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MICROBIAL CHARACTERISTICS OF POST-TRAUMATIC OSTEOMYELITIS

[1]Mzia Tsiklauri, [2]Paata Gudushauri, [3]Iamze Taboridze

[1] Grigol Robakidze University, Associate Professor, Georgia

[2]Georgian State Teaching University of Physical Education and Sport Assistant Professor, Georgia

[3] Professor, David Aghmashenebeli University of Georgia, Georgia

E-mail: [1]mzia_tsiklauri@mail.ru, [3]iataboridze@yahoo.com, [3]pa_ata72@hotmail.com

ABSTRACT

Objective: The one of the most important issues in traumatology is prevention and treatment of purulent-septic complications of traumatic diseases.
The aim of our study was to establish correlations between osteomyelitis caused by bacterial flora and immunological factors.

Methods: On the basis of a comprehensive study of bacteriological and immunological data in 100 patients with various etiologies osteomyelitis, using correlation analysis was determined: that the types of microbial complications following trauma and the date of the body's immune system depends on etiological factors. The frequency of microbes is different and depends on the localization of the injury and the surgical intervention.

Results: frequency of the etiological factors in the contingent we studied, was distributed as follows: S. aureus-36,9%, S.Epidermidis-52,4, Ps. aeruginosa 27,4%, E. coli- 13,1%, Proteus- 27,4%. Associated infection (or co-infection e.g. S. aureus+S. Epidermidis, or St.Epidermidisis+Ps. Aeruginosa and etc) occurred in 22.6% of cases. A significantly high correlation coefficient was observed in patients who came to the clinics spontaneously or with delay, as well as with the early onset of the infectious process (up to two weeks) and surgical treatment. It also correlates positively with a decrease of following immunological parameters: NK, CD4+, CD8+ and CD 19+, the leucocytes phagocytic index is reduced and the blast transformation reaction of lymphocytes rate was increased. There is a significant correlation with benign outcome of treatment, which indicates that, the patient was sent for outpatient treatment (R=0, 79).
Keywords: Trauma, Osteomyelitis, Microorganism, Etiological factor, Immune system data.

The one of the most important issues in traumatology is prevention and treatment of purulent-septic complications of traumatic diseases. According to the received data the frequency of purulent complications depends on the severity of the injury and on the body's immune system data, as well as the etiological factors.
Osteomyelitis is a bacterial infection of the bone or bone marrow often resulting in hospital admission. Osteomyelitis may result from contiguous spread of infection from adjacent soft tissues and joints, hematogenous seeding, or direct inoculation of bacteria into the bone as a result of trauma or surgery [1].
The particular importance in this regard is the determination of the interaction of etiological factors with immunological data of the disease.
Conceivably, there may have been major changes in the microbiology, types of osteoarticular infections, and the characteristics of patients at risk. For example, the widespread use of medical devices in orthopaedic surgery and increased life expectancy of the population are all factors related to the increased rates of some osteoarticular infection [2]. Recent changes in the epidemiology, pathogenesis, diagnosis, treatment, and prognosis of this disease have varied according to population [3].
The annual incidence was higher for men than for women and increased with age ($p < 0.001$) [4].
The aim of our study was to establish correlations between osteomyelitis caused by bacterial flora and immunological factors.

Material and methods: We studied 100 patients with chronic osteomyelitis who were in different clinics. Their age was determined from 16 to 80 years. including 79 men, 21 women.We used immunological, bacteriological, clinical-laboratory research methods. We determined of anti-microbial antibodies titer, and etiological factors. The material was processed by correlation analysis method. The correlation was considered reliable If $r>0.25$ ($p<0.05$).
In the study of immune status, we measured immune cells, and used standard flow cytometric methods using two-colors fluorescence on samples of whole blood, it is possible to establish the ranges of absolute numbers of NK, CD3+, CD4+ and CD8+ , CD19+ (T and B- lymphocytes), by the cytofluorometry of "FACSCount" using monoclonal antibodies of the company Becton Dickinson.subsets in the routine laboratory.
NK cell-activating receptors play an important role in the recognition of targets, which transduce the signals necessary for cellular machinery to induce target injury and cytokine production. NK cells (NKT) are cells with natural non-immune killer activity that have signs of T-lymphocytes.

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Immunoregulatory index CD4+/CD8+ as the name implies, reflects the ratio of CD4 + cells (T-helper cells) to CD8 + cells (T-cytotoxic cells).It is a relative indicator that has an approximate value, Its slight increase or decrease does not have an independent diagnostic value. Nevertheless, changes in the index force the clinician to focus on the reasons for the deviation of the indicated index.

