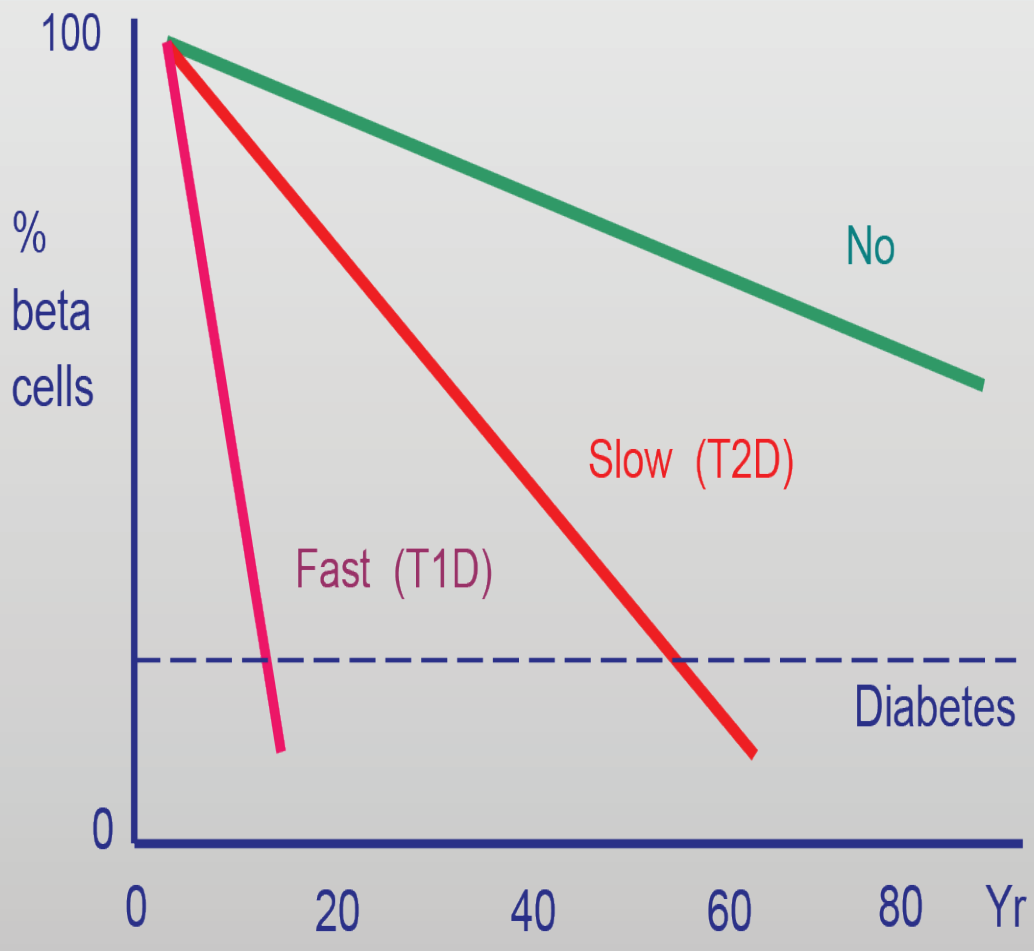
UNIVERSITY OF NIŠ

ISSN 0354-2017 (Print)
ISSN 2406-0526 (Online)
COBISS.SR-ID 32415756

FACTA UNIVERSITATIS

Series
MEDICINE AND BIOLOGY
Vol. 17. N° 2, 2015



Tempo – the central concept underlying the accelerator hypothesis.
(Taken from the paper by Terence J. Wilkin)

Scientific Journal **FACTA UNIVERSITATIS**
UNIVERSITY OF NIŠ
Univerzitetski trg 2, 18000 Niš, Serbia
Phone: +381 18 257 095 Telefax: +381 18 257 950
e-mail: fumeed@junis.ni.ac.rs http://casopisi.junis.ni.ac.rs/

Scientific Journal FACTA UNIVERSITATIS publishes original high scientific level works in the fields classified accordingly into the following periodical and independent series:

Architecture and Civil Engineering
Automatic Control and Robotics
Economics and Organization
Electronics and Energetics
Law and Politics
Linguistics and Literature
Mathematics and Informatics
Mechanical Engineering
Medicine and Biology
Philosophy, Sociology, Psychology and History
Physical Education and Sport
Physics, Chemistry and Technology
Visual Arts and Music
Working and Living Environmental Protection

SERIES **MEDICINE AND BIOLOGY**

Editor-in-Chief: **Ljiljana Šaranac**, e-mail: *fumabed@junis.ni.ac.rs*
University of Niš, Faculty of Medicine, Republic of Serbia
81 Dr. Zoran Đinđić Blvd., 18000 Niš
Phone: +381 18 423 15 50, Fax: +381 18 423 87 70

Tecnical Assistance: **Mile Ž. Ranđelović**, e-mail: *fumabts@junis.ni.ac.rs*
Univerity of Niš, Republic of Serbia

UDC Classification Associate: **Milena Djordjević**, University of Niš, Library of Faculty of Medicine
English Proofreader: **Zorica Antić**, Faculty of Medicine, University of Niš

The authors themselves are responsible for the correctness of the English language in the body of papers.

Secretary: **Olgica Davidović**, University of Niš, e-mail: *olgicad@ni.ac.rs*

Computer support: **Mile Ž. Ranđelović**, University of Niš, e-mail: *mile@ni.ac.rs*
Miloš Babić, University of Niš, e-mail: *milosb@ni.ac.rs*

The cover image taken from the paper from this issue by Terence J. Wilkin, "The Accelerator Hypothesis – an Evolving Concept".

Publication frequency – one volume, two issues per year.

Published by the University of Niš, Serbia

Printed by "UNIGRAF-X-COPY" – Niš, Serbia

ISSN 0354-2017 (Print)
ISSN 2406-0526 (Online)
COBISS.SR-ID 32415756

FACTA UNIVERSITATIS

Series **MEDICINE AND BIOLOGY**
Vol. 17, No 2, 2015

UNIVERSITY OF NIŠ

AUTHOR GUIDELINES

Facta Universitatis, Series: Medicine and Biology (FU Med Biol) is the official publication of the University of Niš, Serbia. It publishes original scientific papers relating to medicine, biology and pharmacy (editorials, original experimental or clinical works, review articles, case reports, technical innovations, letters to the editor, book reviews, reports and presentations from (inter)national congresses and symposiums which have not been previously submitted for publication elsewhere). All manuscripts are assumed to be submitted exclusively unless otherwise stated, and must not have been published previously except in the form of an abstract or as parts of a published lecture and/or academic thesis.

Original papers may not exceed 10 printed pages, including tables and/or figures.

Reviews may not exceed 16 printed pages, including tables and/or figures.

Case reports/technical innovations/book reviews/presentations from congresses may not exceed four printed pages, including tables and/or figures. The figures should not occupy more than two-thirds of one printed page. The editor or co-editor reserves the right to make the decision if a manuscript qualifies to be corresponding type of the article.

Manuscripts are normally subject to the assessments of reviewers and the editor. Manuscripts that have been extensively modified in the editorial process will be returned to the author for retyping. All submitted articles will be reviewed by at least 2 reviewers, and when appropriate, by a statistical reviewer. Authors will be notified of acceptance, rejection, or need for revision within 4–5 weeks of submission.

Paper submitted for publication may be written exclusively in English. Authors for whom English is a second language should have the manuscript professionally edited before its submission.

Each author that participated sufficiently in the work has public responsibility for the content. This participation must include: a) Conception of design, or analysis and interpretation of data, or both, and b) Drafting the article of revising it for critically important intellectual content.

Text

The manuscript should contain following subdivisions:

(1) Title page (with short running page heading, title, authors names and affiliations, corresponding author with full address, e-mail, phone and fax).

Number all manuscript pages consecutively beginning with the title page. Do not hyphenate words at the end of the lines. Do not begin sentences with abbreviations.

(2) Abstract

The main abstract should be maximum 250 words, double-spaced and on a separate page. It should briefly describe respectively the problems being addressed in the study, how the study was performed, the salient results (without abbreviations) and what the authors conclude from the results.

2.1. Key words

Immediately after the Abstract, up to six topical key words for subject indexing must be supplied.

(3) Main body (Introduction, Material and methods, Results, Discussion, Conclusion)

The headings (Introductions; Material and Methods, etc.) should be placed on separate lines.

Abbreviations should be defined at first mention and used consistently thereafter.

The Introduction should give the pertinent background to the study and should explain why the work was done. References should be numbered in the order in which they appear (1, 2 or 1–3, etc.)

Each statistical method and/or other investigation should be described in the Material and Method section. All scientific measurements must be given in SI units.

The Results should present the findings of the research. They must be free of discussion. Results should be written in the past tense. Spell out the word Figure in the text except when it appears in parentheses: Figure 3 (Figs. 2–5). Always spell out numbers when they stand as the first word in a sentence: abbreviated units cannot follow such numbers. Numbers indicating time, mass, and measurements are to be in Arabic numerals when followed by abbreviations (e.g. 1 mm; 3 ml, etc.). All numbers should be given as numerals.

The Discussion should cover, but not simply repeat the new findings and should present the author's results in the broader context of other work on the subject interpreting them with a minimum of speculation.

(4) Acknowledgements

Acknowledgments of people, grants, funds, etc. should be placed in a separate section before the reference list. The names of funding organizations should be written in full.

(5) References

The references should be limited to those relating directly to the content of the manuscript. Authors are responsible for ensuring that the information in each reference is complete and accurate. All references should be numbered in the order in which they appear in the text. Do not use footnotes or endnotes as a substitute for a reference list. At the end of the article the full list of references should give the name and initials of all authors unless there are more than six, when only the first three should be given followed by "et al". The authors' names should be followed by the title of the article, the title of the Journal abbreviated according to the style of Index Medicus, the year of publication, the volume number and page numbers. In case that more than one paper by the same author(s) published in the same year is cited, the letters a, b, c, etc., should follow the year, e.g. Bergmann (1970a) **—** in the reference list.

Examples for journals and other sources are as follow:

Journals:

1. Kuroda S, Ishikawa T, Houkin K, Nanba R, Hokari M, Iwasaki Y. Incidence and clinical features of disease progression in adult Moyamoya disease. Stroke 2005; 36:2148–2153.
2. Papantchev V, Hristov S, Todorova D, et al. Some variations of the circle of Willis, important for cerebral protection in aortic surgery — a study in Eastern Europeans. Eur J Cardiothorac Surg 2007; 31:982–998.
3. Jovanović S, Gajić I, Mandić B, Mandić J, Radivojević V. Oral lesions in patients with psychiatric disorders. Srp Arh Celok Lek 2010; 138:564–569. (Serbian)
4. Valença MM, Martins C, Andrade-Valença LPA. Trigeminal neuralgia associated with persistent primitive trigeminal artery. Migrâneas cefaléias (Brasil) 2008; 11:30–32.
5. Belenkaya RM. Structural variants of the brain base arteries. Vopr neirokhir 1974; 5:23–29. (Russian)

Abstract:

6. Tontisirin N, Muangman SL, Suz P, et al. Early childhood gender in anterior and posterior cerebral blood flow velocity and autoregulation. In Abstract of Pediatrics 2007. (doi:10.1542/peds. 2006-2110; published online February 5).

Books:

7. Patten MB. Human embryology, 3rd edn. McGraw-Hill: New York, 1968.
8. Marinković S, Milisavljević M, Antunović V. Arterije mozga i kičmene moždine—Anatomske i kliničke karakteristike. Bit inžerenjering: Beograd, 2001. (Serbian)

Chapters:

9. Lie TA. Congenital malformations of the carotid and vertebral arterial systems, including the persistent anastomoses. In: Vinken PJ, Bruyn GW (eds) Handbook of clinical neurology, vol. 12. North Holland: Amsterdam, 1972; pp 289–339.

Unpublished data:

10. Reed ML. *Si-SiO_2 interface trap anneal kinetics*, PhD thesis. Stanford University: Stanford, 1987.

Online document:

11. Apostolides PJ, Lawton MT, David CA, Spetzler RF. Clinical images: persistent primitive trigeminal artery with and without aneurysm. Barrow Quarterly 1997; 13(4). http://www.thebarrow.org/Education_And_Resources/Barrow_Quarterly/204843
12. Cerebrovascular embryology, in: power point; 2000. http://brainavm.oci.utoronto.ca/staff/Wallace/2000_curriculum/index.html

(6) Tables

(7) Figure legends

Table and figure legends should be included within the text file and contain sufficient data to be understood without reference to the text. Each should begin with a short title for the figure. All symbols and abbreviations should be explained within the legend. If the magnification is quoted in a sentence, it should appear in parentheses, e.g. (x400); at the end of legend it should appear, e.g., "... fibrils. X20 000".Tables must be typed on separate pages. All tables should be simple without duplicating information given in the text. Numerical results should be expressed as means with the relevant standard errors and/or statistically significant differences, quoting probability levels (p-value).

Illustrations

All figures should be cited in the paper in a consecutive order and submitted in separated files. All figures, photographs, line drawings and graphs, should be prepared in electronic form and converted in TIFF or JPG (max quality) file types, in 300 dpi resolution, for superior reproduction. Figures, line drawings and graphs prepared using elements of MS Drawing or MS Graph must be converted in form of pictures and unchangeable. All illustrations should be planned in advance so as to allow reduction to 8 cm in column width or 16.75 cm in page width. Please review all illustrations to ensure that they are readable.

The manuscripts in above form should be submitted to the Editor-in Chief or Co-editor of the journal in electronic form prepared by MS Word for Windows (Microsoft Word 1997–2003, *.doc or higher Word, *.docx) **—** font Times New Roman (12-point). The manuscript should be typed double-spaced on one side only of A4 paper. The manuscript in electronic form should be submitted through the submission portal: http://casopisi.junis.ni.ac.rs/index.php/FUMedBiol.

FACTA UNIVERSITATIS
Series: **Medicine and Biology** Vol. 17, No 2, 2015, pp. i–i

EDITORIAL

Dear Readers,

It is a great pleasure to present to you the new issue of Facta Universitatis Series Medicine and Biology. We welcome in this issue a contribution from Professor Terence Wilkin, who kindly accepted to write for Facta about the evolving concept of his Accelerator hypothesis.

The growing body of information and discoveries based on autoimmune paradigm have not solved the problem of prevention and cure of type 1 diabetes. Professor Wilkin translates reality into science and offers a new concept – that of tempo in diabetes. Accelerators modulate the tempo of the loss of beta cell function. The Accelerator hypothesis is based on the notion that insulin resistance accelerates beta cell apoptosis, both directly and secondarily by provoking an immune response among those who are genetically susceptible. The logic of the hypothesis is to treat the insulin resistance rather than the immune response, which the hypothesis argues would not occur in its absence. Important support for the accelerator hypothesis comes from the contemporaneous with the rise in childhood obesity and with it, inevitably, insulin resistance. The clinical phenotypes of type 1 and type 2 diabetes are converging and obesity could be "the missing link" between two diabetes types.

. . .

Internationally recognized Academician Vladislav Stefanović, an exeptional personality and brilliant scientist passed away on October 11th, 2015. He was the most successful Editor-in-chief of Facta Universitatis, Series Medicine and Biology, one of the first Academicians of Serbian Academy of Sciences and Arts from Universty of Niš, and one of the first Professor Emeritus. His enormous achievements inspire us and will live on long after him.

His colleague and friend Academician of Macedonian Academy of Sciences and Arts, Momir Polenaković shared with us his memories, his deep sorrow and a profound sense of lost.

Editor-in-Chief
Ljiljana Šaranac

FACTA UNIVERSITATIS
Series: **Medicine and Biology** Vol. 17, No 2, 2015, pp. ii–iv

In Memoriam

VLADISAV STEFANOVIĆ (1943 – 2015)
AN ACADEMICIAN, DOCTOR, SCIENTIST, VISIONARY AND FRIEND

Academician V. Stefanović unexpectedly passed away in October of the last year, leaving his family and friends. However, his work, vision and friendship remain with us and show us the direction our work should take.

I met Stefanovic in the early 80's during one of my visits to Nis, at a meeting he organized together with professor Spira Strahinjic. Professor Spira Strahinjic had built a strong nephrology center in Nis which became well-known in the Balkans and the world. Academician Stefanović, who had been educated in France and became an excellent doctor and researcher, with friends among world-renowned nephrologists, was a key figure in the realization of ideas on scientific development of the Nephrology Clinic of the Faculty of Medicine, University of Nis. He has published a great number of papers and he is one of the most productive medical scientists in Serbia, the Balkans, as well as in Europe. He has pointed to the need of expert scientific development based on research results and he fought for quality of the published papers.

We had the same ideas related to the need for research in nephrology, especially concerning Balkan endemic nephropathy (BEN) and our cooperation, which started in the 80's, lasted until his unexpected death in late 2015. Together with our associates, including the participation of our colleagues from Bulgarian and Macedonian Academy of Sciences we have published several papers about BEN. Some studies and ideas about the research of BEN were among the first in scientific community.

Editorial

Am J Nephrol 1991;11:1–11

0250–8095/91/0111–000$2.75/0

Balkan Nephropathy

Kidney Disease beyond the Balkans?

Vladisav Stefanović[a], *Momir H. Polenaković*[b]

[a] Institute of Nephrology and Hemodialysis, Faculty of Medicine, Niš, Yugoslavia;
[b] Department of Nephrology, Faculty of Medicine, Skopje, Yugoslavia

Introduction

Balkan nephropathy is a chronic tubulointerstitial disease, encountered in some well-defined areas of Yugoslavia, Bulgaria and Rumania. Geographically, settlements where Balkan nephropathy is endemic are in southeastern Europe, along the affluents of the Danube, within an area of 400–500 km diameter (fig. 1). The regions of Balkan nephropathy are limited to a relatively small area north and south of the Danubian Iron gates and located in a few spots along the tributaries of this

Etiology of Balkan Nephropathy

The etiology of Balkan nephropathy has attracted much interest, and broad investigations have been conducted into the possible role of genetic factors, environmental agents (living agents, trace elements, fungal and plant toxins) and immune mechanisms. Despite the failure to show a single specific cause of Balkan nephropathy, evidence has been obtained on the factors associated with the disease.

Stefanović V, Polenaković MH. Balkan Nephropathy: Kidney Disease Beyond the Balkans? *American Journal of Nephrology*. 1991;11:1-11

OXFORD TEXTBOOK OF CLINICAL NEPHROLOGY

Edited by

STEWART CAMERON, ALEX M. DAVISON, JEAN-PIERRE GRÜNFELD, DAVID KERR, and EBERHARD RITZ

with the assistance of

A. J. REES, C. G. WINEARLS, LUIS HERNANDO, CHARLES VAN YPERSELE DE STRIHOU, and CLAUDIO PONTICELLI

VOLUME 2

Momir H. Polenaković
april 1992, Skopje

Oxford New York Tokyo
OXFORD UNIVERSITY PRESS
1992

6.7 Balkan nephropathy

MOMIR H. POLENAKOVIĆ AND VLADISAV STEFANOVIĆ

Balkan nephropathy is a familial chronic tubulointerstitial disease, encountered in some restricted areas of Yugoslavia, Bulgaria, and Rumania. The first description of the disease in Yugoslavia was made by Danilović *et al*. (1957) and in Bulgaria by Tanchev *et al*. (1956). The earliest observation of an increased incidence of renal disease in some of the present endemic settlements was made by practising physicians in about 1941 and 1942.

Geographical distribution

Balkan nephropathy is geographically located in the areas of south-eastern Europe, along the tributaries of the Danube (Fig. 1), within an area of about 400 to 500 km^2. The endemic areas in Yugoslavia, Bulgaria, and Rumania border on one another and the distance between them is not more than 100 km. The disease is limited to a relatively small region north and south of the Danubian Iron Gates and located in a few areas along the tributaries of this river in the plains and low hills at an altitude of 150 to 500 m above sea level, some distance from the mountainous regions of the Balkans and Carpathians. The region where Balkan nephropathy is detected generally have high humidity and high rainfall. No local geological peculiarities hâve been described.

Polenaković MH, Stefanović V. Balkan Nephropathy. In: *Oxford Textbook of Clinical Nephrology*. eds. Cameron S, Davison AM, Grünfeld J-P, Kerr D, Ritz E. Vol.1-3. Oxford University Press; 1992:857-66
Our last study was published in Clinical Nephrology. Vol. 83 – Suppl. 1/2015 (S64-S69)

Clinical Nephrology, Vol. 83 – Suppl. 1/2015 (S64-S69)

clinical nephrology
Original

ISSN 0301-0430

DOI 10.5414/CNP83S064
e-pub: February 23, 2015

Balkan nephropathy

Vladisav Stefanovic[1], Draga Toncheva[2], and Momir Polenakovic[3]

[1]Faculty of Medicine, University of Nis, Nis, and Serbian Academy of Sciences and Arts, Belgrade, Serbia, [2]Department of Genetics, University of Medicine, Sofia, Bulgaria, and [3]Macedonian Academy of Sciences and Arts, Skopje, Macedonia

Key words
Balkan nephropathy – urothelial tumors – etiology – prevention – treatment

Abstract. Balkan endemic nephropathy (BN), frequently associated to upper urothelial cancer, is a familial chronic tubulointerstitial disease with insidious onset and slow progression to end-stage renal disease. After 60 years of research, its cause remains the major unanswered question. Etiology assumed to be linked to the Danube River in Bosnia, Bulgaria, Croatia, Romania, and Serbia [1]. An estimate of more than 10,000 of affected or at-risk individuals makes this disease an important public health problem in the Balkans. A high prevalence of upper tract urothelial tumors (UTUT) of

Stefanovic was an excellent educator of young doctors in nephrology, internal medicine and wider medical field. In cooperation with the members of the Bulgarian Academy of Sciences we have been researching the etiology of Balkan endemic nephropathy and kidney tumors. He was particularly interested in molecular biology, genetics, proteomics and epigenetics. Together with his colleagues from Europe and the rest of the world, he worked on those areas that might contribute to etiology and pathogenesis of Balkan endemic nephropathy. He participated in numerous scientific meetings and I here provide a photo of our BEN research team taken in Skopje in 2014 on the occasion of my birthday at the Macedonian Academy of Arts and Sciences.

Left to right: D. Plaseska-Karanfilska, N. Pop-Jordanova, M. Polenkovic, D. Tonceva, K. Vagner, V. Stefanovic and A. Galabov

V. Stefanovic had many new ideas for researching in nephrology, especially concerning the research of BEN. We were in the process of writing a book on BEN and we are obliged to finish it and dedicate it to our dear academician. He lived a modest life, filled with energy and enthusiasm in his work with patients, students and colleagues. He will remain a role model – a pioneer in nephrology research.

He was dedicated to his family, particularly to his grandson – a musician and a guitar artist.

He and his work will be a constant inspiration to our future profession.

Academician Momir H. Polenković

FACTA UNIVERSITATIS
Series: **Medicine and Biology** Vol. 17, No 2, 2015, pp. 49–53 UDC 616.379-008.64

Invited Review Article

THE ACCELERATOR HYPOTHESIS – AN EVOLVING CONCEPT

Terence J. Wilkin

University of Exeter Medical School, Exeter, UK

Abstract. *Clinical trials designed to prevent type 1 diabetes (T1D) based on the autoimmunity paradigm have proved disappointing, and have not so far translated into patient benefit. Meanwhile, the incidence of T1D continues to rise. The accelerator hypothesis explores the role of weight gain in childhood diabetes, as both islet cell immunity and T1D are associated with BMI. Insulin resistance, which results largely from weight gain, increases insulin demand, and demand puts stress on beta cells, which accelerates their apoptotic loss. An immune response to the stress in those who are genetically predisposed ('autoimmunity') hastens the loss further, and may explain by default why autoimmunity is a feature of diabetes in the young. The accelerator hypothesis was proposed in 2001 and, like most hypothesis, has evolved over the years.*

Key words: *Accelerator hypothesis, type 1 diabetes, clinical trial, insulin resistance,classification of diabetes, tempo in diabetes, hybrid diabetes*

Historical Reports of Insulin Resistance in Diabetes

Himsworth was the first to describe insulin resistance in diabetes nearly 80 years ago but not, as is often thought, so as to distinguish adults from juveniles with the disease – insulin resistance was noted in both [1, 2]. Others repeated Himsworth's observations using simple insulin-glucose tolerance tests [3–5], until a more sophisticated measure of insulin sensitivity, the glucose clamp, provided direct evidence that impaired insulin action is '…..a common feature of T1D' [6]. Indeed, while conceding it was possible to separate patients according to insulin sensitivity, Elliott Joslin concluded that testing for it was of little use because the overlap in clinical phenotype was so great [7]. Insulin resistance was associated with diabetes from earliest times, in both young and old, and posed no threat to its oneness.

The Categorisation of Diabetes

Diabetes remained one until the 1970's, when three observations made largely in children (lymphocytic insulitis [8], islet cell antibodies 9] and HLA genotype [10]) were interpreted by opinion leaders at the time to mean that childhood diabetes, unlike adult diabetes, was caused by dysregulation of the immune system (autoimmunity). A previously single disorder was now deemed to be two categorically distinct entities of different aetiology, and the autoimmune paradigm has been deeply rooted since. Importantly, however, the classification was based on observation, and not on experiment. Indeed, some 20 human trials using immunotherapy to test the autoimmunity paradigm since have proved unsuccessful [11], and none has translated into patient benefit. Interest in the relationship of insulin resistance to autoimmunity emerged only because of mounting concern that the original interpretation may not have been correct [12]. Autoimmunity is clearly present in T1D, but its primacy in the sequence of events is being questioned. Rather than the driver of beta cell loss, could autoimmunity be an immune response to islets which are stressed by the demands of insulin resistance?

Experimental Basis for Autoimmune Diabetes

The experimental data cited in support of the autoimmunity hypothesis for T1D is substantial, but drawn largely from prevention studies in animals [13]. Such trials are often successful, but animals are not human, and biomedical research is frequently confronted with hypotheses that work in animals, but not in man. In the case of T1D, the models are not just animals, but animals abnormal to the point where they fail to develop diabetes unless their environment is rigidly controlled. The models most used, the NOD mouse and Biobreeding rat, are inbred for immununogenetic anomalies that are essential to the model, but not part of the human disease. The models show that the immune system *can* destroy the beta cells of inbred rodents, but say little about the

*Correspondence to: Terence J. Wilkin, MD, FRCS
University of Exeter Medical School, Exeter
RILD 3, Barrack Road, EXETER EX2 5DW
Phone: +44 1392 406758
E-mail: t.wilkin@exeter.ac.uk
Received February 22th, 2016

mechanisms responsible for T1D in outbred man. The ongoing TRIGR study using hydrolysed protein formula (Nutramigen) in human infants has an impressive pedigree, and will report in 2017, but care must be taken with confounders in its interpretation. Nutramigen, like breast-milk, may be associated with slower growth rates than cow's milk and breast-milk is associated with a lower incidence of T1D [14].

The Doctrine of Immunological Tolerance

Any suggestion that autoimmunity might be a response to beta cell stress, rather than its cause, must first confront one of the pillars of immunology – tolerance to self antigens. The issue was addressed by the author some 25 years ago [15], in the wake of Pierre Grabar's construal of the immune system's primordial role as the body's housekeeper, clearing up the detritus of apoptotic (and, where needed, necrotic) cell death [16]. Being shape-specific and clonal, the immune system was ideally adapted to expand and contract in response to specific housekeeping need. What to others before him had been a canon of absolute tolerance to self antigens, was to Grabar the absence of a technology sufficiently sensitive to detect a natural process of waste removal – until it was intense, when it was given the label 'autoimmunity' in order that it should comply with the tolerance paradigm [17]. Grabar's great contribution was to breach the doctrine of self-tolerance that had previously obliged autoimmunity to be a pathology. Autoimmunity is nevertheless inflammatory, and may be expected to further accelerate apoptotic death of the troubled beta cell [18].

Orphan Observations

'Orphan observations' are facts which don't fit, and which tend to be ignored as a result. Concerns over the duality of diabetes first emerged through epidemiology, though few noted their significance at the time. Yemenite immigrants to Israel in the 1950's suffered very little diabetes but, after 25 years in a land of plenty, experienced a 40-fold increase in its prevalence. Intriguingly, it wasn't just T2D – the proportion of insulin dependency among the new diabetics was similar to that among Israelis of European origin [19]. The observation is a classic orphan, but fundamentally important because it suggests a common driver for both major forms of diabetes. Again, it is seldom remarked upon, but clearly documented, that wherever in the world there has been a rise in T2D, there has been a corresponding increase in type 1 [20], and many studies report how the frequency of T1D among the relatives of those with type 2 is many times greater than that in the general population [21, 22]. Most recently, Hussen et al report how having a parent with any type of diabetes increases the risk of T1D in the child [23]. More fundamental still is the changing status of islet autoantibodies. Sero-positivity was always the exclusive hallmark of T1D, but reports of isle-related autoantibodies in people T2D have posed serious taxonomic difficulty [24]. Finally, there is now evidence for insulin resistance, not just in those with type 1 disease, but in those at-risk as well [25–27]. When weighed together, orphan observations can shape a new paradigm, and the notion that T1D may be T2D accelerated into childhood by a reactive genotype is an example.

The Accelerator Hypothesis

Insulin resistance, largely (but not always) the result of excess weight gain, is generally believed to drive type 2 diabetes. The metabolic up-regulation of the islets, and the glucotoxicity and lipotoxicity that result from the metabolic disturbance associated with insulin resistance, are thought to stress the beta cell and hasten its apoptosis [28–30]. Excess weight gain is a feature of childhood over recent time, and it has been known for 40 years (though little mentioned) that children who develop T1D are on average heavier as toddlers than their peers who do not [31]. The observation resurfaced during the 1990's [32–34], and in 2001 the accelerator hypothesis formalised an alternative paradigm to autoimmunity – that *Type 1 and type 2 diabetes are the same disorder of insulin resistance, set against different genetic backgrounds* [35]. Beta cell stress, according to the hypothesis, provokes an immune response (autoimmunity) which is particularly intense in the small proportion of the population that carries reactive HLA genotypes, and a recent meta-analysis found in all the studies it reviewed that people with T1D showed greater weight gain during the first year of life compared with controls [36]. Crucially, if the immune reaction (the autoimmunity of T1D) is the response to beta cell stress, rather than the driver, it is arguably not the appropriate target for prevention. Evidence for the hypothesis has been set out in a number of reviews [37–42], and its early predictions have held firm in several reports worldwide [43–46], though not in all [47–49], and for diverse reasons [50–52]. The hypothesis anticipates that measures to reduce insulin demand will reduce the incidence of T1D but it does not dismiss autoimmunity. Rather, autoimmunity is regarded as a response to beta cell stress, not its cause, but inflammatory in its own right. The hypothesis is conceptually simple, but important if it resets the target for prevention of childhood diabetes from the immune system to insulin demand.

Tempo – the Central Concept Underlying the Accelerator Hypothesis

Diabetes is ultimately a disorder of beta cell loss [53], and the accelerator hypothesis is concerned with variation in the tempo of the loss. Beta cells are lost progressively over a lifetime [54], but the loss is of no consequence for most, given the substantial reserve [55]. However, if for whatever reason the loss is accelerated, it may become critical, and the age at presentation of diabetes will

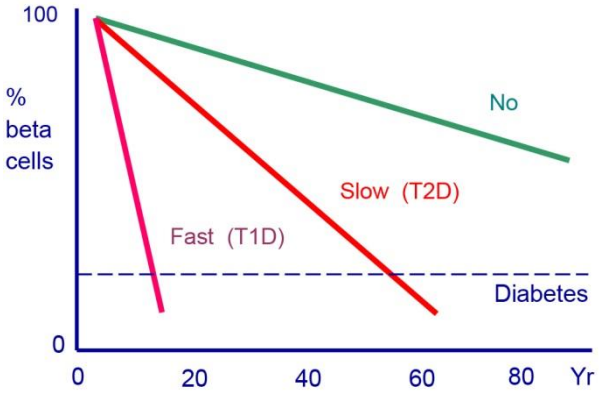


Fig. 1. The concept of tempo as it applies to diabetes. A single process advancing at different rates.

depend on the degree of acceleration (Figure 1). Rather than categorise diabetes into types 1 and 2 (or indeed 1½ [56], LADA [57], hybrid [58], or double diabetes [59]), the accelerator hypothesis sees a continuous spectrum – a single process of beta cell loss which progresses at different rates, from 'no' diabetes during the lifetime of most people, through 'slow' diabetes in adulthood to 'fast' diabetes in childhood. The probability of developing diabetes is defined by an infinitely variable interaction between level of demand and immune response. The variation in diabetes is one of tempo, not of type. Only tempo can explain how T2D, that a generation ago was confined to middle age and beyond, has now become the fasting growing chronic disorder of childhood and how T1D, for decades a disorder of adolescence, is now rising fastest in the under 5's [60].

Testing the Accelerator Hypothesis

No evidence is complete without a randomized controlled trial, and no hypothesis is complete without a mechanism. If the accelerator hypothesis is to progress beyond speculation, it will be necessary to demonstrate that beta loss is slowed (and the incidence of T1D reduced) by protecting the beta cell against stress, and that beta cell rest is indeed the mechanism that drives the immune response that we call autoimmunity. Glucose is the principal stressor of the beta cell, and metformin is a recognized hypoglycaemic agent that is safe in children.

The editor-in-chief of this journal was the first to test the ability of metformin to slow the progression of beta cell loss in a pilot study of 21 children recently diagnosed with T1D [61]. There were 26 control children on insulin alone. Six of the metformin-treated group entered complete insulin remission for 12 months or more, and their C-peptide at the end of the study was significantly higher than that of the control group. It is not clear whether the metformin was simply re-sensitising the children to their own residual insulin, or preserving beta-cell function (the higher C-peptide might suggest true preservation), but the study provided impetus to the planning and ultimately funding by JDRF of the autoimmune diabetes Accelerator Prevention Trial (adAPT) currently recruiting in the UK. adAPT will expose children at high risk of T1D (double antibody positive) to metformin for five years in order to establish whether beta cell protection can reduce the incidence of diabetes. Mechanistic studies involving T cells (B. Roep, Leiden) will also seek to determine whether beta cell rest reduces immune reactivity to specific beta cell antigens.

adAPT (Eudract # 2015-000748-41) is currently seeking youngsters throughout Scotland and the North of England who are the siblings or offspring age 5-16y of people who themselves developed T1D before the age of 25y. The 4-5% who are double antibody positive have a 40% chance of developing T1D over the course of the trial [62], and will be invited to join a three stage randomised controlled trial of metformin. Stage 1 (four months, Pilot study) will validate the protocol, and establish the numbers that may ultimately be needed to achieve a reliable result. Stage 2 (36 months, Proof of principle) will indicate whether the rate of beta cell loss is slower in the treated group. C-peptide levels measured during the course of a multi-point mixed meal tolerance test will provide the outcome measure, but a subgroup will also be invited to participate in 7-day studies of continuous glucose monitoring. Stage 3 of adAPT (60 months, T1D incidence) will compare the numbers who develop T1D in the active and placebo groups. adAPT will not report fully until 2022.

adAPT is testing a new paradigm in type 1 diabetes. Where the immune activity in T1D has been looked upon previously as an immune attack by a dysregulated immune system, adAPT views it as a normal, if intense, response to beta cell stress caused by metabolic overload in people carrying a particular immunogenotype. A successful outcome to the trial may lead towards a safe, cheap and universally available approach to the prevention of type 1 diabetes.

References

1. Himsworth, HP. Diabetes mellitus: its differentiation into insulin-sensitive and insulin-insensitive types. Lancet 1936; i:127–130.
2. Himsworth HP, Kerr RB. Insulin sensitive and insulin-insensitive types of diabetes mellitus. Clin Sci 1939; 4:119–152.
3. Martin FIR, Stocks AE. Insulin sensitivity and 131l-insulin metabolism in juvenile-type diabetics. Aust Ann Med 1967; 76:289–296.
4. Ginsberg HN. Investigation of insulin sensitivity in treated subjects with ketosis prone diabetes mellitus. Diabetes 1977; 26:278–283.
5. Harano Y, Ohgaku S, Hidaka H, Haneda K, Kikkawa R, Shigeta Y, et al. Glucose, insulin and somatostatin infusion for the determination of insulin sensitivity. J Clin Endocrinol Metab 1977; 45:1124–1127.
6. Defronzo RA, Bendler R, Simonson D. Insulin resistance is a prominent feature of insulin-dependent diabetes. Diabetes 1982; 37:795–801.
7. Joslin EP, Root HF, White P, Marble A, Bailey CC. The treatment of diabetes mellitus. London: Henry Kimpton; 1947. p. 144–146.

8. Gepts W. Pathologic anatomy of the pancreas in juvenile diabetes mellitus. Diabetes 1965; 14:619–633.
9. Nerup J, Platz P, Anderson OO, et al. HLA antigens and diabetes mellitus. Lancet 1974; 2:864–866.
10. Bottazzo GF, Florin-Christensen A, Doniach D. Islet-cell antibodies in diabetes mellitus with autoimmune polyendocrine deficiencies. Lancet 1974; 2:1279–1283.
11. Bonifacio E. Immunotherapy in T1D: a shorter but more winding road? Diabetes 2012; 61:2214–2215.
12. Greenbaum CJ. Perspective: rethink the immune connection. Nature 2012; 485:S9.
13. von Herrath M, Nepom GT. Animal models of human type 1 diabetes. Nat Immunol 2009; 10:129–132.
14. Nucci AM, Becker DJ, Virtanen SM, Cuthbertson D, Softness B, Huot C, et al. Growth differences between North American and European children at risk for type 1 diabetes. Pediatr Diabetes 2012; 13:425–431.
15. Wilkin TJ. Autoimmunity: attack, or defence? Autoimmunity 1989; 3:57–73.
16. Grabar P. Autoantibodies and the physiological role of immunoglobulins. Immunol Today 1983; 4:337–340.
17. Grabar P. Hypothesis. Auto-antibodies and immunological theories: an analytical review. Clin Immunol Immunopathol 1975; 4:453–466.
18. Donath MY, Størling J, Maedler K, Mandrup-Poulsen T. Inflammatory mediators and islet beta-cell failure: a link between type 1 and type 2 diabetes. J Mol Med (Berl) 2003; 81:455–470
19. Keen H, Jarrett RJ. Environmental factors and genetic interactions. In: Creutzfeld W, Kobberling J, Neel JV (eds) The Genetics of Diabetes Mellitus. Berlin: Springer-Verlag; 1976. pp. 203–214.
20. Gale EAM The rise of childhood T1D in the 20th century. Diabetes 2002; 51:3353–3361.
21. Gottlieb MS. Diabetes in offspring and siblings of juvenile- and maturity-onset-type diabetics. J Chronic Dis 1980; 33:331–339.
22. Dahlquist G, Blom L, Tuvemo T, Nyström L, Sandström A, Wall S. The Swedish childhood diabetes study: results from a nine year case register and a one year case-referent study indicating that type 1 (insulin-dependent) diabetes mellitus is associated with both type 2 (non-insulin-dependent) diabetes mellitus and autoimmune disorders. Diabetologia 1989;32:2–6.
23. Hussen H, Persson M, Moradi T. Maternal overweight and obesity are associated with increased risk of type 1 diabetes in offspring of parents without diabetes regardless of ethnicity. Diabetologia 2015; 58:1464–1473.
24. Reinehr T, Schober E, Wiegand S, Thon A, Holl R; DPV-Wiss Study Group. Beta-cell autoantibodies in children with type 2 diabetes mellitus: subgroup or misclassification? Arch Dis Child 2006; 91:473–477.
25. Fourlanos S, Harrison LC, Colman PG. The accelerator hypothesis and increasing incidence of T1D. Curr Opin Endocrinol Diabetes Obes 2008; 15:321–325.
26. Xu P, Cuthbertson D, Greenbaum C, Palmer JP, Krischer JP, and Diabetes Prevention Trial-Type 1 Study Group. Role of insulin resistance in predicting progression to T1D. Diabetes Care 2007; 30:2314–2320.
27. Mrena S, Virtanen SM, Laippala P, Kulmala P, Hannila ML, Akerblom HK, et al. Models for predicting type 1 diabetes in siblings of affected children. Diabetes Care 2006; 29: 662–667.
28. Maedler K, Spinas GA, Lehmann R, Sergeev P, Weber M, Fontana A, et al. Glucose induces b-cell apoptosis via upregulation of the Fas receptor in human islets. Diabetes 2001; 50:1683–1690,
29. Donath MY, Gross DJ, Cerasi E, Kaiser N. Hyperglycemia-induced beta-cell apoptosis in pancreatic islets of Psammomys obesus during development of diabetes. Diabetes 1999; 48: 738–744.
30. Robertson RP1, Harmon J, Tran PO, Poitout V. Beta-cell glucose toxicity, lipotoxicity, and chronic oxidative stress in type 2 diabetes. Diabetes 2004; 53:S119–S124.
31. Baum JD, Ounsted M, Smith MA. Weight gain in infancy and subsequent development of diabetes mellitus in childhood. Lancet 1975; 2:866
32. Johansson C, Samuelsson U, Ludvigsson J. A high weight gain in early life is associated with an increased risk of type 1 (insulin-dependent) diabetes. Diabetologia 1994; 37: 91–94.
33. Hyppönen E, Kenward MG, Virtanen SM, Piitulainen A, Virta-Autio P, Tuomilehto J, et al. Infant feeding, early weight gain and risk of type 1 diabetes. Diabetes Care 1999; 22:1961–1965.
34. Bruining GJ. Association between infant growth before onset of juvenile type-1 diabetes and autoantibodies to IA-2. Netherlands Kolibrie study group of childhood diabetes. Lancet 2000; 356:655–656.
35. Wilkin TJ. The accelerator hypothesis: weight gain as the missing link between Type I and Type II diabetes. Diabetologia 2001; 44:914–922.
36. Harder T, Roepke K, Diller N, Stechling Y, Dudenhausen JW, Plagemann A. Birth weight, early weight gain, and subsequent risk of type 1 diabetes:systematic review and meta-analysis. Am J Epidemiol 2009;169:1428–1436.
37. Wilkin TJ. The great weight gain experiment, accelerators, and their implications for autoantibodies in diabetes. Arch Dis Child 2006; 91:456–458.
38. Wilkin TJ. The Accelerator Hypothesis in: Nutritional Management of Diabetes Mellitus and Dysmetabolic syndrome (eds. JP Bantle and G Slama). Nestle International Workshops 2006; Karger, Basel pp. 139–153.
39. Wilkin TJ. Changing perspectives in diabetes: their impact on its classification. Diabetologia 2007; 50:1587–1592.
40. Wilkin TJ. Diabetes: 1 and 2, or one and the same? Progress with the accelerator hypothesis. Pediatric Diabetes 2008; 9:23–32.
41. Wilkin TJ The accelerator hypothesis; a review of the evidence for insulin resistance as the basis for type 1 as well as type 2 diabetes. Int J Obes (Lond) 2009; 33:716–726.
42. Wilkin TJ. The convergence of type 1 and type 2 diabetes in childhood: the accelerator hypothesis. Padiatr Diabetes 2012; 13:334–339.
43. Kibirige M, Metcalf B, Renuka R, Wilkin TJ. Testing the accelerator hypothesis: the relationship between body mass and age at diagnosis of type 1 diabetes. Diabetes Care 2003; 26: 2865–2870.
44. Betts P, Mulligan J, Ward P, Smith B, Wilkin TJ. Increasing body weight predicts the earlier onset of insulin-dependant diabetes in childhood: testing the 'accelerator hypothesis' (2). Diabet Med 2005; 22:144–151.
45. Knerr I, Wolf J, Reinehr T, Stachow R, Grabert M, Schober E, et al. DPV Scientific Initiative of Germany and Austria. The 'accelerator hypothesis': relationship between weight, height, body mass index and age at diagnosis in a large cohort of 9,248 German and Austrian children with type 1diabetes mellitus. Diabetologia 2005;48: 2501–2504.
46. Kordonouri O, Hartmann R. Higher body weight is associated with earlier onset of Type 1diabetes in children: confirming the 'Accelerator Hypothesis'. Diabet Med 2005; 22:1783–1784.
47. Dabelea D, D'Agostino RB Jr, Mayer-Davis EJ, Pettitt DJ, Imperatore G, Dolan LM, et al. SEARCH for Diabetes in Youth Study Group. Testing the accelerator hypothesis: body size, beta-cell function, and age at onset of type 1(autoimmune) diabetes. Diabetes Care 2006; 29:290–294.
48. O'Connell MA, Donath S, Cameron FJ. Major increase in T1D - no support for the accelerator hypothesis. Diabet Med 2007; 24:920–923.
49. Field SF, Howson JMM, Smyth DJ, Walker NM, Todd JA Analysis of the type 2 diabetes gene, TCF7L2, in 13,795 T1D cases and control subjects. Diabetologia 2007; 50:212–213.
50. Wilkin TJ. Testing the accelerator hypothesis: body size, beta-cell function, and age at onset of type 1 (autoimmune) diabetes: response to Dabelea et al. Diabetes Care 2006;29: author reply 1462–1463.
51. Wilkin TJ. Major increase in T1D: no support for the accelerator hypothesis. Diabet Med 2008; 25: author reply 377; discussion 377–378.