For measure sensitive lymphocytes we used the method of lymphocytes blast-transformation reaction (RBLT), which is necessary for patient's inspection with immunologic infringements. It is applied in the different fields of medicine to identification of a sensitization to antigens and may be used for assessing the functional state of human lymphocytes. During this reaction, we used bacterial polysaccharide as an activator of lymphocytes. That is ensured by assessing 72-hour phytohemmagutinin-stimulated lymphocyte blast-transformation reaction (LBTR) by immunocytochemical method in a luminescence microscope in indirect immunofluorescence test. A Ki-67 nuclear antigen marker is Ki-67 monoclonal antibody. The functional capability of lymphocytes is described by a quantity of visualized (light-producing) Ki-67-positive cells having light emission foci in the cell nucleus visualized after the artificial stimulation to PHA proliferation. If the antigen-positive cell value is less than 49%, the lower functional activity of lymphocytes is stated in the individuals suffering the disordered immune status, using the given method enables the early immune diagnosis.

Antimicrobial antibodies were detected by the passive hemagglutination reaction (RPHA) , modified by the Boyden (1952).RPHA is placed in plastic plates or in test tubes with dilutions of the patient's blood serum, to which erythrocyte antigenic diagnosticum is added. Serum dilution occurs as follows1:20, 1:40, 1: 80, 1: 160, 1: 360 and etc.

Phagocytes index of neutrophils. A leukocyte suspension is obtained from the blood in a certain way, which is mixed with the exact number of microorganisms (1 billion microbes in 1 ml). After 30 and 120 minutes, smears are prepared from this mixture and stained according to Romanovsky-Giemsa.

About 200 cells are examined under a microscope and the number of phagocytes that have absorbed bacteria, the intensity of their capture and destruction is determined. The phagocytic index is the percentage of phagocytes that have swallowed bacteria after 30 and 120 minutes to the total number of cells examined. Phagocytic index - the average number of bacteria in the phagocyte after 30 and 120 minutes (produce a mathematical division of the total number of bacteria absorbed by phagocytes by the phagocytic index. Phagocytosis completeness index - calculated by dividing the number of killed bacteria in phagocytes by the total number of absorbed bacteria and multiplying by 100. Phagocytic index: after 30 minutes - 94.2 ± 1.5, after 120 minutes - 92.0 ± 2.5

We studied the following groups of factors: age, localization of trauma, forms of fractures, methods of treatment, indicators of cellular and humoral immunity, etiological factors and etc. The material was processed by Speamen correlation analysis method, what was considered reliable if $r>0.25$ ($p<0.05$). Data were analyzed using the SPSS 23.

Results: Frequencies of etiological factors in patients with osteomyelitis are given in Figure 1.