52. Wilkin TJ. The accelerator hypothesis cannot be tested using the type 2 diabetes gene, TCF7L2. Diabetologia 2007; 50:1780.
53. Butler AE, Janson J, Bonner-Weir S, Ritzel R, Rizza RA, Butler PC. Beta-cell deficit and increased beta-cell apoptosis in humans with type 2 diabetes. Diabetes 2003; 52:102–110.
54. Weir GC, Bonner-Weir S. Five stages of evolving beta-cell dysfunction during progression to diabetes. Diabetes 2004; 53:S16–S21.
55. Matveyenko AV, Butler PC. Relationship between beta-cell mass and diabetes onset. Diabetes Obes Metab 2008; 10(Suppl 4):23–31.
56. Juneja R, Palmer JP. Type 1 1/2 diabetes: myth or reality? Autoimmunity 1999; 29:65–83.
57. Tuomi T, Groop LC, Zimmet PZ, Rowley, MJ, Knowles W, Mackay IR. Antibodies to glutamic acid decarboxylase reveal latent autoimmune diabetes mellitus in adults with a non-insulin-dependent onset of disease. Diabetes 1993; 42:359–362.
58. Pozzilli P, Guglielmi C, Pronina E, Petraikina E. Double or hybrid diabetes associated with an increase in type 1 and type 2 diabetes in children and youths. Pediatr Diabetes 2007; 8(Suppl 9):88–95.
59. Libman IM, Becker DJ. Coexistence of type 1 and type 2 diabetes mellitus: "double" diabetes? Pediatr Diabetes 2003; 4:110–113.
60. Patterson CC, Gyürüs E, Rosenbauer J, Cinek O, Neu A, Schober E, et al. Trends in childhood type 1 diabetes incidence in Europe during 1989–2008: evidence of non-uniformity over time in rates of increase. Diabetologia 2012; 55:2142–2147.
61. Saranac LM, Bjelakovic B, Zivanovic S, Novak M. Intervention with metformin in childhood diabetes may slow decline of C-peptide – the accelerator hypothesis. Abstr 931 EASD annual scientific meeting, Stockholm 2010.
62. Achenbach P1, Warncke K, Reiter J, Naserke HE, Williams AJ, Bingley PJ, et al. Stratification of type 1 diabetes risk on the basis of islet autoantibody characteristics. Diabetes 2004; 53:384–392.

FACTA UNIVERSITATIS
Series: **Medicine and Biology** Vol. 17, No 2, 2015, pp. 54–59 UDC 615.222.065

Original Article

REASONS FOR UNJUSTIFIED ADMINISTRATION OF AMIODARONE IN CORONARY CARE UNIT

Sanja Marković

Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia

Abstract. *Although clinical use of amiodarone is supposedly well-known since the drug has been in use for over fifty years, there have been some concerns that it is often used inappropriately. This paper aims to describe clinical and adverse events observed in patients treated in Coronary Care Unit and to check if the drug was being used in proper indication and dose. Also, the purpose of this survey was to determine whether the medical staff is familiar enough with adverse events and right indications of amiodarone administration. This qualitative study was based on three methods: interview with physicians operating in Coronary Care Unit, insight into patient files and observation of the amiodarone prescription. Five physicians operating in Coronary Care Unit were interviewed and patient files of seven patients have been observed. Amiodarone prescription was observed by making rounds together with physicians. Several problems regarding amiodarone administration have been established. Amiodarone was often diluted in physiological solution instead of 5% glucose solution and it was administered via peripheral vein, not the central one. Physicians are using amiodarone more often than they are supposed to, mainly due to lack of other antiarrhythmic agents. It was also noticed that medical staff do not strictly follow the guidelines for atrial fibrillation treatment, often using amiodarone as the first choice antiarrhythmic. Finally, physicians are not fully familiar with adverse events of amiodarone, especially with acute adverse events. It was concluded that inappropriate use is present in some cases. Thus, physicians should follow guidelines more carefully when prescribing the drug and additional education should be implemented.*

Key words: *antiarrhythmic, atrial fibrillation, inappropriate use, adverse event*

Introduction

Amiodarone is one of the most common drugs used to treat arrhythmias. According to Trappe, Brandts and Weismueller, typical arrhythmias in intensive care patients are atrial fibrillation (AF), atrial flutter, AV-nodal reentry tachycardia with rapid ventricular response, atrial ectopic tachycardia, and pre-excitation syndromes combined with atrial fibrillation or ventricular tachyarrhythmia. Immediate DC-cardioversion in all patients with unstable hemodynamics is indicated, while conversion to sinus rhythm is possible using antiarrhythmic drugs. In their opinion, short-term intravenous administration of amiodarone, as superior antiarrhythmic agent, is absolutely necessary in critically ill patients with recent onset atrial fibrillation [1]. Rhythm control and rate control management strategies are defined for treatment of atrial fibrillation and flutter as the most frequent arrhythmias in emergency department. Amiodarone may be used for both cardioversion and heart rate control [2].

*Correspondence to: Sanja Marković, MsPharm
Deligradska 19, 11000 Belgrade, Serbia
Phone: +381 60 510 2040
E-mail: msanja_87@hotmail.com
Received December 14th, 2015 / Accepted February 1st, 2016

Amiodarone has been developed in 1960s as a coronary vasodilator (with 13-year-long period of investigation [3]), which brings us to conclusion that amiodarone is a drug with long term usage. Amiodarone is currently used as antiarrhythmic agent for treatment of a variety of arrhythmias but there have always been concerns about its side effects. Mild adverse events are often seen in patients treated with amiodarone, but serious life-threatening adverse events are also possible. This is the reason why systematic interdisciplinary follow-up protocol for outpatients treated with amiodarone is necessary [4]. One of the most severe systemic side effects of amiodarone chronic use is pulmonary toxicity which may lead to death. This is the reason why administration of amiodarone in intensive care unit should not last more than 24/48h [5]. Extent and speed of onset of pulmonary damage is linked with severity of amiodarone-introduced pulmonary toxicity [6, 7]. Special care is needed when amiodarone is prescribed because its administration may increase the risk of acute pancreatitis [8]. Thyroid dysfunction, corneal micro deposits, gastrointestinal problems and photosensitivity are also linked with amiodarone use, but this is not relevant to acute intravenous administration in intensive care. If thyroid dysfunction is indicated, collaboration between cardiologist and endocrinologist is mandatory [9]. Due to

possibility of intracardiac thrombus formation, conversion of AF should not be attempted 48h after onset without anticoagulation or transesophageal echocardiography [10]. Amiodarone is well tolerated in patients with both normal and impaired left ventricular systolic function [11]. Drug-drug interactions are also observed where the most important are between digoxin and warfarin. When amiodarone is administered with other QT prolonging drugs, especially class 1A antiarrhythmics or in the presence of hypokalemia, torsades de pointes mostly occurs [5].

Arrigo, Bettex and Rudiger recommend treatment of AF in intensive care unit setting with substances with a low risk profile and short half-life, such as beta blockers, while amiodarone is indicated in cases of contraindications or inefficacy of the initial treatment. Compared to beta blockers and calcium channel blockers, amiodarone has less negative inotropic effects and is safer for patients with structural heart disease. Long half-life and potential severe side effects are limiting its usage in intensive care unit. It is up to clinician to decide which agent he will use in critically ill patient based on efficiency/risk ratio [12].

According to recent research where amiodarone, as preferential antiarrhythmic drug, was compared with non-amiodarone antiarrhythmic drugs, amiodarone was not supported as a drug of choice in patients with left ventricular hypertrophy [13]. According to Brendorp, Pedersen, Torp-Pedersen, Sahebzadah and Køber, beta-blockers are the first line therapy in patients at high risk of sudden death while amiodarone is favorable only in patients with heart failure [14]. Collected data from the research on adverse effects in randomized placebo-controlled trials has shown that treatment with amiodarone for the prophylaxis of sudden cardiac death has less favorable net clinical benefit. Treatment with amiodarone in this setting should be used only in selected cases [15].

The term unreasonable use of the drug means it is being used beyond the protocol and thus costs of treatment are increasing but without improvement of patient condition or shortening hospitalization period. According to Kosińska and Brandy, amiodarone was potentially inappropriately prescribed in 7.47% of geriatric patients in Poland [16]. Napolitano, Izzo, Di Giuseppe and Angelillo's survey has shown that amiodarone was potentially inappropriately prescribed in 19.1% of cases of elderly patients in Italy with 24.9% of potentially inappropriate doses [17].

Clinical trials with amiodarone have been conducted for many years and will likely continue in the future [18]. Obviously, doubts about administration of amiodarone are present. In this paper, we wanted to provide one more piece of evidence to reduce the dilemma. Research was done, including interviews with physicians from coronary care department and observation of patients. Scientific method was used to reach conclusions with general procedure consisting of six steps: 1- State the problem, 2- Formulate the hypothesis, 3- Design the experiment or survey, 4- Make observations, 5- Interpret the data and 6- Draw conclusions [19].

Material and Methods

This qualitative study was based on three methods: interview with physicians operating in Coronary Care Unit of Cardiology Department, University Hospital Center "Bezanijska Kosa" in Belgrade, Republic of Serbia, insight into patient files and observation of the amiodarone prescription.

Starting from January of 2015th five physicians operating in Coronary Care Unit were interviewed using semi-structured interview. Nineteen questions were asked and anticipated time for conversation was twenty minutes. Before the study, the Head of Cardiology Department and the Director of the Hospital were contacted personally to present the study protocol and to obtain their approval to conduct the survey. Also, the study design and the Head of Department's statement have been submitted to the Ethics and Scientific Committee of the Hospital and their approval was obtained. Interviews were held in person with doctors at beforehand agreed time. Questions were asked from the prepared paper form and answers were recorded by audio device. The paper form was signed by an examinee *(physician)* as consent that interview will be recorded.

Beside interviews with the above-mentioned staff, records of seven patients hospitalized in Coronary Care Unit and prescribed with amiodarone were used as a source of the data. For each patient being studied, the data included age, sex, ethnic affiliation, weight and height of the patient, followed by the history of disease with onset, type of arrhythmia, and other cardiac and non-cardiac illnesses. In addition to this, the patient records included concomitant medication, duration, dose and route of amiodarone administration, adverse reactions (if any) and how they have been solved (by which agent) as well as outcome of the therapy.

Finally, the third part of the study was observation of amiodarone prescription by making ward-rounds together with physicians. The main objective of the third part is to recognize why amiodarone is prescribed, particularly paying attention to indication, dose, route and duration of amiodarone administration.

Results

Interview was conducted with five medical doctors employed by the University Hospital Centre „Bežanijska Kosa", Department of Coronary Unit, between 28th January and 9th of March 2015. Three participants were female and two were male. Physicians were interviewed by audio recording, using semi-structured interview. Based on the analysis of the interviews, seven categories have been created.

A The patients: Coronary Unit has eleven beds. The Unit treats around a hundred patients per month. One of the interviewed doctors has stressed out that patients with acute coronary syndrome are mostly hospitalized for three days in the Unit. Patients with more serious rhythm abnormalities, ischemic cardiomyopathy with,

for example, non-sustained VT or repeated ventricular tachycardia are hospitalized longer, up to five or six days. All the interviewed medical doctors have noticed that there is a correlation between the dynamic of admission and season, i.e. atmospheric conditions. In winter, the number of admitted patients increases, while in summer the number decreases. Also, in fall and spring, when atmospheric conditions (temperature, humidity …) change significantly, the number of hospitalized patients is higher. In Coronary Unit the admission of patients is mainly based on the following diagnosis: acute coronary syndrome; patients with ST and non-ST elevated myocardial infarction; supraventricular arrhythmias type tachyarrhythmia absoluta and ventricular rhythm abnormality with heart decompensation symptoms; complications of coronary diseases, in terms of dilative ischemic cardiomyopathy followed by malignant rhythm disorder; lung edema, embolism, state of shock of various etiology. According to Journal of the American College of Cardiology (JACC) guidelines for the management of patients with atrial fibrillation, amiodarone should only be used after consideration of risks and when other agents have failed or are contraindicated because of its potential toxicities.

B Drug preparation: Amiodarone is mainly diluted in 5% glucose 'even for diabetics, because it is noticed that prepared in such way it reacts protectively on veins due to its negative influence on venous system and development of thrombophlebitis. Very rarely, for diabetics with irregular diabetic condition and with significantly expressed hyperglycemia we are diluting amiodarone in physiological solution.'**(4)** According to guidelines and summary of drug characteristics, diluting amiodarone in physiological solution is not allowed because amiodarone and physiological solution are incompatible.

C Drug availability and price: All participants point out that the price of amiodarone is not a determining fact in administration especially emphasizing that 'we are using it because we have it.' **(2)** Also, they stress that 'the choice of antiarrhythmic drugs which you have is something that the management of the institution may afford you, so probably the price of antiarrhythmic drug is in these regards determining, but it is not a determining factor for doctor's selection, doctor will decide and select something which he sees as the best choice for his patient. "**(3)** However, participants are stressing that there is a problem of availability of other, alternative drugs. "We do not have any other serious antiarrhythmic drugs except amiodarone for parenteral use for such kind of arrhythmias." **(5)** "Shortage of the wider palette of antiarrhythmics leads us to use amiodarone very often... For supraventricular rhythm disorders, adenosine should absolutely be the first choice, and we use it, but it is limited."**(4)** "Adenosine we have, but it is very expensive. For supraventricular arrhythmia we are using mainly Isoptine®-verapamil, when we are not using amiodarone. And some drugs such are bretilium and some even better antiarrhythmics for malignant rhythm disorders we don't have."**(5)** "Dronedarone we don't have. Or even some other drugs, maybe adenosine, which we should use in my opinion. These are drugs which are not used by routine, they are more expensive and simply we don't have them in Coronary Unit available for the reaction in particular moment." **(3)** One of the reasons why amiodarone is often used is that the doctors have experience working with it. "We have a lot of positive experience working with it" **(3)** and because it is comfortable for use. "The majority of the arrhythmias might be treated by amiodarone so its use is the most comfortable in Coronary Unit." **(5)** In accordance with the above mentioned, the lack of other antiarrhythmics may be a reason for more frequent although unjustified amiodarone administration.

D Administered dose: In Coronary Unit amiodarone is most often administered parenterally, first by bolus and afterwards by infusion. Peripheral vein is used for application, not the central one. "I think that in 90% of cases we are using peripheral vein. Central vein we use very rarely because patients don't require central vein puncture, that's the first reason, and the second is that our patients are very often decompensated, so it is very difficult to lay the patient on a flat, it is very difficult to punctuate the central vein." **(5)** Furthermore, they consider that "all of our patients simply don't have central vein." **(1)** Related to administered dose of drug all participants are stressing that "Mainly we are giving to the all patients same dose, minimal one." **(1)** "We are giving one bolus of hundred and fifty milligrams, which means one ampoule, after that we are applying infusion. We apply infusion beside per os therapy, achieving of the maximum dosage of one thousand and two hundred milligrams amiodarone daily." **(4)**

In extreme cases, a higher dose of amiodarone is administered "if the patient is extremely overweight and has huge body mass." **(5)** The duration of amiodarone administration is related to clinical outcome, "referring to ECG." **(2)** All participants are intended to use amiodarone as shortly as possible, until achieving the desired effects and in order to reduce adverse effects caused by usage of amiodarone. "I rarely keep patient on the therapy with amiodarone in some longer period of time." **(5)** According to the summary of drug characteristics, amiodarone must be administered through a central vein, except in cases of cardiopulmonary resuscitation in the event of cardiac arrest caused by ventricular fibrillation resistant to external electric shock, when due to inaccessibility of the central vein, peripheral veins can be used.

E Systemic side effects: Participants have pointed out systemic side effects which they have noticed in the Coronary Unit, as well as procedure during the occurring such side effects. The most often side effects are: thyroid malfunction, cornea deposits, extension of QT interval, hepatotoxic effect, photosensitivity with skin changes. Literature data mention lung fibrosis as one of the possible side effects in acute amiodarone administration although none of the doctors came upon this side effect. Amiodarone effects on thyroid, regarding hypo- or

hyperthyreosis, are often seen. "I have to say that almost 50% of patients who I'm treating with heart insufficiency and with dilative cardiomyopathy in some period used to have either hypo- or hyperthyreosis. Since they had malignant ventricular rhythm disorder and since the majority of those patients are having defibrillator, in consultation with endocrinologist, we have never, or rarely, in 10% of patients, we have excluded amiodarone when they had thyrotoxicosis. We have reduced the dose of amiodarone to one hundred milligrams per day, five days a week, and we have tried to resolve a problem with thyroid by application of thyro-suppressive therapy or by substitutional therapy". **(4)** In a case of cornea deposits "ophthalmologist assesses are the deposits significant and is it necessary to exclude amiodarone from the therapy. But if the treatment without amiodarone is impossible, we are just temporarily ceasing with amiodarone. And we are trying to proceed with some other antiarrhythmic." **(2)** In case of QT interval extension "over 500 milliseconds, or if significant bradycardia or conductivity disorder on a level of AV node, such as second or third degree AV block, occurs we are absolutely excluding amiodarone. This is ultimate indication to stop the therapy with amiodarone." **(4)** "Photosensitivity with skin hyperpigmentation is noticed only in amiodarone long term usage, not in acute administration." **(4)** Hepatotoxicity is very difficult to determine because "we are not certain that if patient has ischemic liver or it is a consequence of amiodarone use or some synergistic reaction with some other drugs, so we cannot give the precise answer. We are seeing such patients, but we don't know the real reason for this. Very often we have patients with increased AST and ALT markers of liver necrosis. Even if significant numbers of patients have liver ischemia we cannot say for sure is it ischemic hepatitis or side effect of amiodarone. Those patients are in very bad condition and they are admitted to Coronary Unit critically ill." **(5)** Since the majority of patients in Coronary Unit are in critical condition tests related to condition of the thyroid, liver, lungs are not performed immediately but upon improvement of the patient condition. "I mandatorily advise to perform AST and ALT tests, as well as lung's X-ray." **(2)** In case of side effects and cessation of amiodarone application, the most common choice is beta blocker or Dilacor®.

F Local side effects: All participants mentioned local adverse events. "I have to say that almost thirty percent of patients in Coronary Unit suffer from some kind of thrombophlebitis." **(4)** The reason for this may be found in infusion of amiodarone as well as application and infusion preparation. The problem caused by amiodarone itself is "amiodarone, followed by high concentrated glucoses, is very aggressive agent and probably damages veins", **(1)** or happens "due to quick application of infusion." **(2)** One physician pointed out that the problem may be "not sufficient monitoring by medical nurses in Coronary Unit." **(3)** Injection itself may be a problem, especially if the patient is older with weak blood vessel and if infusion takes too long. The participants pointed out that this local adverse reaction may be avoided by using the central vein for infusion instead of peripheral, which is mainly used at the moment. In case of obvious local side effects the most often response is "we are replacing cannula, in fact we are changing the position of cannula." **(2)** "We are changing place of injection or if possible we are shifting to per os use." **(5)** Concerning thrombophlebitis, no therapy is applied except for placing of compresses.

G Inappropriate use: Four out of five participants consider that inappropriate use is very rare. "The fact is that we don't have huge choice of antiarrhythmics and whenever we are applying amiodarone, we are applying that due to obvious reasons." **(4)** One out of five participants thinks that it is very often used inappropriately. "Very often amiodarone is used as the first antiarrhythmic, even if it is not necessary. Primarily, I think on supraventricular arrhythmia where we may practically use calcium antagonist, so I think that inappropriate application in Coronary Unit is present. I have experienced that in supraventricular arrhythmias, which may be simply treated by other antiarrhythmic, which has less complications and side effects." **(5)** All participants have emphasized that amiodarone is generally used inappropriately when it is not necessary to convert the patient into sinus rhythm, but only to calm down heart rate, and a lot of physicians are already using this approach. The participants also gave their recommendations for reducing inappropriate use of amiodarone. They state that guidelines should be followed more carefully, and more frequent educations/trainings should be held. "Education of the doctors has to be focused on not to be scared of arrhythmias. Amiodarone is in fact a good medicine if it is applied in proper indications." **(4)**

Participants: 1-male, 42 years old; 2-female, 40 years old; 3-female, 43 years old; 4-female, 52 years old; 5-male, 43 years old

Besides interview with physicians operating in Coronary Care Unit, medical records of seven patients treated by amiodarone have been observed. Of the total number of patients, six were male and one was female, age range from 25 to 82. Six out of seven patients have been treated with amiodarone parenterally and one patient received amiodarone per os. Diagnoses on admission were: Tachyarrhythmia absoluta; Tachyarrhythmia absoluta with decompensation of newfound dilated cardiomyopathy; Fibrillation Atriorum paroxysmal (Myopericarditis virosa suspecta); ST elevation myocardial infarction infer posterior, upon admission to the Coronary Unit the patient developed primary ventricular fibrillation; decompensating of chronic dilated valvular cardiomyopathy and terminal condition of heart failure. Retention period in Coronary Care Unit was up to five days. Two cases ended fatally, while others were converted into sinus rhythm within 48 hours. Amiodarone was indeed applied as a bolus followed by infusion, at the dose of two plus four ampoules. It was noted that amiodarone is often dissolved in physiological solution instead of 5% glucose solution, which is mandatory according to Summary of Product

Characteristics (SPC). It was observed that even with the same patient amiodarone was occasionally diluted in a glucose solution and occasionally in physiological solution. When asked to explain this discrepancy, physicians could not give an appropriate answer. In some cases amiodarone was combined with Dilacor®, usually accompanied by anticoagulation therapy and IV diuretics. One patient's lab results have showed elevated values of thyroid hormones, forcing amiodarone exclusion from the therapy. In consultation with the endocrinologist, thyroid suppressive therapy was introduced. Other adverse events were not observed.

Finally, the third part of the study was visiting hospitalized patients together with physicians. Patients' therapy is prescribed exclusively by doctors employed in the Coronary Care Unit Department. Twenty four hours a day the attending physician is present in order to react immediately when it comes to hospitalization. Six out of eleven beds in Coronary Care Unit were occupied. All patients were on 24-hour ECG monitoring. Three out of six patients had visible thrombophlebitis caused by amiodarone infusion.

Discussion

From our results, we noticed that amiodarone is often inappropriately used for supraventricular rhythm disturbances. It is used for frequency correction. If a patient suffers from atrial fibrillation and we do not expect sinus rhythm to be reached, and there is a rapid chamber activity, usually another reason is present (worsening of heart function, heart failure) due to which the patient is in absolutes. In such cases, correction is achieved by solving heart failure problem, not by amiodarone administration. When the probability of converting a patient into sinus is minimum, amiodarone should not be administered, but this was not always the case. Such patients are usually on long-term amiodarone administration which is practically contraindicated and many of adverse events may occur. The Journal of the American College of Cardiology (JACC) in its guidelines for the management of patients with atrial fibrillation, states that amiodarone should only be used after consideration of risks and when other agents have failed or are contraindicated because of its potential toxicities [20]. According to data collected during interviews, this was not always the case. Amiodarone was sometimes administered as first line antiarrhythmic, not considering a less toxic solution. Also, the participants were not aware of the fact that amiodarone is incompatible with physiological solution. Insight into patient files shows that even with the same patient, amiodarone was sometimes diluted in physiological solution and other times it was diluted in in 5% glucose. Analysis of patient medical files has showed that amiodarone was not prescribed inappropriately; it was prescribed in proper indication and in proper dose. As excuse for unjustified administration, the interviewed doctors said that amiodarone does not have too many significant adverse effects and it is useful and provides safety and comfort. Besides, Coronary Unit does not have wide range of antiarrhythmics available and which may be a better solution than amiodarone in patient treatment. The reason for unjustified administration of amiodarone may be found in lack of knowledge and awareness of medical staff about indications for use and adverse events. Thus, training of medical staff has to be implemented more frequently in order to overcome this problem. However, according to some data, amiodarone is being used inappropriately in other countries as well. For example, amiodarone is approved by the US Food and Drug Administration only for refractory ventricular arrhythmias but it is one of the most frequently prescribed antiarrhythmic medications in the United States [21]. Research conducted in Poland has shown that amiodarone was potentially inappropriately prescribed in 7.47% of cases in geriatric patients [16] and a survey taken in Italy has shown that amiodarone was potentially inappropriately prescribed in 19.1% cases in elderly patients with 24.9% of potentially inappropriate doses [17].

Discussion about obtained results was based on two facts. First, the research was carried out in the University Hospital Centre "Bezanijska Kosa" which is a tertiary health institution. We could expect less inappropriate use than in other health care institutions because medical staff has higher expertise. Considering the fact that the drug was developed in 1961 and there are precise guidelines for its use as well as numerous scientific papers which are publishing unjustified administration and adverse events [22], inappropriate use should be minimum. Secondly, all interviewed doctors said that they have experience with amiodarone administration.

Unjustified administration of amiodarone in Coronary Care Unit is rare, as considered by the majority of the interviewed doctors. Some of the interviewed doctors indicated that one of the reasons of unjustified administration is lack of other antiarrhythmics. However, the rational application of the drug would reduce costs and thus procurement of other medicines would be possible. Some studies have confirmed that costs increase by unjustified application of the drugs [23].

Conclusion

Research conducted at Coronary Care Unit of University Hospital Centre "Bezanijska Kosa" pointed to existence of inappropriate use of amiodarone in some cases. There are two reasons for this occurrence. The first one is due to objective reasons. The Coronary Unit has a sufficient number of antiarrhythmics available and amiodarone is always accessible. How often amiodarone was prescribed due to lack of other agents could not be determined. The nature of the second reason is subjective. Doctors opt for amiodarone because it is secure and convenient. This problem may be alleviated by strictly applying the scheduled treatment protocol.

Finally, we may conclude that besides the lack of other antiarrhythmics available, amiodarone was mostly inappropriately prescribed due to the lack of familiarity with its side effects. Also, physicians were not aware that amiodarone is incompatible with physiological solution and they were often administering it as a first line antiarrhythmic, not considering another, less toxic solution. Thus, physicians should follow guidelines when prescribing the drug and additional education should be implemented.

References

1. Trappe HJ, Brandts B, Weismueller P. Arrhythmias in the intensive care patient. Curr Opin Crit Care 2003; 9:345–355.
2. Hamilton A, Clark D, Gray A, Cragg A, Grubb N; on behalf of the Emergency Medicine Research Group, Edinburgh (EMERGE). The epidemiology and management of recent-onset atrial fibrillation and flutter presenting to the Emergency Department. In Abstract of European Journal of Emergency Medicine 2015 (doi: 10.1097/MEJ.0000000000000198 p155–161; published online June)
3. Wesselingh JA, Kiil S, Vigild EM. Design and development of biological, chemical, food and pharmaceutical products. West Sussex, England: John Wiley & Sons Ltd; 2007.
4. Adelborg K, Ebbehøj E, Nielsen JC, Grove EL. Treatment with amiodarone. Ugeskriftfor Laeger. 2015; 177: 1168–1171. (in Danish)
5. Hughes M, Binning A. Intravenous amiodarone in intensive care, Time for a reappraisal? Intensive Care Medicine. 2000; 26:1730-9.
6. Fadahunsi O, Krol R. Acute amiodarone pulmonary toxicity following lung resection. Int J Biomed Sci 2014; 10:217–220.
7. Mankikian J1, Favelle O2, Guillon A3, Guilleminault L4, Cormier B5, Jonville-Béra AP, et al. Initial characteristics and outcome of hospitalized patients with amiodarone pulmonary toxicity. Respir Med 2014; 108:638–646.
8. Lai SW, Lin CL, Liao KF, Lin CY. Amiodarone use and risk of acute pancreatitis: A population-based case-control study. Heart Rhythm 2015; 12:163–166
9. Olsen JS, Carlé A, Thomsen HH. Every sixth patient in amiodarone treatment develops thyrotoxicosis or hypothyreosis. In Abstract of Ugeskrift for Laeger. 2014;176(34) http://www.ncbi.nlm.nih.gov/pubmed/25293567
10. Hoffmann B, Vilke I, Drevitz I, Steven D, Rostok T, Willems S. Rational management of atrial fibrillation in intensive care. Kardiologiia 2010; 50:84–90. (in Russian)
11. Hudzik B, Zubelewicz-Szkodzinska B. Amiodarone-related thyroid dysfunction. Intern Emerg Med 2014; 9:829–839.
12. Arrigo M, Bettex D, Rudiger A. Management of Atrial fibrillation in critically ill patients. Criti Care Res Pract 2014; 2014:840615 (doi: 10.1155/2014/840615)
13. Chung R, Houghtaling PL, Tchou M, Niebauer MJ, Lindsay BD, Tchou PJ, et al. Left ventricular hypertrophy and antiarrhythmic drugs in atrial fibrillation: impact on mortality. Pacing Clin Electrophysiol 2014; 37:1338–1348.
14. Brendorp B, Pedersen O, Torp-Pedersen C, Sahebzadah N, Køber L. A benefit-risk assessment of class III antiarrhythmic agents. Drug Saf 2002; 25:847–865.
15. Santangeli P, Di Biase L, Burkhardt JD, Bai R, Mohanty P, Pump A, et al. Examining the safety of amiodarone. Expert Opin Drug Saf 2012; 11:191–214
16. Kosińska K, Brandys J. Potentially inappropriate drugs for geriatric patients. Przegl Lek. 2007; 64:19-23
17. Napolitano F, Izzo MT, Di Giuseppe G, Angelillo I. Collaborative Working Group. Frequency of inappropriate medication prescription in hospitalized elderly patients in Italy. PLoS One 2013; 8:e82359 (doi: 10.1371/journal.pone.0082359; published online December 12)
18. Naccarelli G, Wolbrette D, Dell 'Orfano J, Patel H, Luck J. Amiodarone: What have we learned from clinical trials? Clin Cardiol 2000; 23:73–82.
19. Dowdy S, Weardon S,Chilko D. Statistics for research. 3rd ed. New Jersey (USA); John Wiley & Sons: 2004.
20. January CT, Wann S, Alpert JS, Calhins H, Cigarroa JE, Cleveland JC Jr, et al. A report of the American College of Cardiology/ American Heart Association Task Force on Practice Guideline and the Heart Rhythm Society. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: Executive Summary. J Am Cardil Coll 2014; 64:2246–2280.
21. Vassallo P, Trohman R. Prescribing Amiodarone. An evidence-based review of clinical indications. JAMA 2007; 298: 1312–1322. http://jama.jamanetwork.com/article.aspx?articleid=208819
22. Ocak T, Duran A, Erdem A, Öztürk S, Erdem K. Is electrocardiography sufficient for supraventricular tachycardia treatment? A Case Report. J Exp Clin Med 2013; 30: 357–359.
23. Perren A, Previsdomini M, Cerutti M, Soldini D, Donghi D, Marone C. Omitted and unjustified medications in the discharge summary. Qual Saf Health Care 2009; 18: 205–208.

FACTA UNIVERSITATIS
Series: **Medicine and Biology** Vol. 17, No 2, 2015, pp. 60–62

UDC 616.346.2-006-07
616.346.2-002-07

Case Reports

FOUR CASES OF APPENDICEAL NEUROMA MIMICKING ACUTE APPENDICITIS

Ivan R. Ilić[1*], Nikola M. Stojanović[2], Pavle J. Randjelović[3], Niko S. Radulović[4], Ratko S. Ilić[1]

[1]*Institute of Pathology, Faculty of Medicine, University of Niš, Serbia*
[2]*Faculty of Medicine, University of Niš, Serbia*
[3]*Department of Physiology, Faculty of Medicine, University of Niš, Serbia*
[4]*Department of Chemistry, Faculty of Science and Mathematics, University of Niš, Serbia*

Abstract. *Herein we report four cases of appendiceal neuroma found during a short (one month) monitoring period in patients with severe pain in the lower right abdominal quadrant that underwent appendectomies. Tissue samples were routinely processed to obtain histological sections that were stained with hematoxylin and eosin (H&E) and further with anti-S100 protein antibody. Characteristics of appendiceal neuroma were noted in these cases and they included the absence of mucosal and lymphoid tissue of the appendices, stroma with spindle-shaped cells that were positively stained with anti-S100 protein antibody. This clinical entity is important due to a possible misdiagnosis with acute appendicitis or exacerbation of inflammatory bowel disease and great attention should be paid during the clinical evaluation of similar symptoms.*

Key words: *appendiceal neuroma, misdiagnosis, lumen obliteration, immunohistochemistry, S100 protein*

Introduction

Acute appendicitis is the most frequent appendiceal disease and abdominal surgical condition [1]. The differential diagnosis of appendicitis is often a clinical challenge because appendicitis can mimic several abdominal conditions and should be conducted in several directions in order to determine the cause; however, sometimes it can be challenging even with the modern radiological equipment at hand.

Among others, the fibrous obliteration (appendiceal neuroma (AN)/neuronal hyperplasia) should be taken into consideration when the diagnosis of acute appendicitis is considered. The WHO classification of appendiceal tumors puts the fibrous obliteration in the group of miscellaneous tumors of the appendix [2] with the estimated incidence around 30% [3].

This paper aims to present four cases of appendiceal neuroma diagnosed in a period of one month and to give a survey of the literature on the same topic.

Case Reports

All four cases were first admitted to the Department of Abdominal Surgery, for severe pain in the lower right abdominal quadrant, where the operations were performed after radiological and laboratorial surveys were made. None of the patients had a history of inflammatory bowel disease (IBD). The clinical diagnoses of the mentioned patients were acute phlegmonous appendicitis.

Case No. 1

The removed appendix, from a 23-year-old male, was 5.5 cm long with 2–3 mm thick walls, blurred serosa and hyperemic blood vessels. There was no gross tumor mass present.

Case No. 2

The removed appendix, from a 61-year-old female, was 8 cm long with 1–2 mm thick walls; a macroscopically visible obliterated lumen and an abundant periappendicular fatty tissue were visible. There was no gross tumor mass present.

Case No. 3

The removed appendix, from a 38-year-old male, was 5.5 cm long with 2 mm thick walls, hyperemic blood vessels and a reduced periappendicular fatty tissue. There was no gross tumor mass present.

Case No. 4

The removed appendix, from a 60-year-old female, was 9 cm long, and had 3 mm thick walls; the lumen was mostly obliterated, whereas the entrance and distal part were wider. There was no gross tumor mass present.

[*]Correspondence to: Ivan R. Ilić, MD, PhD
Institute of Pathology, Faculty of Medicine, University of Niš
81 Dr Zorana Đinđića Blvd., 18000 Niš, Serbia
E-mail: ilicko81@gmail.com
Received October 26th, 2015 / Accepted February 23rd, 2016

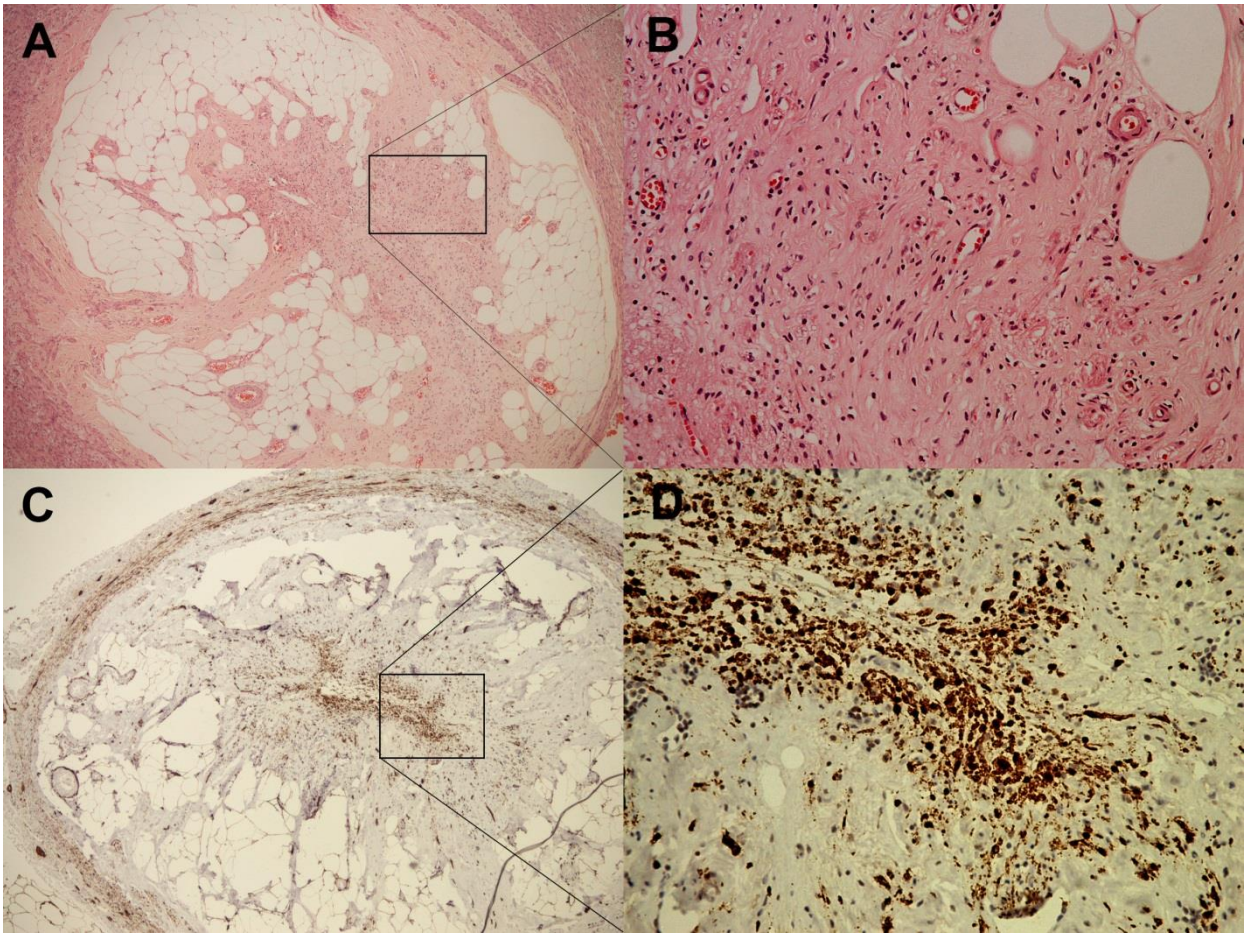


Fig. 1 Neuroma of the appendix. (A) The obliterated lumen of the appendix; the mucosal and lymphoid tissues are replaced with fatty, collagenous and myxoid stroma (H&E, ×40). (B) The proliferation of spindle-shaped cells that formed an eosinophilic bundle together with nerve fibers and occasional eosinophils (H&E, ×200). (C) and (D) Spindle-shaped cells positive for the S100 protein (S100 protein, ×40 and ×200, respectively).