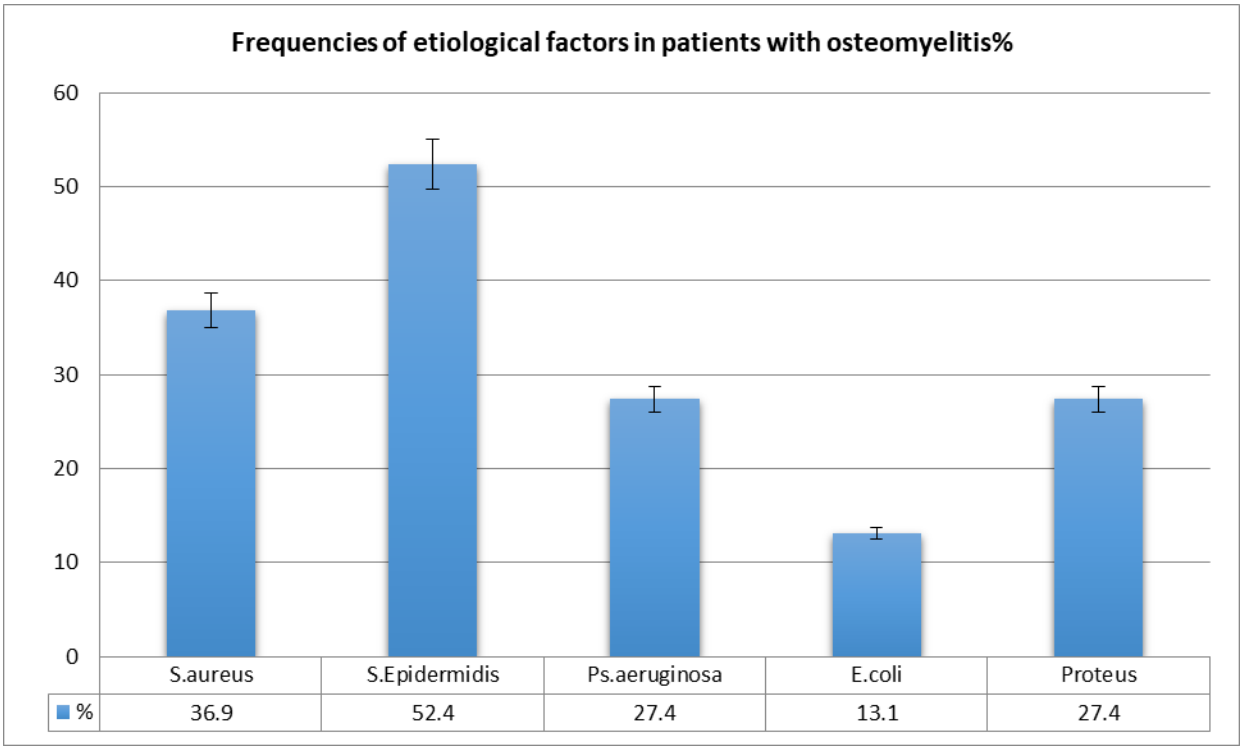

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Figure 1. Frequencies of etiological factors in patients with osteomyelitis%

The frequency of the etiological factor in the contingent we studied, was distributed as follows: S. aureus-36,9%, S.Epidermidis-52,4, Ps. aeruginosa 27,4%, E. coli- 13,1%, Proteus- 27,4%.Associated infection (or co-infection e.g. S. aureus+S. Epidermidis, or St.Epidermidisis+Ps. Aeruginosa and etc) occurred in 22.6% of cases.

The table 1 below shows the correlations between S.Aureus frequency and immunological data during osteomyelitis. S. Aureus predominantly found in 16-30 year old patients, and shows a credible positive correlation with a gunshot and open fractures.

Table 1. Correlations between S. aureus frequencyand immunological parameters during osteomyelitis

N	Name the factors	Correlation - r	N	Name the factors	Correlation - r
1	Age 16-30 years	0.32		General anesthesia	0.90
2	Fracture of femoral neck	-0.40		Anti-microbial antibody titer varied from 1:160 to 1:320 (at norm 1:20)	0.50
3	Fracture of femur	0.252		NK cells >	-0.59
4	Malleolar fractures	-0.33		NK <	0.56
5	Displaced fracture	0.29		CD 3+>	-0.78
6	Open fracture	0.87		CD 3+<	0.81
7	Closed fracture	-0.78		CD 4+>	-0.56
8	Gunshot fracture	0.55		CD 4+<	0.32
9	Fracture of ribs and chest bone	-0.40		CD 8+>	-0.58
10	Entering spontaneously into a clinic	0.74		CD 8+<	0.38
11	Entering toa clinic by ambulance	-0.61		Immunoregulatory index CD4+/CD8+ >	-0.55
12	Entering to a clinic within 24 hours to 2 weeks	0.29		Reaction of blast- transformation of lymphocytes (RBLT) rate (N 6-15%) <	0.41
13	Surgical treatment. due to the secondary purulent process	0.90		Reaction of blast- transformation of lymphocytes (RBLT) rate (N 6-15%) > 15%	0.29
14	Surgical treatment	0.63		CD 19>	-0.78
15	Conservative treatment	-0.81		CD 19<	0.74
16	Local analgesia	-0.72		Factocytic index of neutrophils <	0.51

r>0.25, p<0.05

Table N 2- shows the correlations between the frequency of S. epidermidys and immunological parameters during osteomyelitis.
The frequency of S. epidermis is reliably positively correlated with this localization of trauma: femoral neck fracture, malleolar fractures, rib fracture, brought to the clinic by ambulance, conservative treatment, and local anesthesia.

Table 2. Correlations between S. epidermis and the cells of the immune system during osteomyelitis.

N	Name the factors	Correlation - r	N	Name the factors	Correlation - r
1.	Fracture of femoral neck	0.32	15.	Anti-microbial antibody titer was measured from: 1:160 to 1:320:160-1:320	-0.29
2.	Malleolar fractures	0.44	16.	NK cells >	0.61