The entire appendix was processed further to obtain three transversal microscopic sections, from the entrance, middle and distal parts. The slides were routinely stained with H&E and further with an anti-S100 protein antibody (Ready to use; Dako, Glostrup, Denmark). An examination of the slides revealed that the mucosal and lymphoid tissues of the appendices were completely absent and replaced with collagenous, fatty and myxoid stroma (Fig. 1A and B). The cells within the stroma were spindle-shaped (in different ratios) with occasional mast cells, eosinophils and lymphocytes. The additional staining (anti-S100 protein) revealed that the spindle-shaped cells immunoexpress this protein (Fig. 1C and D) which led us to the final diagnosis of AN in all four cases.

Discussion

During a one month period a total of 37 consecutive cases (48% female and 52% male) of appendectomies were submitted to pathological examination with the median patient age of 35.5. All patients were clinically diagnosed with acute appendicitis (*Appendicitis acuta*), whereas some of the diagnoses (n=15) were phlegmonous or gangrenous acute appendicitis. The final pathological diagnosis of these cases included: acute appendicitis of differing genesis (n=28; 75%), chronic appendicitis (n=4; 11%), AN (n=4; 11%) and lymphoreticular hyperplasia (n=1; 3%).

Appendiceal neuroma was first described in 1928 and represents the hyperplastic proliferation of unmyelinated nerves and Schwann cells [4]. When the lumen of the appendix is obliterated and other characteristics are present, diagnosis is straightforward; however, AN can affect the mucosa and submucosa without an obliteration of the appendix lumen and this is more challenging to diagnose [2]. The triggers for these neuroendocrine-cell-proliferation-related changes are thought to be repeated subclinical attacks of appendiceal inflammation [5].

The data describing the incidence of this entity varies and one cannot be sure about the exact percentage. In one study, out of 8699 patients who underwent appendectomy, only 5 AN were observed out of a total 101 appendiceal tumors [6]. According to a recent publication, the incidence of AN in a 12-year period is 3.7% [7]. Our one month monitoring period revealed the incidence of 11% which is most certainly less than the suggested 30% [3].

The association of AN with clinical symptoms, such as abdominal pain, is unclear. Although AN can sometimes mimic the acute/chronic appendicitis, the diagnosis of this entity can be found only after pathological examinations [6,8].

Alongside acute appendicitis, AN could be misdiagnosed in patients with IBD. The appendices of most patients with IBD, that were surgically removed, displayed chronic inflammation due to Crohn's disease or ulcerative colitis [9]. In the literature, there are some extreme examples, such as when the right lower quadrant abdominal pain, in a patient with IBD, was misinterpreted as Crohn's disease of the distal ileum for 20 years. Only after exploratory laparotomy, an appendectomy was performed and a pathological examination revealed AN [10]. Although AN is rare in children (one can say that it is the disease of adults), a study that involved 41 cases of children with IBD that underwent appendectomy revealed the presence of AN (among other rare diagnoses) in 20% of cases [9]. As in IBD, AN also has no known causes and the overlaps between these two entities are probably only coincidental.

The diagnosis of patients with possible appendicitis/ IBD, both clinical and pathological, should be reached cautiously and one should not forget that appendiceal neuroma (AN) exists, although it is a relatively rare entity, and that as such it deserves more attention from those making the diagnosis.

Acknowledgements: The authors acknowledge the Ministry of Education and Science of Republic of Serbia for the financial support (Project 172061).

References

1. Radojković MD, Veličković L, Stevanović G. Pseudoparasitic acute appendicitis. Report of a rare case. FU Med Biol 2014; 16: 104–105.
2. Bosman FT, Carneiro F, Hruban RH, Theise ND. WHO Classification of tumours of the digestive system, Volume 3, 4th edn. WHO Press, 2010.
3. Stanley MW, Cherwitz D, Hagen K, Snover DC. Neuromas of the appendix. A light-microscopic, immunohistochemical and electron-microscopic study of 20 cases. Am J Surg Pathol 1986, 10:801–815.
4. Auböck L, Ratzenhofer M. "Extraepithelial enterochromaffin cell—nerve fibre complexes" in the normal human appendix, and in neurogenic appendicopathy. J Pathol 1982; 136:217–226.
5. Gupta K, Solanki A, Vasishta RK. Appendiceal neuroma: report of an elusive neuroma. Trop Gastroenterol 2011; 32:332–333.
6. Schmutzer KJ, Bayar M, Zaki AE, Regan JF, Poletti JB. Tumors of the appendix. Dis Colon Rectum 1975; 18:324–331.
7. Yilmaz M, Akbulut S, Kutluturk K, Sahin N, Arabaci E, Ara C, Yilmaz S. Unusual histopathological findings in appendectomy specimens from patients with suspected acute appendicitis. World J Gastroenterol 2013; 19: 4015–4022.
8. Misdraji J, Graeme-Cook FM. Miscellaneous conditions of the appendix. Semin Diagn Pathol 2004; 21:151–163.
9. Kahn E, Markowitz J, Daum F. The appendix in inflammatory bowel disease in children. Mod Pathol 1992; 5:380–383.
10. Patel AV, Friedman M, Mac Dermott RP. Crohn's disease patient with right lower quadrant abdominal pain for 20 years due to an appendiceal neuroma (Fibrous obliteration of the appendix). Inflamm Bowel Dis 2010; 16:1093–1094.

FACTA UNIVERSITATIS
Series: **Medicine and Biology** Vol. 17, No 2, 2015, pp. 63–66 UDC 616.124-008.318

Case Report

CASE REPORT OF A 17 - YEAR OLD GIRL WITH ATYPICAL CLINICAL PRESENTATION OF - ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY

Bojko Bjelaković[1,2*], Goran Vukomanović[3,4], Sanja Knežević Rangelov[5] , Marko Jović[2]

[1]*Clinic of Pediatrics, Clinical Center, Niš, Clinic of Pediatrics, Serbia*
[2]*Faculty of Medicine, University of Niš, Serbia*
[3]*University Children's Hospital, Belgrade, Serbia*
[4]*Faculty of Medicine, University of Belgrade, Serbia*
[5]*Clinic of Pediatrics, Clinical Center, Kragujevac, Serbia*

Abstract. *We report a case of a 17-year-old girl diagnosed with arrhythmogenic right ventricular cardiomyopathy (ARVC), who has been wrongly considered as having idiopathic ventricular extrasystoles for 13 years. The only noteworthy clinical finding until the final diagnosis was made, were complex ventricular arrhythmias (VA) during exercise as well as nonspecific repolarisations changes in inferolateral leads. We would like to increase paediatricians alertness to children presenting with so called "idiopathic" exercise induced VA that at time could turn out to be markers of arrhythmogenic condition.*

Key words: *arrhythmogenic right ventricular cardiomyopathy, ventricular arrhythmias*

Case report

Here we report a case of a 17-year-old girl diagnosed with ARVC, who has been wrongly considered as having idiopathic ventricular extrasystoles for 13 years.

The patient was initially presented at age 4, with abdominal discomfort and feeling of irregular heartbeat.

At that time her ECG revealed ventricular ectopic beats (VEBs) of left bundle branch morphology and inferior axis; 24-hour Holter electrocardiogram revealed merely isolated VEBs but also alternative and repetitive forms with total number amounting to 1500/ 24 hours (Figs 1,2).

Other clinical examination (echocardiography, hematology, serum *biochemistry*) was unremarkable.

She was considered as having idiopathic ventricular arrhythmia and an *annual r*eevaluation *follow-up* by a cardiologist was defined.

At age 9, exercise stress test was performed and VEBs at maximal HR of 192/min.

Until 2014 (age 15) the results of cardiovascular examination were almost unchangable. In the same year one ventricular couplet during maximal exercise stress test was noted (Fig 3) and a thorough echocardiographic examination *showed* a dilated right ventricle outflow and inflow tracts together with enhanced apical RV trabecularisation (Figs 4 a,b,c). The patient finally underwent a cardiac MRI which definitely confirmed clinical suspicion of arrhythmogenic right ventricular cardiomyopathy (Fig. 5).

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited heart muscle disease characterized by arrhythmias of right ventricle (RV) origin, due to transmural fatty or fibro-fatty replacement of atrophic myocardium [1].

In general, the clinical expression of ARVC is normally postponed until youth and adulthood and the diagnosis is seldom confirmed under the age of 10. Although there is no definite diagnostic standard, the best approach to reaching the diagnosis of ARVC is combining different diagnostic tests and clinical presentations.

The diagnosis of ARVC in children is especially difficult to establish due to the broad spectrum of phenotypic variations as well as nonspecific and inconclusive clinical findings in this age group. Inverted T waves in the right precordial leads (V1–V3) on ECG are normal findings until the age 12 and MRI is of low-yield as the anatomical, histological, and functional changes are frequently subtle or not present in the early phase of the disease [2–4]. On the other hand, right ventricular assessment by transthoracic echocardiography is by far less accurate than cardiac magnetic resonance. Hence, many ARVC cases in childhood are also diagnosed at autopsy after the occurrence of SCD [5,6].

*Correspondence to: Bojko Bjelakovic MD, PhD
Clinic of Pediatrics, Clinical Center Niš
48 Dr Zorana Đinđića Blvd. 18000 Niš, Serbia
Phone: +381184288332, Fax: +381184238770
E-mail: bojko968@gmail.com
Received February 17th, 2016 / Accepted February 23rd, 2016

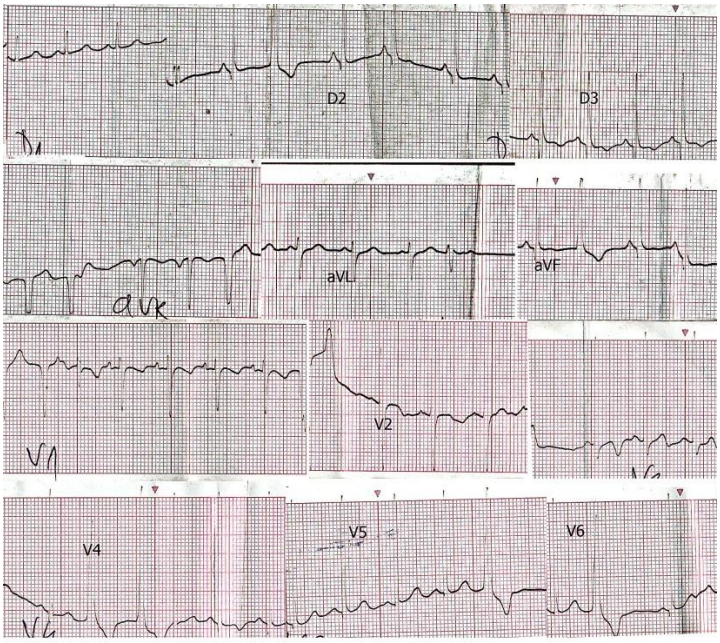


Fig. 1 Ventricular ectopic beats of left bundle branch morphology and inferior axis.

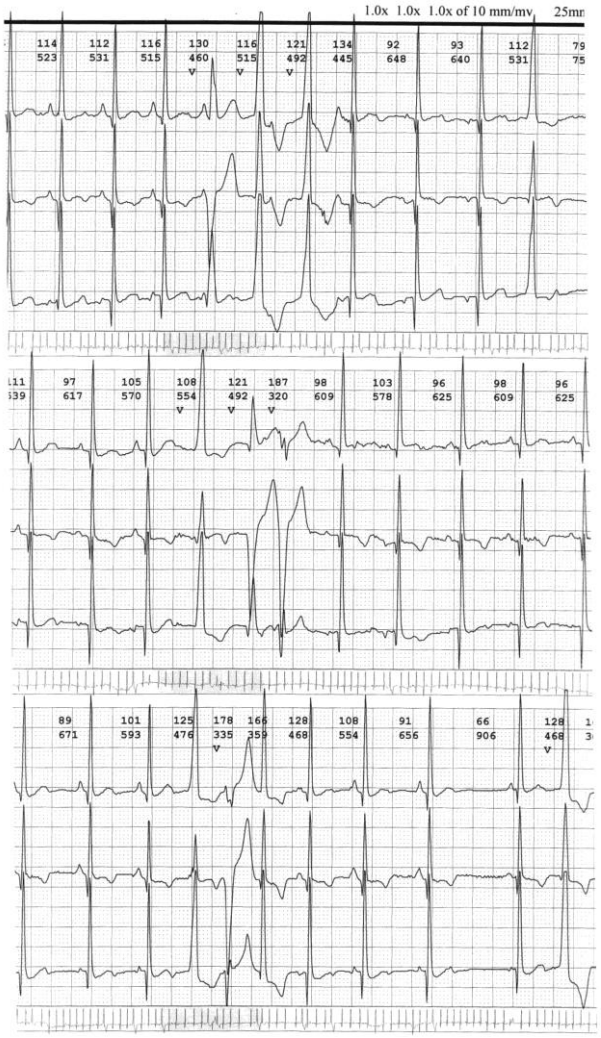


Fig. 2 Repetitive VEBs on 24 ECG Holter

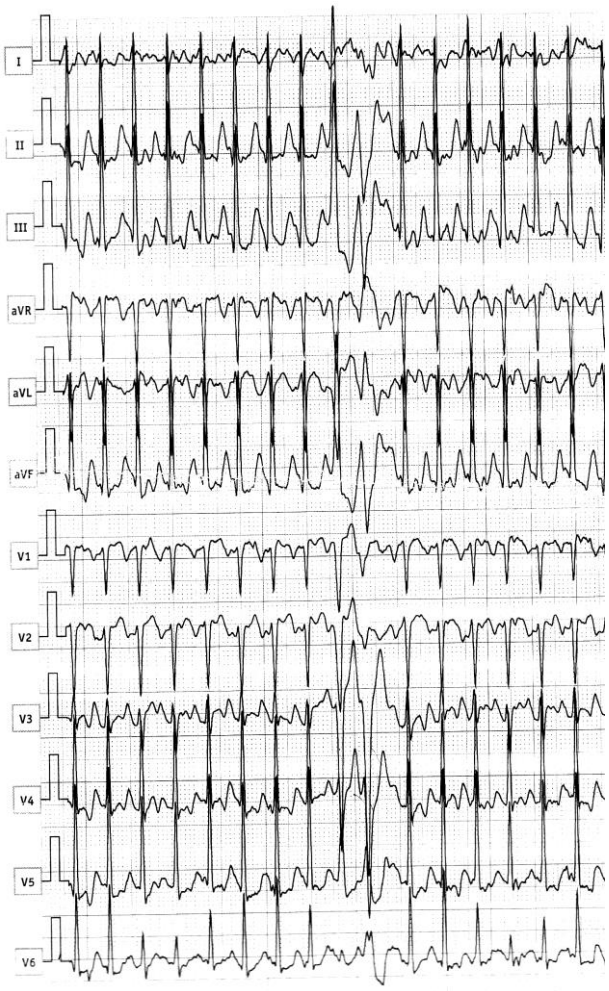


Fig. 3 Ventricular couplet during maximal exercise stress

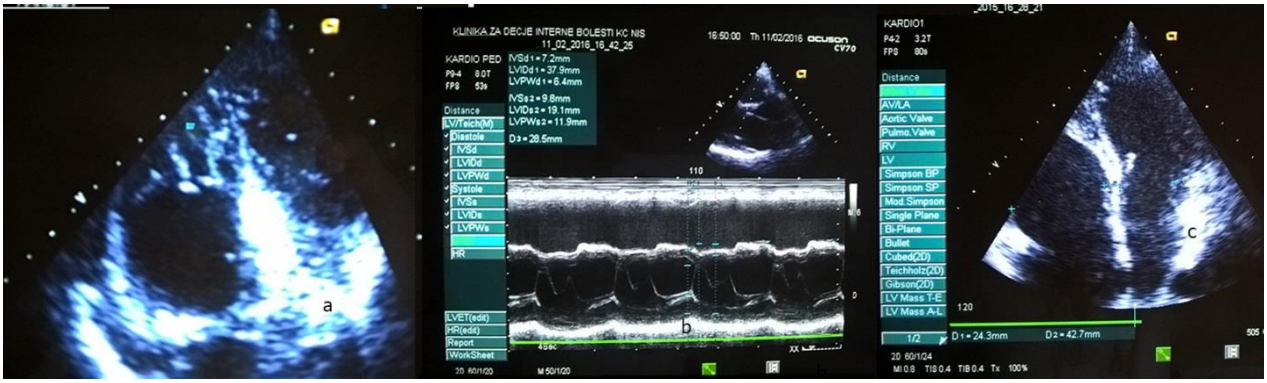


Fig. 4 a – moderator band hyper-reflectivity; b – dilatation of right ventricle outflow tract (PLAX/BSA > 19 mm/m^2); c – dilatation of right ventricle inflow tract.

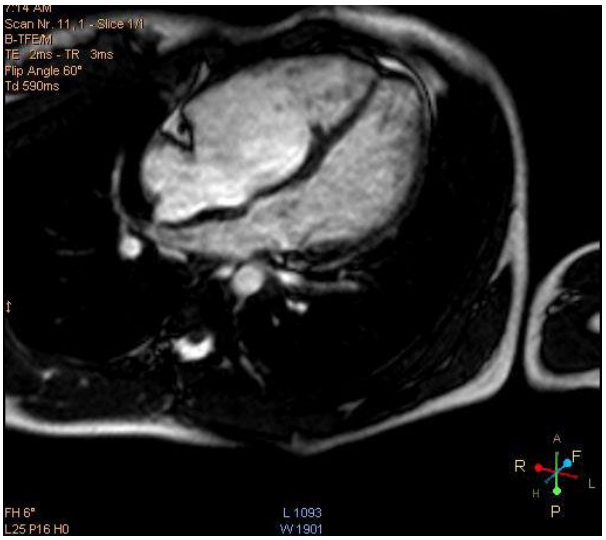


Fig. 5 Aneurismal outpouchings of RV on MRI

Recent research suggests that electrical abnormalities in the form of complex VEBs or VT precede structural changes in ARVC. Of them ventricular tachycardia with LBBB morphology and superior axis is the most characteristic presentation in children.

Among other pathologic findings, echocardiographic abnormalities (dilated and hypokinetic, akinetic or dyskinetic right ventricle) even in asymptomatic patients, should arouse suspicion of this cardiomyopathy. Right ventricle endomyocardial biopsy, if positive, is a gold standard for diagnosis, but often yields a false-negative result (sensitivity is approximately 67%) [7].

Of note is that ARVC in our patient had begun insidiously. Except for the presence of complex VAs (left bundle branch block and inferior axis disappearing at submaximal HR during stress test) at the time of disease presentation, all the other clinical and cardiovascular examinations were normal. The arrhythmias were considered idiopathic and the patient was free of symptoms over months to years although she had been an active football player from age 9 to age 15.

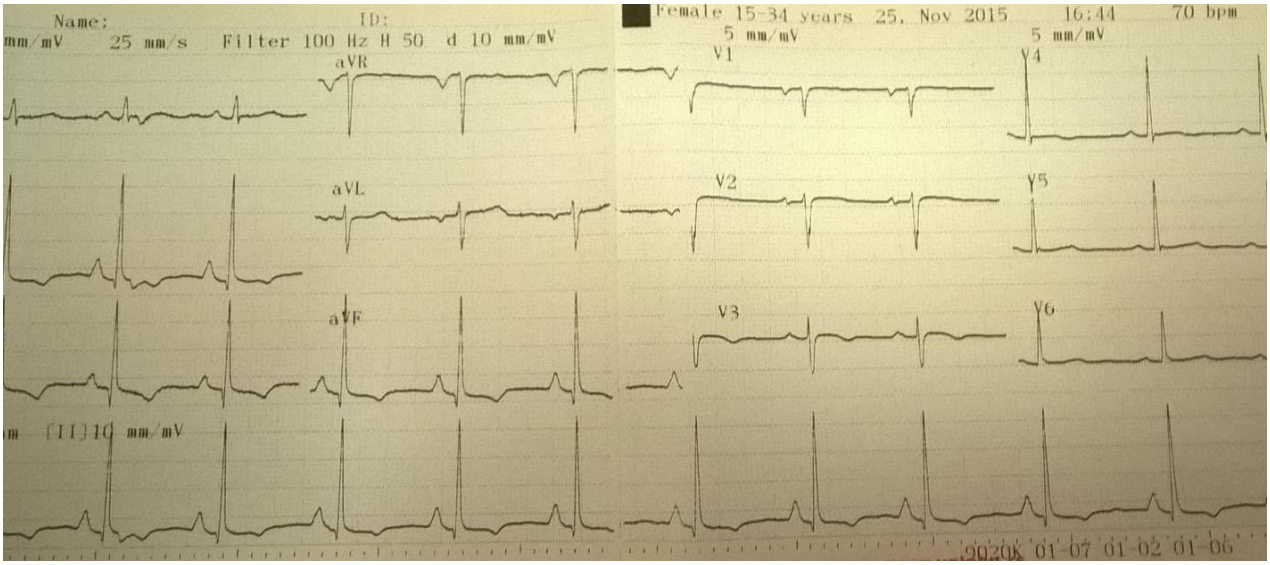


Fig. 6 Nonspecific repolarisations changes in inferolateral leads

Distinctively, her 12 leads ECG was not suggestive of ARVC at any time of the disease course and only nonspecific repolarisation abnormalities in left precordial leads were noticed at age 12 (Fig 6). The more suggestive clinical characteristics in the form of pathologic major echocardiographic criteria that facilitate the recognition of ARVC were not discernible until the patient reached 15 years (Fig 4 a,b,c).

Of note is that in contrast to the apparently non-life-threatening implication of idiopathic ventricular arrhythmias (IVAs) at rest, IVAs elicited during exercise, even in apparently normal individuals, appear to imply risk over time [8]. To date, a number of publications have confirmed that IVAs might be the initial and unique manifestation of clinically silent arrhythmogenic conditions such as myocarditis [9, 10]. On the other hand it is well known that a large majority of patients with ARVC have histological evidence suggestive of inflammation [11].

The only noteworthy clinical finding in our patient, until the occurrence of typical echocardiographic changes, were complex VAs during exercise as well as nonspecific repolarisation changes in inferolateral leads on ECG (Fig 6).

However, their clinical significance was not questioned as the patient was asymptomatic during routine follow-up, despite actively plying football for a decade. Although of not yet defined clinical significance, exercise induced VA is not a common finding in children with benign IVAs etiology. In our opinion, the early appearance of VA (VEBs) is unlikely due to right ventricle structural changes and might be explained more simply by assuming that their origin is a consequence of an inflammatory process which modulated the clinical progression of ARVC in our patient.

With this case report, we would like to increase paediatricians' alertness to children presenting with so called "idiopathic" exercise induced VA, that are probably the earliest biomarkers of more severe arrhythmogenic condition. Prolonged *r*eevaluation follow-up of children with IVAs by pediatric cardiologist should be recommended in similar cases.

References

1. Romero J, Mejia-Lopez E, Manrique C, Lucariello R. Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC/D): A Systematic Literature Review. Clin Med Insights Cardiol [Internet]. 2013; 7:97–114. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3667685&tool=pmcentrez&rendertype=abstract
2. Yoo SJ, Grosse-Wortmann L, Hamilton RM. Magnetic resonance imaging assessment of arrhythmogenic right ventricular cardiomyopathy/dysplasia in children. Korean Circ J 2010; 40:357–367.
3. te Riele AS, Tandri H, Bluemke DA. Arrhythmogenic right ventricular cardiomyopathy (ARVC): cardiovascular magnetic resonance update. J Cardiovasc Magn Reson [Internet]. 2014; 16: 50.
4. Marcus FI, Zareba W. The electrocardiogram in right ventricular cardiomyopathy/dysplasia. How can the electrocardiogram assist in understanding the pathologic and functional changes of the heart in this disease? J Electrocardiol 2009; 42:136.
5. Gajewski KK, Saul JP. Sudden cardiac death in children and adolescents (excluding Sudden Infant Death Syndrome). Ann Pediatr Cardiol 2010; 3(2):107–112.
6. Dupuis JM, Tabib A, Reix P, Dupuis L, Daudet G, Jocteur-Monrozier D, et al. Sudden unexpected death of cardiac origin in the 6 to 18 years population. Pathologic data. Role of sports? How can we prevent it?. Arch Pediatr 2005; 12:1204–1208.
7. Asimaki A, Saffitz JE. The role of endomyocardial biopsy in ARVC: looking beyond histology in search of new diagnostic markers. J Cardiovasc Electrophysiol 2011; 22:111–117.
8. Bjelakovic B, Ilic S, Chouliaras K, Milovanovic B, Vukomanovic V, Bojic T, et al. Heart rate variability in children with exercise-induced idiopathic ventricular arrhythmias. Pediatr Cardiol 2010; 31:188–194.
9. Sun Y, Chan KL, Krishnan SM. Life-threatening ventricular arrhythmia recognition by nonlinear descriptor. Biomed Eng Online 2005; 4:6.
10. Kuo CS, Munakata K, Reddy CP, Surawicz B. Characteristics and possible mechanism of ventricular arrhythmia dependent on the dispersion of action potential durations. Circulation 1983; 67:1356–1367.
11. Nishikawa T, Ishiyama S, Sakomura Y, Nakazawa M, Momma K, Hiroe M, et al. Histopathologic aspects of endomyocardial biopsy in pediatric patients with idiopathic ventricular tachycardia. Pediatr Int 1999; 41:534–537.

FACTA UNIVERSITATIS
Series: **Medicine and Biology** Vol. 17, No 2, 2015, pp. 67–72 UDC 616.314-089.23

Case Report

ORTHODONTIC-SURGICAL TREATMENT OF CLASS III MALOCCLUSION (*HYPOPLASIO MAXILLAE*) A CASE REPORT

Tatjana Perović[1,2*], Zoran Pešić[1,3], Ilija Aleksić[4], Julija Radojičić[1], Zorica Blažej[2]

[1]*Faculty of Medicine, University of Niš, Serbia*
[2]*Dental Clinic, Department of Orthodontics, Niš, Serbia*
[3]*Dental Clinic, Department of Maxilofacial Surgery, Niš, Serbia*
[4]*Independent dental technician*

Abstract. *Establishment of a treatment plan is based on efficiency and easy application by the clinician and acceptance by the patient. Treatment of patients with Class III malocclusion (hypoplasio maxillae) might require orthognathic surgery, especially when the deformity is severe, with a significant impact on facial esthetics. We report here the case of a 16-year-old boy who had a skeletal Class III malocclusion, leading to remarkable deviation of the maxillary midline; this was his chief complaint. Treatment included rapid maxillary expansion followed by leveling, alignment, correction of compensatory tooth positioning, and orthognathic surgery to correct the skeletal Class III malocclusion because of the severe maxillary deficiency. This treatment approach allowed correction of the maxillary dental midline discrepancy to the midsagittal plane and establishment of good occlusion and optimal esthetics*.

Key words: *class III malocclusion, hypoplasio maxillae, orthognatic surgery*

Introduction

Class III malocclusions represent complex irregularities, which can be of a dentoalveolar or skeletal nature. Skeletal class III malocclusions can be presented as false mandibular prognathism (hypoplasio maxillae), or real mandibular prognathism. Not so rarely, there is a combination of these two conditions, which additionally complicates the already existing difficult status of a dentofacial deformity and its therapy. Its frequency is different and it has racial distinctions: in white race it ranges from 1% to 5%, in yellow race from 9% do 19%, whereas in Latin population it is around 5% [1].

The ethology of this group of deformity is mostly hereditary but there are also some nonhereditary factors (e.g. oral respiration) which affect the deterioration of the existing intermaxillary ratio [1–3]. A therapy may go two ways:

- dentoalveolar camouflage- if there is not overexposed skeletal discrepancy, in which case only orthodontic therapy is applied without the correction of basal jaw ratio [3, 4];
- Combined surgical and orthodontic therapy, whereby the satisfying leveling of tooth arches is achieved by presurgical orthodontic treatment, and the optimal intermaxillary ratio is achieved by osteotomy [5].

What represents a problem for most orthodontists is that the severity of deformity by the end of the growth cannot always be predicted with certainty, regardless of the number of applied analyses of types of growth [6]. Sometimes it can happen, especially in borderline cases, that camouflage therapy begins and by the end of the growth it is established that the existing state has deteriorated and the therapy ends in surgical intervention.

The review of the case

- The paper presents a combined, orthodontic and surgical therapy of a patient with a pronounced hypoplasia of the maxilla. A young man of 16 came to the Dental Clinic after two unsuccessful attempts to solve the problem. During that period the upper right second premolar was extracted, most likely due to the lack of space for a canine and lower first left molar. The anamnestic information is especially important and it indicated a long history of infections of upper respiratory pathways and adenectomy, which did not give the expected result (redirection of breathing)
- The outer clinical finding indicates a patient of asthenic constitution of a concave profile with a pronounced long adenoid face with characteristic paranasal depression, narrow alar base, with dark circles under the eyes, broad buccal corridors, hypotonic upper

*Correspondence to: Tatjana Perović DDS, PhD
16/22 Sestre BakovićStreet, 18000 Niš, Serbia
Phone: 063 1045363
E-mail: tatjana.tanic@gmail.com
Received January 3th, 2016 / Accepted February 23rd, 2016

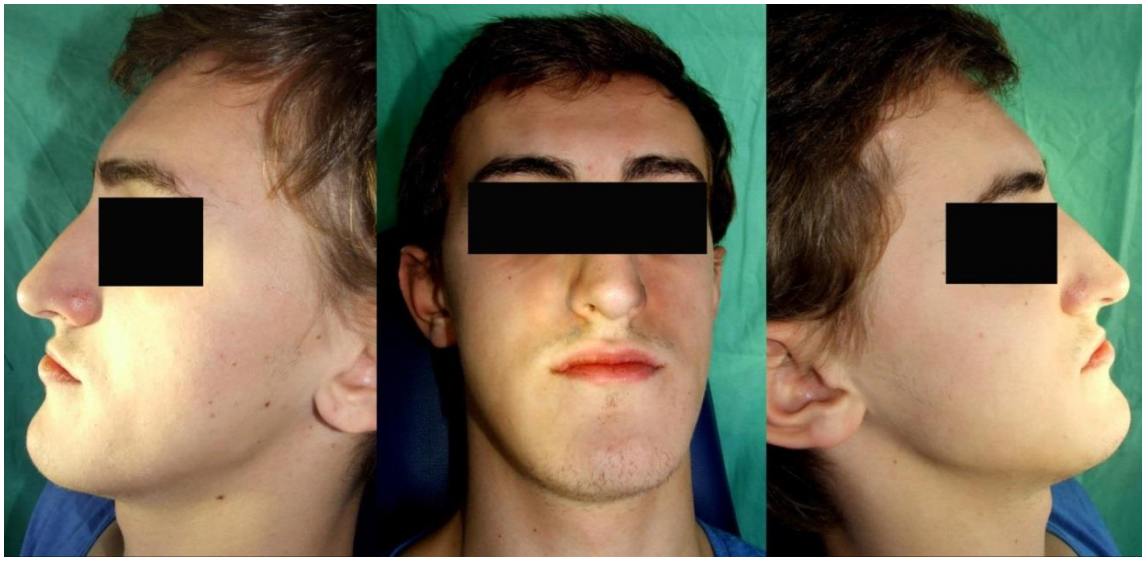


Fig. 1 Pretreatment extraoral photographs

lip... (Fig. 1) The functional finding is unsatisfactory in terms of breathing function, since the patient breathes through the mouth, regardless of the negative rhinological finding. He states that 'he does not get enough air when he breathes only through his nose'. The cutting and chewing of food is also difficult.

- The intraoral finding shows extremely narrow and asymmetrical upper dental arch, mildly crowded in the frontal part with a fractured incisal edge of the upper right central incisor. There is a very high, so called gothic palate. The lower dental arch is broad and long with the extracted right first molar. The occlusion of lateral teeth is in full III class. There is a severe degree of bilateral cross bite (the upper dental arch is 11mm narrower in the front and back width from the lower arch). There is a positive incisal step, and the incisors do not lap (Fig. 2).

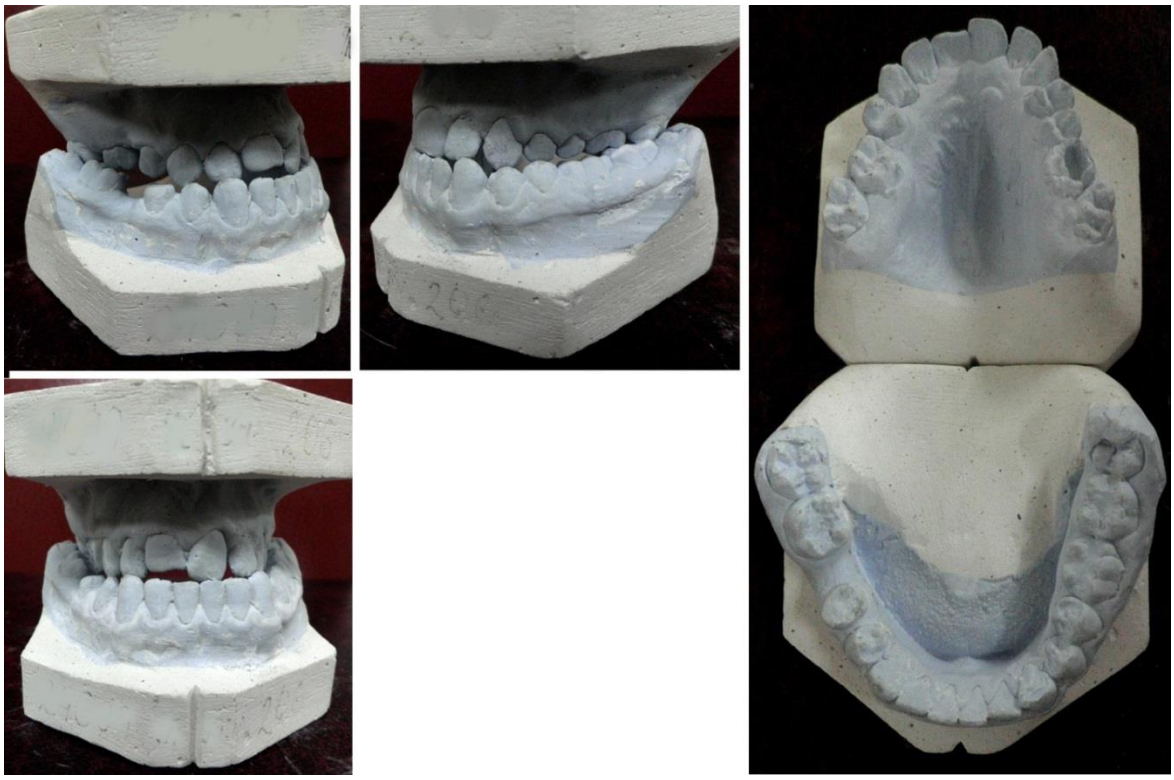


Fig. 2 Pretreatment models

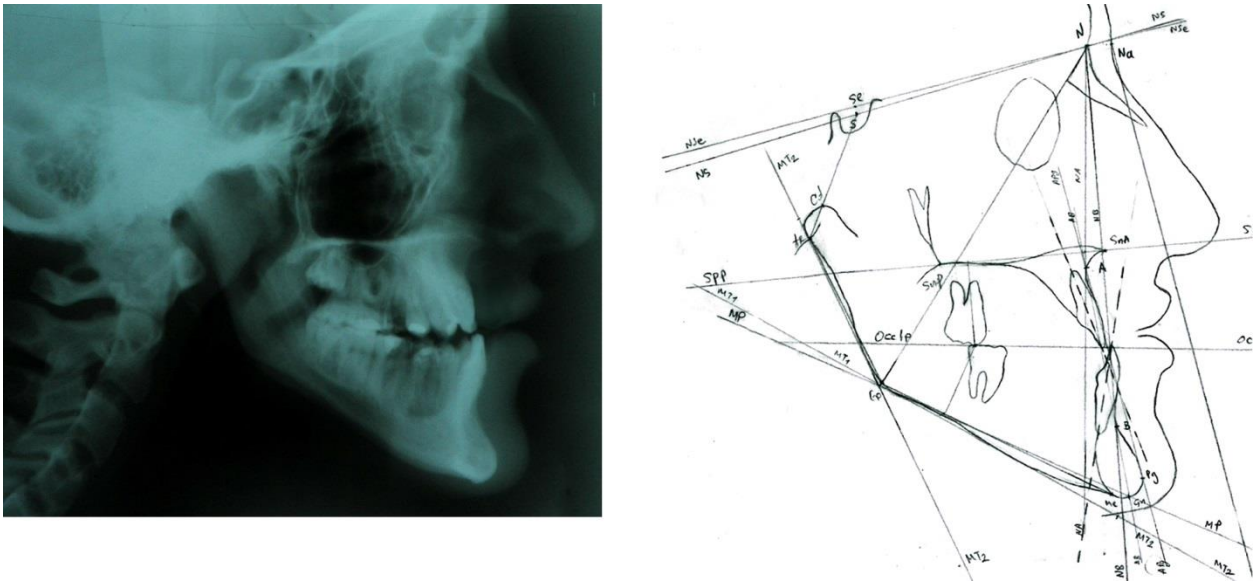


Fig. 3 Pretreatment cephalograf and cephalometric tracing

- The analysis of a profile cephalogram showed conspicuous maxillary retrognathism (SNA =72˚), followed by mild mandibular retrognathism (SNB= 78˚). The sagittal intermaxillary angle (ANB) of -6% indicates skeletal relation of III class caused by hypoplasia of the maxilla. The sum of Bjork's polygon of 401˚ and the ratio of the front and back height of the face of 60% suggest hyperdivergent growth (Fig. 3).

The goals of therapy:

1. Transversal alignment of maxillary with mandibular arch, using the method of midpalate distraction (rapid palatal expansion);
2. The leveling of dental arch with fixed appliances;
3. Surgical plan: Le Fort I osteotomy and forward placement of maxilla;
4. Long term retention plan.

In the plan of the therapy, the priority was given to rapid palatal expansion. For rapid palatal expansion, an appliance made on the basis of Rapid expander screw was used (manufacturer Leone, stock No A0620-13). The goal of this treatment was to transversally post-surgically align upper and lower dental arch. The alignment with retention was achieved in 12 months. Two months after placing an appliance for rapid palatal expansion (Fig. 4) an upper fixed appliance was placed (full arch, prescribed by Roth, slot 0,022”) for the leveling of dental arch, for the purpose of pre-surgical preparation. The patient refused the application of a lower fixed appliance. He stated that for the mentioned period of palatal expansion his breathing "drastically improved and facilitated" which eliminated "hunger for oxygen", which is common in patients with hypoplasia of the maxilla. During this phase of therapy, positive incisal step increased and the bite slightly opened, which was expected due to posterior rotation and

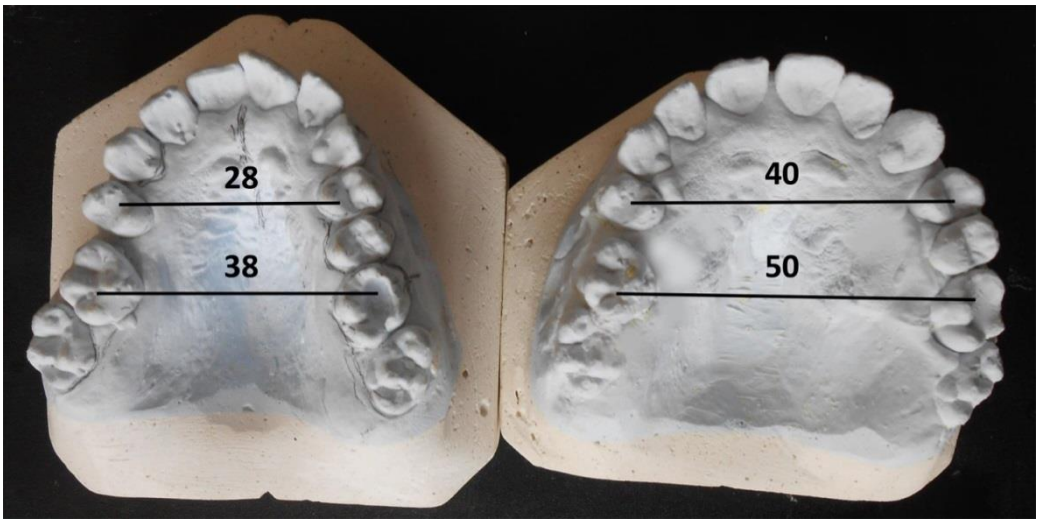


Fig. 4 Pretreatment upper model and upper model after rapid palatal expansion

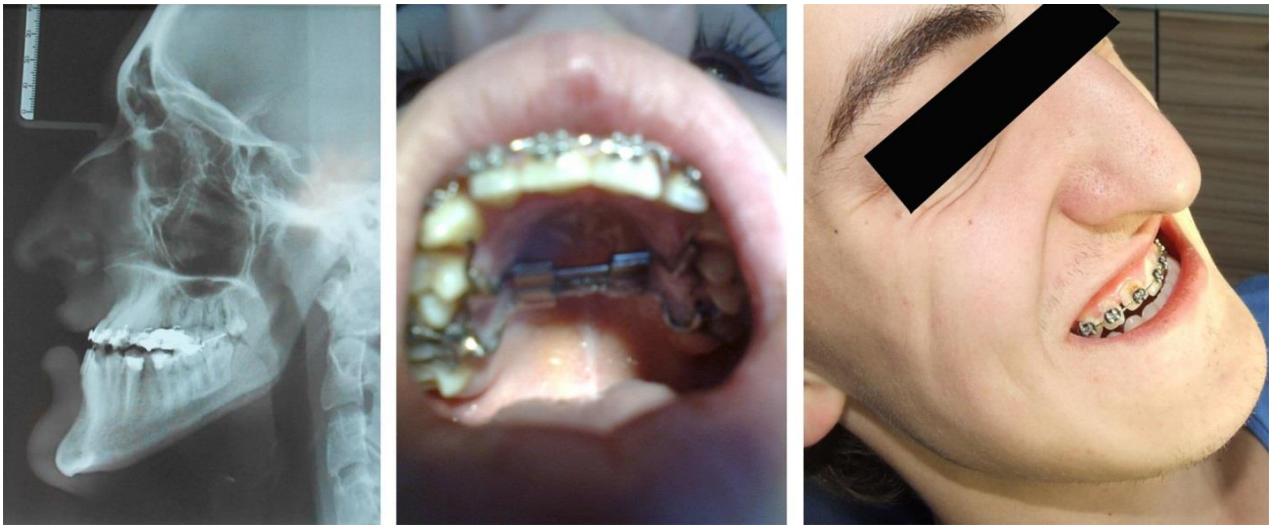


Fig. 5 Presurgical appearance and cephalograph

transferring cusps into a normal bucco-oral position (Fig. 5). After the removal of a fixed appliance, modified Hawley plate was used as a retention appliance and it was worn only during the night within the period of two years before surgery.

The description of surgery

Surgical procedure – After standard preoperative measures, surgical intervention was performed in general anesthesia. Air way intubation was transnasal. Incision and access through soft tissue was in horseshoe manner from first molar to first molar. Maxillary osteotomy at Le Fort I level was performed with preservation of palatal mucogingival pedicle. After osteotomy cuts and dissection of nasal spine from nasal mucosa as well as elevating nasal mucosa from a palatal, nasal septum and lateral nasal walls, nasal septum was separated from palatal segment. Pterygomaxillary disjunction was performed by curved chisel and disjunction and detachment of maxilla were finished. Then, maxillary segment was advanced in desired position checked by occlusion, as well as to mandibular and to other parts of facial skeleton. Maxillary segment was fixated in desired position by using mini plates (Stryker Leibinger Midface mini plates). Mini plates were removed nine months after surgical intervention.

Two years after the surgery, extraoral finding shows the improvement in facial visage with the normalization of facial features (Fig. 6). Nasal respiration is stabilized. Corrective occlusion was achieved intraorally in all three directions (Fig. 7, Table 1). The analysis of a profile cephalogram shows the improvement of dentoskeletal ratio (Fig. 8, Table 2).

Table 1. The values of the dentoalveolar parameters before and two years after whole treatment

Features	Pre-treatment	Post-treatment
Incisor relationship	reverse overjet	normal overjet
Overjet value	-2 mm	2 mm
Overbite	0 mm	2 mm
Midlines	shifted	co-incident
Left molar	class III	class I
Right molar	class III (after reconstr.)	class I

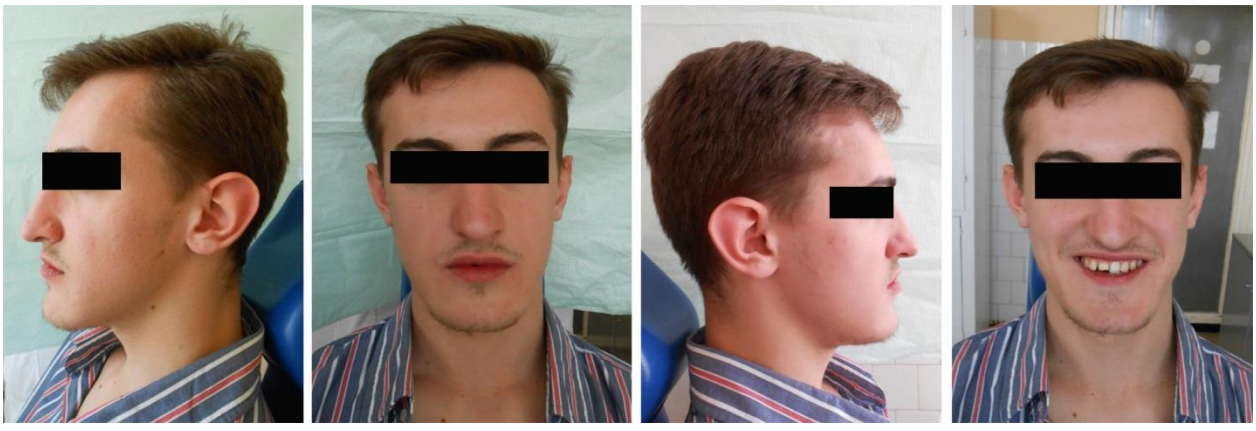


Fig. 6 Extraoral photographs, two years after surgery

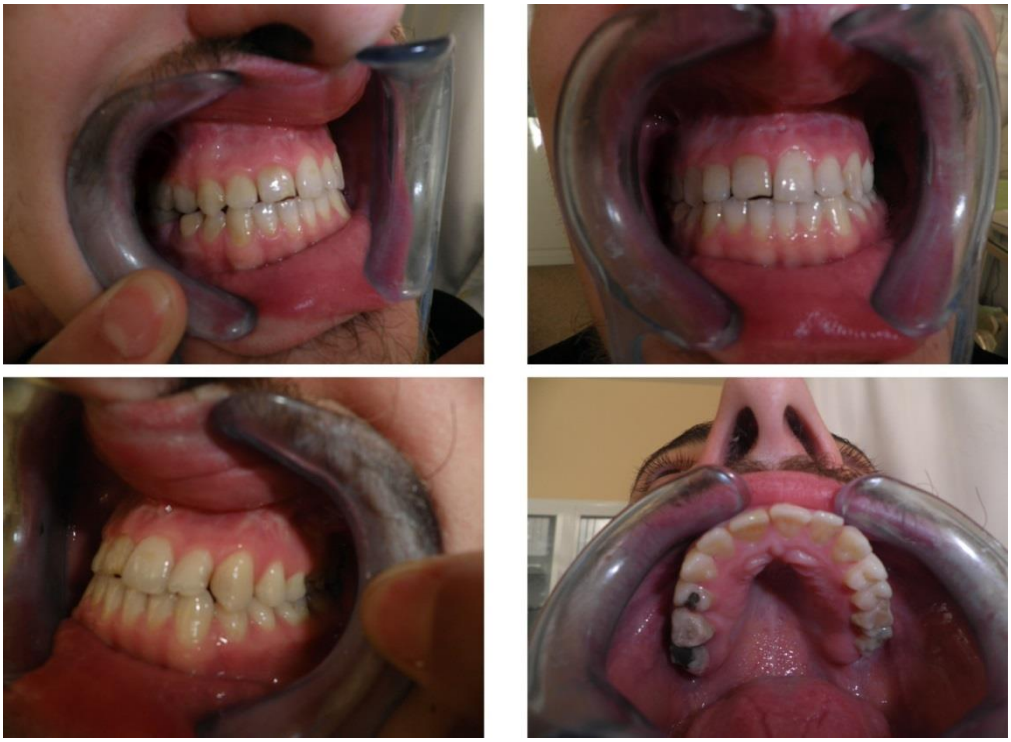


Fig. 7 Intraoral photographs, two years after surgery

Table 2. The values of the SNA, SNB and ANB angles before and two years after whole treatment

Angles	(referent values)	Pre-treatment values	Post-treatment values
SNA	(82˚)	72˚	80˚
SNB	(80˚)	78˚	78˚
ANB	(2˚)	-6˚	2˚

SNA – position of the maxilla (normal, prognathic, retrognathic);
SNB – position of the mandible (normal, prognathic, retrognathic);
ANB – skeletal relationship between the maxilla and the mandible

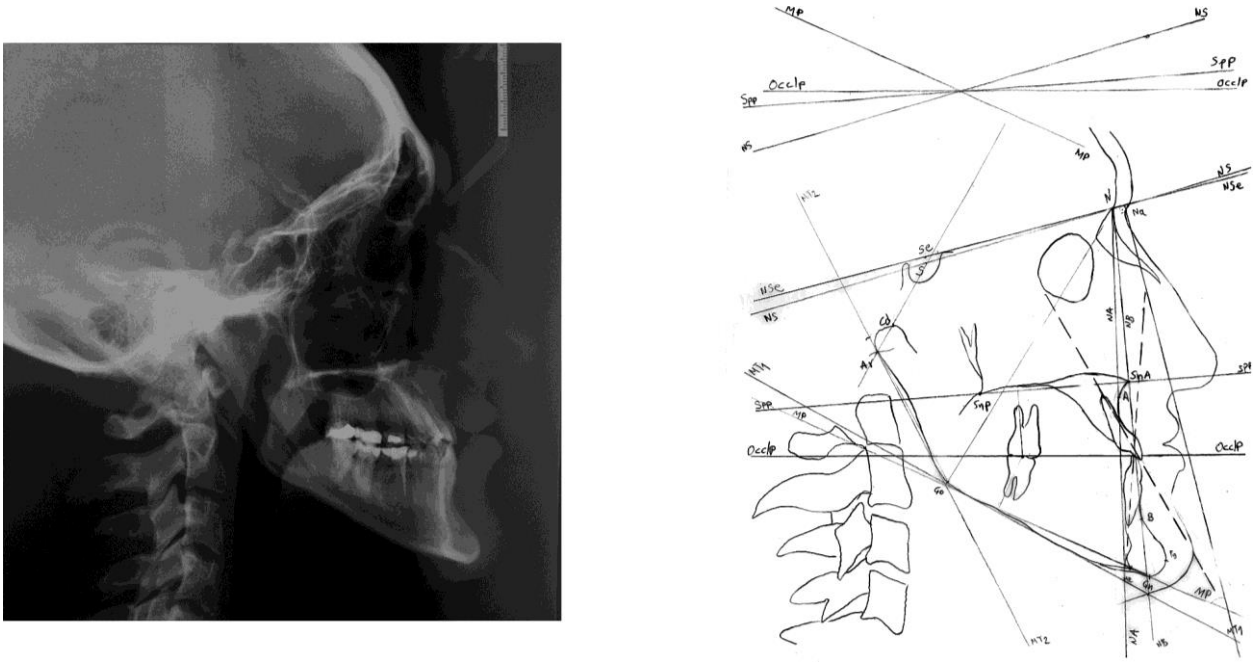


Fig. 8 Cephalograf and cephalometric tracing, two years after surgery

Discussion

Hypoplasia of the maxilla represents a severe orthodontic problem, which is usually conspicuous in early childhood. It is considered to be primarily of hereditary ethology with strong effects on oral respiration [2]. With years, in most of the cases, the deformity progresses. Patients have aesthetic motivation to solve this problem [7], but functional difficulties should not be neglected as well. Aside from crowded upper tooth line, common effects of this condition are impacted canines [8, 9], asymmetrical upper tooth line [8], obligatory (uni- or bilateral) cross bite, often followed by apertognathia [10], sometimes turning of mandibula [11] which further complicates the therapy of the already existing condition.

The early therapy of hypoplasia of the maxilla has a great influence on the normalization of intermaxillary ratio, especially if facial mask by Delair is applied [12]. If this period is skipped, it is hard to camouflage this problem due to advancement of irregularities in the future, so this problem is usually treated orthodontically and surgically.

The motives for treating this type of deformity are often different. Patients usually cite aesthetics as the primary motivational factor. That was not the case with the portrayed patient. He cited functional discomforts (breathing, chewing) as primary. Facial aesthetics was not on his priority list. Still, after the completed treatment, he was thrilled with the change in the appearance of his face.

The main problem that appeared during the treatment was one-sided extraction of premolars in the upper jaw. Such an asymmetrical dental arch compromised all the phases of therapy. First of all, it is hard to make an appliance for rapid palatal expansion if there is not an adequate number of lateral teeth on both sides. During the phase of expansion, asymmetrical expanding can easily develop due to the lack of reciprocity on the left and right side. Luckily, that did not happen here.

During the leveling of tooth line with a fixed appliance, the lack of one premolar leads to disbalance inside dental arch so that the planned corrective leveling of tooth arch remains at the level of compromise. Over time, this can lead to early contact and compromise the results of the entire therapy. For the mentioned reasons, the symmetry of dental lines should be imperative in orthodontic therapy, whenever it is possible [13, 14].

Conclusion

Surgical-orthodontic treatment is sometimes the only option for achieving an acceptable occlusion and a good esthetic result in a patient with Class III dentofacial deformity. A correct diagnosis and planning as well as an appropriate execution of the treatment plan are determining factors for achieving success and long-term stability. It should be performed by a multidisciplinary team to ensure a satisfactory outcome.

Acknowledgements: The Authors are grateful to Dr Vasilija Teoharidu for technical support.

References

1. Toffol LD, Pavoni C, Baccetti T, Franchi L, Cozza P. Orthopedic treatment outcomes in Class III malocclusion. A systematic review. Angle Orthod 2008; 78:561–573.
2. Stojanović LS, Mileusnić I, Mileusnić B, Cutović T. Orthodontic-surgical treatment of the skeletal class III malocclusion: a case report. Vojnosanit Pregl 2013; 70:215–20.
3. Bhandari PK, Anbuselvan G J. Nonsurgical management of class III malocclusion: A case report. J Indian Acad Dent Spec Res 2014; 1:35–38.
4. Satish HA, Daokar S, Gulati M. Different Non – Surgical Treatment Modalities for Class III Malocclusion. IOSR-JMDS 2013; 9:48–52.
5. Lamtiur PE. Orthodontic-surgical treatment of a severe class III malocclusion. Dent J (Majalah Kedokteran Gigi) 2013; 46: 229–234.
6. Benyahia H, Azaroual MF, Garcia C, Hamou E, Abouqal R, Zaou F. Treatment of skeletal Class III malocclusions: orthognathic surgery or orthodontic camouflage? How to decide. Int Orthod 2011; 9:196–209.
7. Lopez RG, Paz CS, Velazquez SS. Correcting a class III malocclusion with presurgical orthodontics and oblique ramus osteotomy. Case Report. Revista Mexicana de Ortodoncia 2014; 2:120–127.
8. Janson M, Janson G, Santana E, de Castro RC, de Freitas MR. Orthodontic-surgical treatment of Class III malocclusion with extraction of an impacted canine and multi-segmented maxillary surgery. Am J Orthod Dentofacial Orthop 2010; 137:840–849.
9. Mittal SK, Sharma R, Singla A, Grover V. Orthodontic-surgical correction of class III malocclusion with bilateral maxillary impacted canines. J Innov Dent 2011; 1(2).
10. Paraschivescu EG, Szuhanek C. Surgical-orthodontic treatment in Class III skeletal anomalies. Proceedings of the World Medical Conference 2011: 227–230.
11. Bergamo AZ, Andrucioli MC, Romano FL, Ferreira JT, Matsumoto MA. Orthodontic-surgical treatment of Class III malocclusion with mandibular asymmetry. Braz Dent J 2011; 22:151–156.
12. Glišić B, Šćepan I, Nikolić Z, Đorđević D. Changes in position and relationship between jaws in. children treated with Delair's mask. Stom Glas S 2004; 51:177–182. (in Serbian)
13. Kaán M. Unilateral space-creating extraction in orthodontics. Fogorv Sz 1994; 87:337–343. (in Hungarian)
14. Melgaço CA, Columbano Neto J, Jurach EM, Nojima Mda C, Sant'Anna EF, Nojima LI. Rapid maxillary expansion effects: an alternative assessment method by means of cone-beam tomography. Dental Press J Orthod. 2014; 19:88–96.

FACTA UNIVERSITATIS
Series: **Medicine and Biology** Vol. 17, No 2, 2015, pp. 73–78 UDC 616.314-089.23

Case Report

CLASS II DIVISION 1 MALOCCLUSION THERAPY WITH THE HELP OF EXTRAORAL HEADGEAR APPLIANCE WITH CERVICAL PULL – CASE REPORT

***Konstantinos Papadopoulos*[1], *Tatjana Perović*[2,3]**

[1]*Specialistic Orthodontic Practice, Katerini, Greece*
[2]*Faculty of Medicine, University of Niš, Serbia*
[3]*Dental Clinic, Department of Orthodontics, Niš, Serbia*

Abstract. *Case report of a ten-year-old boy with a Class II division 1 malocclusion is presented. Non extraction treatment was undertaken with the use of cervical headgear appliance. The treatment time was 25 months. The results of non-extraction orthodontic treatment was the sagittal correction of skeletal Class II malocclusion as well as the reduction of overjet and overbite. The effects of the cervical headgear were mainly in the skeletal level*.

Key words: *Class II division 1 malocclusion, Cervical headgear appliance*

Introduction

The use of extraoral forces in the treatment of Class II division 1 malocclusion was introduced for the first time in 1800. Since then, many studies have reported on its treatment effects.

Kloehn [1] established that the use of the cervical headgear could achieve an inhibition of maxillary growth in the correction of the mentioned malocclusion.

In the following years, the effects of the cervical headgear application on the craniofacial complex has been proved by a great number of experimental [2, 3] and clinical studies [4–10]. Many investigators have stated that in treating patients with cervical headgear the mandible is rotated back because of the excessive extrusion of the upper first molars [11, 12].

Because of this negative effect many orthodontists abandoned the use of cervical pull and continued with the use of high pull or combination pull, especially in the patients with vertical growth pattern.

Forces which have been applied in the headgear treatment are the following: 1. Low forces of 150–250 grams per side can be applied for a distal movement of upper molars [13–14], 2. Heavy forces of 450–500 grams per side to produce more skeletal effect or to provide a reliable maxillary posterior anchorage system [15–18].

*Correspondence to: Konstantinos Papadopoulos, DDS, PhD
Specialistic Orthodontic Practice, Katerini, Greece
Kassandrou 49, 60100 Katerini, Greece
E-mail: kl_papadopoulos@yahoo.gr
Received January 5th, 2016 / Accepted February 23rd, 2016

Treatment Objectives

- Redirection of maxillary growth
- Correction of distal sagittal relationship to Class I
- Overbite correction and overjet reduction to normal values
- Establishment of normal torque and inclination of the teeth with well-coordinated dental arch forms
- Improvement of soft tissue relationship and patient's facial appearance.

Case Report

The case of a 10-year-old boy with Class II division 1 malocclusion is presented. The chief complaint was excessive protrusion of the maxillary anterior teeth. A similar malocclusion existed in his mother as well, which shows an inherited etiology of this orthodontic problem. The patient's motivation was largely internal, and he decided to cooperate with the nonextraction cervical headgear treatment.

Diagnosis

The patients face was symmetric and soft tissue profile was the convex one. The lips were competent because of the soft tissue enlargement. Mentolabial sulcus was strongly distinctive. The height of the lower third of the face was reduced. There was a reduced nasolabial angle (Fig. 1 a–c). The patient had a Class II division 1 malocclusion in the permanent dentition. There was an excessive protrusion of the upper incisors. Overjet was 9mm and a deep, impinging overbite, with a moderate maxillary and mild mandibular crowding (Fig. 2 a–e).

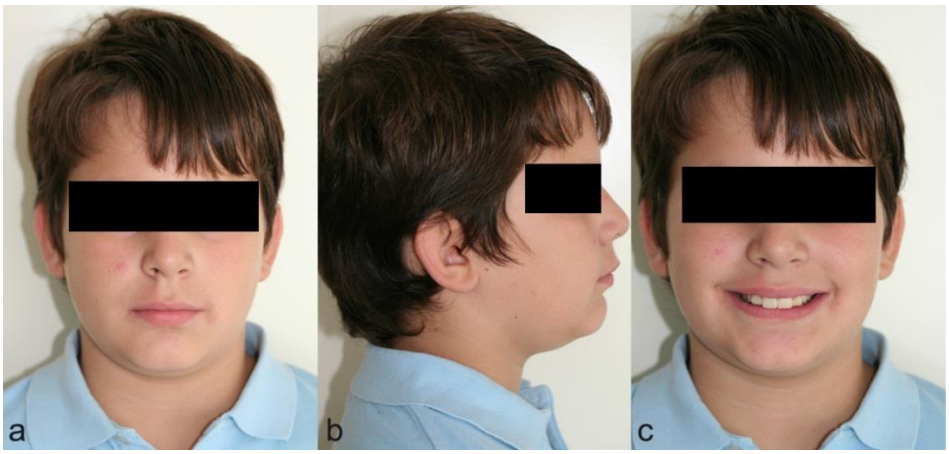


Fig. 1 Patient's facial appearance before therapy a) "en face", b) profile, c) smile

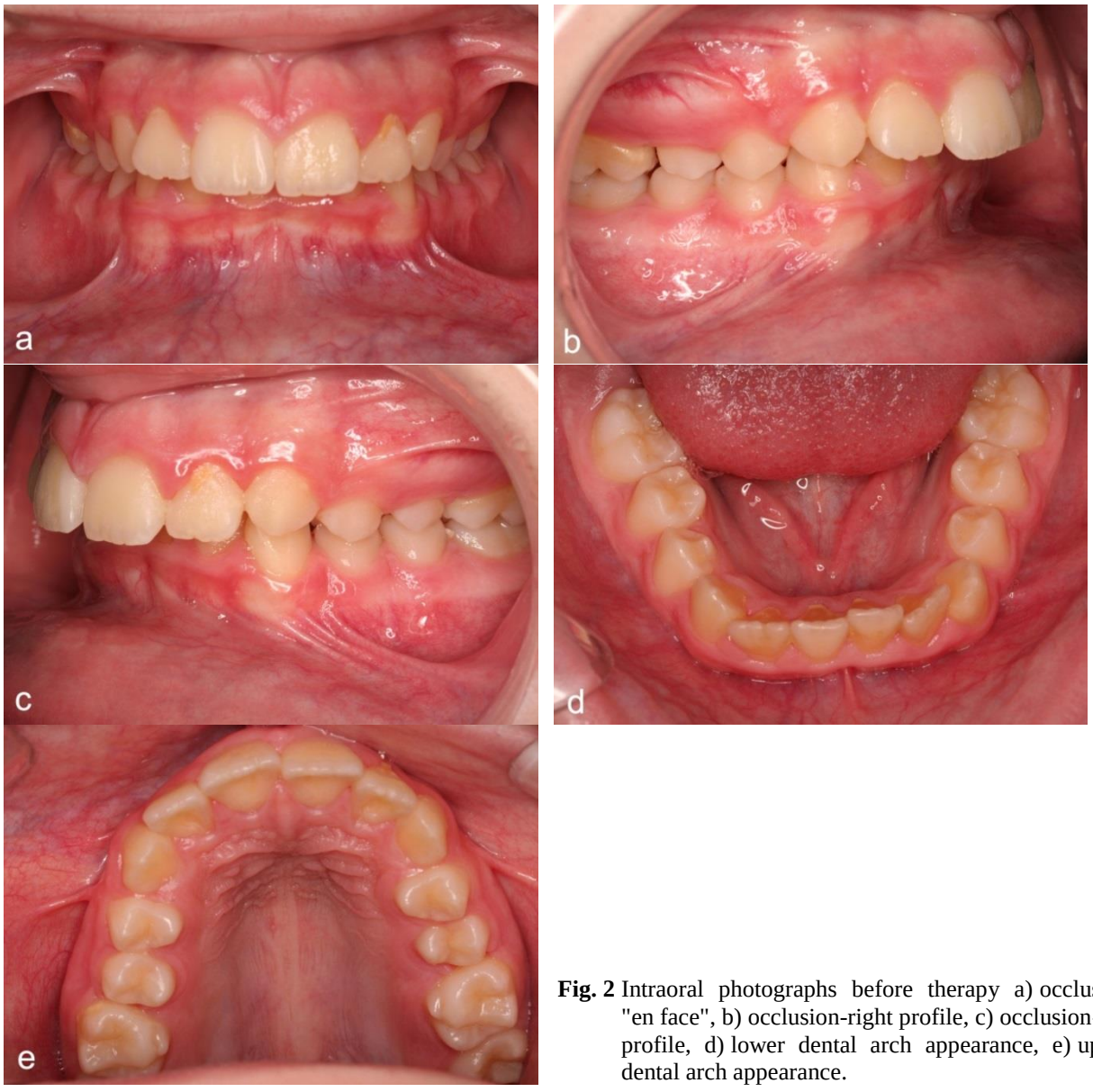


Fig. 2 Intraoral photographs before therapy a) occlusion "en face", b) occlusion-right profile, c) occlusion-left profile, d) lower dental arch appearance, e) upper dental arch appearance.

The measurements of the lateral head radiogram showed the following (Table 1):

Table 1 Cephalometric analysis results

Measurements	Avg.	Min.	Max.	Initial	Final
Skeletal anteroposterior					
NSBa	131°			133°	134°
FH – SN	6°	4°	8°	10°	12°
FH – NA	88°			94°	91°
FH – NPog	87.8°	82°	95°	87°	88.5°
SNA	80°	76.2°	83.8°	85°	82°
SNB	78°	75°	81°	77°	78°
ANB	2.8°	0.5°	5.1°	8°	4°
Skeletal Vertical					
FH – MP	23°	17°	28°	20°	21°
SN – MP	32°	30°	34°	29°	29°
SN– PP	8.5°	7°	10°	5.5°	7°
NSGn	68°	63°	72°	65°	68°
Y – AXIS	59.4°	53°	66.2°	56°	58°
Upper face height	44%	44%	45%	48%	45%
Lower face height	56%	55%	56%	52%	55%
Dental relationships					
AB – FOP	90.1°	80.75°	96°	74°	80°
FOP – PP	11.3°	9.6°	13.8°	7°	5°
U1 – FH	110°	105°	115°	116°	108°
U1 – PP	110.2°	105°	115°	114°	105°
U1 – APog	22°	19°	25°	39°	24°
Dist1 – APog	2.7 mm	-1 mm	+5 mm	8mm	3.5mm
L1 – FH	65°	60°	70°	63°	55°
L1 – MP	91.4°	-8.5°	+7°	96°	105°
L1 – FOP	72.3°	68.6°	76.7°	66°	58°
L1 – APog	23°	20°	26°	16°	25°
Dist L1 – APog	0 mm	-2 mm	+3 mm	3.5 mm	0 mm
U1 – L1	135.4°	139°	150°	128°	128°
Soft tissues					
Dist UL – EP	-2 mm	-3 mm	-1 mm	0.5mm	-3 mm
Dist LL – EP	-1 mm	-2 mm	0 mm	0 mm	-2mm

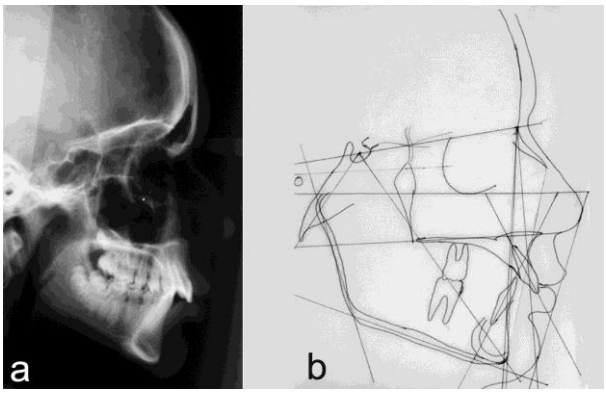


Fig. 3 a) Lateral head radiograph before therapy;
b) Cephalometric tracing before therapy.

Skeletal Class II malocclusion (ANB 8°), maxillary protrusion (SNA 85°, angle Lande 94°). A forward rotation of the mandible with the angle FMA 20° and SN-MP 29°. Horizontal type of growth lower face height 52%. Labial inclination of the upper incisors U1-APog 39°, linear 9mm. Reduced interincisive angle of 128° (Table 1, Fig. 3). Panoramic radiogram has shown the existence of the third molars (Fig. 4)

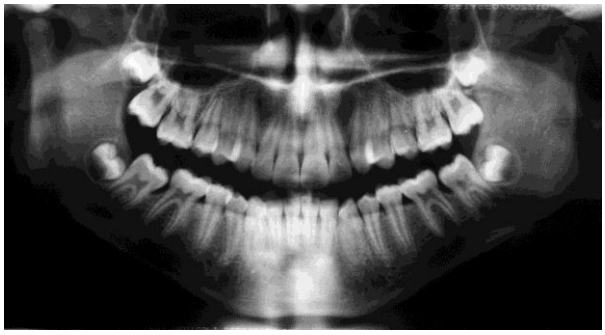


Fig. 4 Panoramic radiograph before therapy.

Treatment plan

Treatment goals included the inhibition and redirection of maxillary growth, correction of Class II malocclusion, overjet and overbite reduction and establishing normal torque and inclination of the teeth. The final goal was improvement in the relation between soft tissue and patient's profile. Priority in the treatment planning was the correction of the skeletal deformation with a modification of growth because the patient was in the beginning of the pubertal growth spurt. Cervical headgear (Kloehn type) was applied with the inner bow of the facebow expanded 8 to 10mm and placed in molar headgear tube. To prevent the extrusion of molars the outer bow was long and bent upward 15° to 20°. The force applied during the first week was 250 g per side, in order to be more comfortable for the patient. After that the applied force was enlarged to 450 g per side. Patient was urged to wear the headgear 14 to 16 hours a day.

Treatment progress

After 10 months of treatment with cervical headgear, correction of the sagittal relation of the molars was achieved (Class I). The maxillary first molars were distalized and that was a sign of dentoalveolar effect of the appliance. Posterior spaces in the maxillary arch were needed to resolve the problems of crowding and incisors protrusion. However, since the fourth month of treatment, there has been noticed a reduction in overjet with a simultaneous overbite correction. Fixed appliances were placed in the upper and lower jaw and the patient was wearing the headgear only at night. The retraction of the premolars and canines started when the position of the upper first molars was stable. Once the premolars and canines were fully retracted with lacebacks, the incisors were retracted with T-loops, bent to a 0,016× 0,022 stainless steel arch wire. Treatment results have been accomplished during a period of 25 months. For the retention, the invisible plastic retainers were used in the upper and lower jaw.

Treatment results

Treatment has led to the facial aesthetic improvement with an obvious correction of the position and the relationship between the upper and lower lip (Fig. 5 a–c), Class I canine and molar relationships were present, overjet reduction from 9mm to 2mm and normalization of overbite (Fig. 6 a–f).

Fig. 5 The patient's appearance after therapy a) "en face", b) profile, c) smile

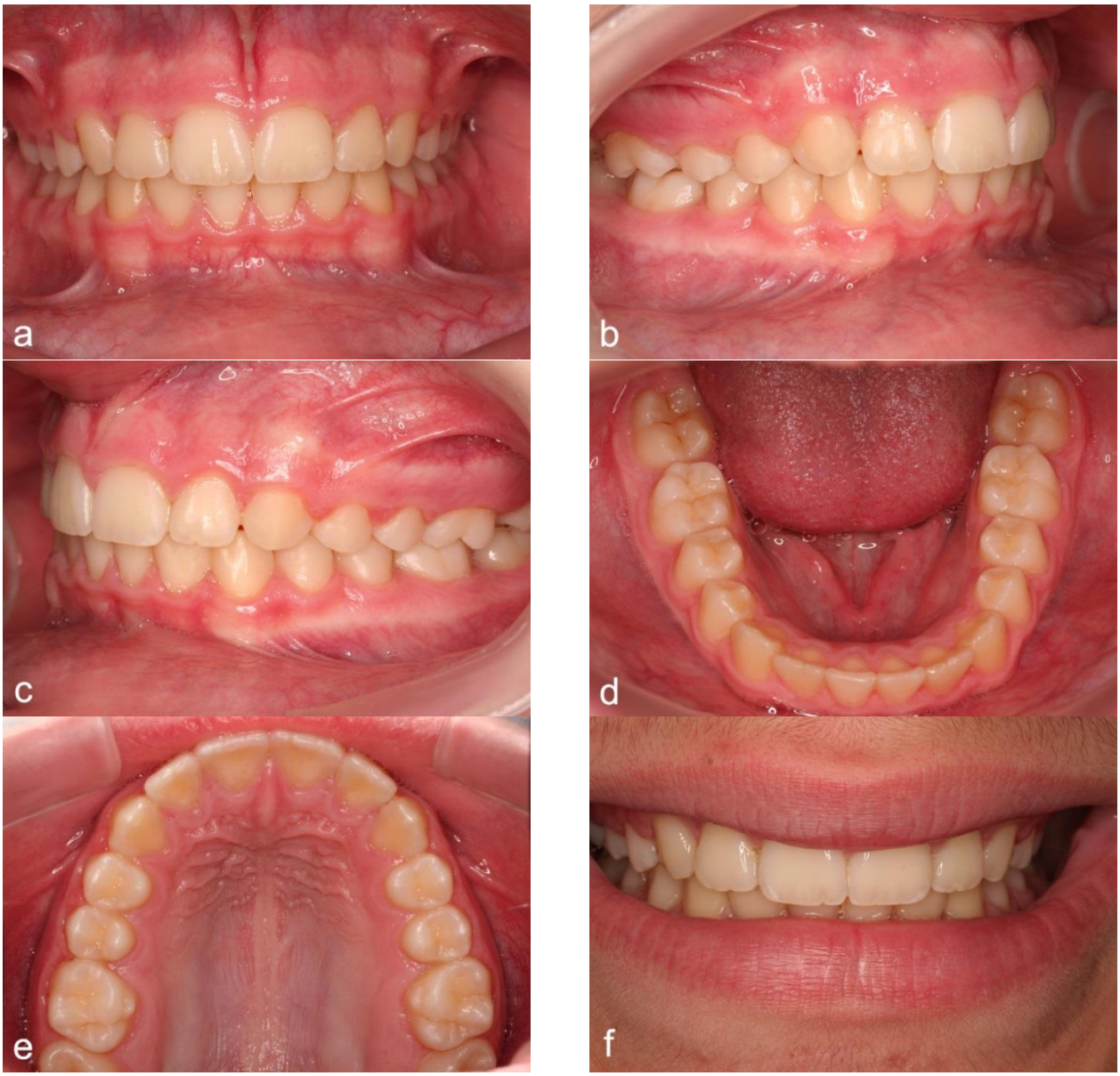


Fig. 6 Intraoral photographs after therapy a) occlusion - "en face", b) occlusion-right profile, c) occlusion-left profile, d) lower dental arch appearance, e) upper dental arch appearance, f) smile

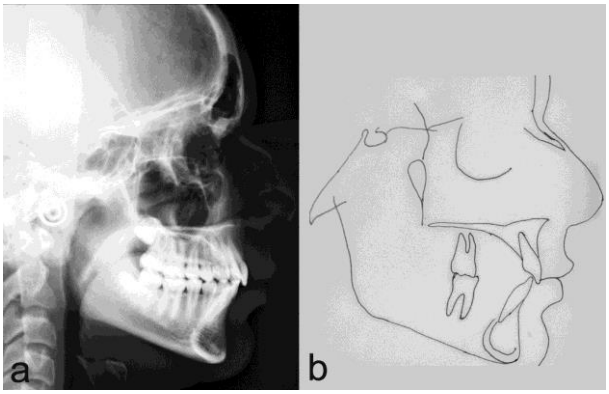


Fig. 7 a) Lateral head radiograph after therapy; b) cephalometric tracing after therapy.

Cephalometric measurements (Table 1) have shown a significant amount of skeletal and dental changes. Reduction of ANB angle from 8° to 4° and SNA angle from 85° to 82°. The lower third of the face was increased NSGn from 65° to 68°. Correction in the inclination and position of upper incisors (U1-FH from 116° to 108°, U1-PP from 114° to 105°, U1-Apog from 39° to 24°, and DistU1-APog from 8mm to 3,5mm. Labial inclination of lower incisors L1-FH from 63° to 55°, L1-MP from 96° to 105°, and interincisal angle remained the same (U1-L1 128°) (Fig. 7).

Radiographic examination indicated satisfactory root paralleling without any loss of tissue (Fig. 8).

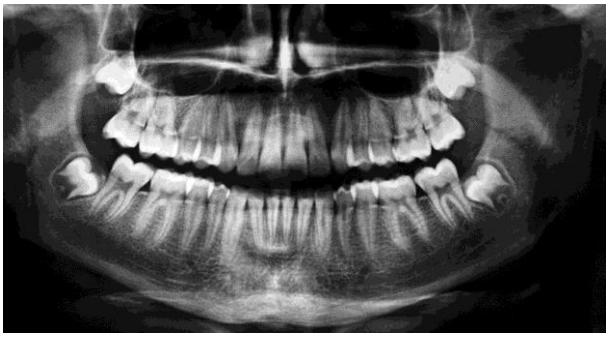


Fig. 8 Panoramic radiograph after therapy.

Discussion

Treatment results indicate the validity of cervical headgear use in patients with Class II div.1 malocclusion, in which case it is necessary to achieve inhibition of maxillary growth and ensure the normal growth of the mandible. With the use of this appliance there is no need for maxillary first premolar extractions which makes the cervical headgear preferable to the patient. Cervical headgear showed a greater effect in distal tipping of the upper first molars and changes in the rotation of the distal part of the maxilla. However, the impact of this type of appliance on the rotation of jaws was reversible because after cervical headgear treatment and the continued growth of the maxilla and mandible the forward rotation remained [4].

Other authors also consider that there is a significant change in the rotation, but the change is related to the inclination of the frontal part of the maxilla [9, 10].

Reduction in the convexity of facial profile was mentioned by all the authors who proved with longitudinal studies the changes from the beginning to the end of the treatment [6, 8, 14, 17] and the same was observed in our patient too.

The disadvantage in this appliance is mainly related to the dependence of the outcome of the treatment on the patient's compliance.

Conclusion

The main treatment planning for the patients with skeletal Class II malocclusion associated with maxillary protrusion is the modification, inhibition of maxillary growth and distal movement of the upper first molars. This can be achieved by an application of cervical headgear and extraoral vector of force acting through the center of resistance of the upper first molars. In this case report inhibition of maxillary growth and distal movement of the upper first molars was achieved by the combination of skeletal and dentoalveolar effects of the appliance.

References

1. Kloehn SJ. Guiding alveolar growth and eruption of teeth to reduce treatment time and produce a more balanced denture and face. Angle Orthod 1947; 17:10–33.
2. Holberg C, Holberg N, Rudski-Janson I. Sutural strain in orthopedic headgear therapy: A finite element analysis. Am J Orthod 2008; 134:53–59.
3. Pawan G, Ashima V, Raviraj A.Craniofacial displacement in response to varying headgear forces evaluated biomehanichally with finite element analysis. Am J Orthod 2009; 135:507–515
4. Melsen B. Effects of cervical anchorage during and after treatment: an implant study. Am J Orthod 1978; 73: 526–540.
5. Hubbard GW, Nanda RS, Currier GF. A cephalometric evaluation of nonextraction cervical headgear treatment in Class II malocclusions. Angle Orthod 1994; 64:359–370.
6. Godt A, Kalwitzki M, Goz G. Effects of cervical headgear on overbite against the background of existing growth patterns. Angle Orthod 2007; 77:42–46.
7. Godt A, Kalwitzki M, Goz G. Cephalometric analysis of molar and anterior tooth movement during cervical headgear treatment in relation to growth patterns. J Orofac Othop 2008; 69:189–200.
8. Kirjavainen M, Hurmerinta K, Kirjavainen T. Facial profile changes in early Class II correction with cervical headgear. Angle Orthod 2007; 77:960–967.
9. Ramos Pinto DS, de Lima EM. A longitudinal evaluation of the skeletal profile of treated and untreated skeletal Class II individuals. Angle Orthod 2005; 75:47–53.
10. Cangialosi TJ, Meistrell ME, Leung MA, Ko JY. A cephalometric appraisal of Edgewise Class II non extraction treatment with extraoral force. Am J Orthod Dentofacial Orthop 1988; 93: 315–324.
11. Lima Filho RM, Lima AL, de Oliveira Ruellas AC. Mandibular changes in skeletal class II patients treated with Kloehn cervical headgear. Am J Orthod Dentofacial Orthop 2003; 124:83–90.

12. Bowden DE. Theoretical considerations of headgear therapy: a literature review. 1. Mechanical principles. Br J Orthod 1978; 5:145–152.
13. Godt A, Kalwitzki M, Goz G. Cephalometric analysis of molar and anterior tooth movement during cervical headgear treatment in relation to growth patterns. J Orofac Othop 2008; 69:189–200.
14. Reitan K. Biomechanical principles and reactions. In: Graber TM, Swain BE (eds). Current othodontic concepts and techniques. Vol. 1, Philadelphia: WB Saunders; 1975:111–228.
15. Klein PL. An evaluation of cervical traction on the maxilla and the upper first permanent molar. Angle Orthod 1957; 27:61–68.
16. Armstrong MM. Controling the magnitude, direction and duration of extraoral force. Am J Orthod 1971; 59:217–243.
17. Ricketts RM. The influence of orthodontic treatment on facial growth and development. Angle Orthod 1960; 30: 103–133.
18. Baumrind S, Korn EL, Isaacson RJ, West EE, Molthen R. Quantitative analysis of the orthodontic and orthopedic effects of maxillary traction. Am J Orthod 1983; 84:384–398.

CIP - Каталогизација у публикацији
Народна библиотека Србије, Београд

61+57

FACTA Universitatis. Series:, Medicine and Biology / editor-in-chief Ljiljana Šaranac. - Vol. 1, No. 1 (1993)- . - Niš : University of Niš, 1993- (Niš : Unigraf-X-Copy). - 29 cm

Dva puta godišnje. - Drugo izdanje na drugom medijumu: Facta Universitatis. Series: Medicine and Biology (Online) = 2406-0526. ISSN 0354-2017 = Facta Universitatis. Series: Medicine and Biology

COBISS.SR-ID 32415756

FACTA UNIVERSITATIS

Series
Medicine and Biology

Vol. 17, N° 2, 2015

Contents

Co-funded by the
Tempus Programme
of the European Union