3.	Displaced fracture	-0.34	17.	NK cells <	-0.43
4.	Open fracture	-0.62	18.	CD 3 >	0.71
5.	Closed fracture	0.72	19.	CD 3 <	-0.54
6.	Gunshot fracture	-0.47	20.	CD 4>	0.48
7.	Fracture of ribs and chest bone	0.32	21.	CD 4<	0.57
8.	Entering spontaneously into a clinic	-0.62	22.	immunoregulatory index CD4+/CD8	0.53
9.	Entering to a clinic by ambulance	0.64	23.	CD 19 >	0.71
10.	Surgical treatment	-0.41	24.	CD 19 <	-0.52
11.	Conservative treatment	0.73	25.	Factocytic index of leukocytes	0.29
12.	Surgical treatment. due to the secondary purulent process	-0.65	26.	The patients were sending tooutpatient treatment	-0.61
13.	Local analgesia	0.67	27.	Complicated by sepsis	0.66
14.	General anesthesia	-0.65			

$r>0.25$, $p<0.05$

A significantly high correlation coefficient was observed in patients who came to the clinics spontaneously or with delay, as well as with the early onset of the infectious process (up to two weeks) and surgical treatment. It also correlates positively with a decrease of following immunological parameters: NK, CD4+, CD8+ and CD 19+, the leucocytes phagocyte index is reduced and the blast transformation reaction of lymphocytes rate was increased. There is a significant correlation with benign outcome of treatment, which indicates that, the patient was sent for outpatient treatment(r=0.79).
Such a correlation is manifested on the part of immune cells: CD3+, CD4+, CD8+ and CD19 are activated, the immunoregulatory index is also elevated, while the phagocyte index of leukocytes is reduced. The presence of S. epidermis correlates with the development of sepsis r=0,66.
Frequency of purulent process caused by Ps. Aeruginosa shows a positive correlation with open fracture(r=0.34.), as well as with femoral and gunshot fractures (r=0.351 and r=0.35 respectively). Bringing the patient to the clinics by ambulance(r=0,64), general anesthesia(r=0,33), age>60(r=0,34).
E. coli reveals a reliable correlation with lung damage (r=0,27). Proteus Reveals a significant correlation with a fracture of the shin bones (r=0,31), foreign body (bullet, bone fragment or other dense body left in a tissue)(r=0,28), as well as surgical treatment (r=0,28).

Discussion

Osteomyelitis is a bone marrow inflammation, usually caused by an infectious agent. It has a heterogeneous pathophysiology [5].
Chronic bone infections are more often linked with diverse bacterial biofilms [6]. According our study, Frequency of purulent process caused by Ps. Aeruginosa shows a positive correlation with open fracture, as well as with femoral and gunshot fractures. Bringing the patient to the clinics by ambulance, general anesthesia.
The annual incidence was higher for men than for women and increased with age ($p < 0.001$) [7]. According to our data, the majority of patients are male, although **S. aureus** correlates with young age and by Ps. Aeruginosa age >60.
Hypervirulent *K.pneumoniae* linked to osteomyelitys [8]. According this data, E. coli reveals a reliable correlation with lung damage.
Proteus reveals a significant correlation with a fracture of the shin bones, foreign body (bullet, bone fragment or other dense body left in a tissue), as well as surgical treatment.
According to the literature, Staphylococcus aurous was the most common bacteria (64.36%, n=97) followed by Pseudomonas Aeruginosa (17.10%,n=26), E. Coli (11.84%,n=18) and Proteus Mirabilis (7.24%,n=11) [9].
Thus, our research showed that the forms of post-traumatic complications and the reactivity of the organism depend on the etiological factors. The frequency of different etiological factors varies according to the location of the injury and the surgical intervention. The conditions in which the patient enters the clinic have a certain value. High frequency is observed, the risk of complication with S. Epidermidis and P. Aeruginosa in patients who are admitted by ambulance, wile S. Aureus shows a reliable correlation in spontaneously admitted patients.

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METHODS OF EXPRESSING OF LEO TOLSTOY'S PSYCHOLOGISM IN THE PROSE OF 1960-1980 YEARS

Aynur Badalova

PhD student of Azerbaijan State Pedagogcal University, the department of " Literature" on the speciality of "World Literature"

Email: baku_2007@mail.ru

ABSTRACT

If psychologism artistic method has reached to the high level of development in Azerbaijani literature from the second half of the twentieth century, the development of psychologism in world literature dates back to the beginning of the previous century. Thus, the development of psychologism in Azerbaijani prose associates its roots to world literature.
There are many artists in the world literature who write with psychologism method. Many of them can be named. But I would like to focus on the great classic writer Leo Tolstoy. He had influenced to readers' spirit and heart with his works, had an irresistible influence on the development of their personalities by cultivating in them the best human qualities, aroused love to the motherland, people, language, nature and the world. I think that Tolstoy, used the most unique methods of psychologism, also had an impact on Azerbaijani literature. It is more correct to evaluate the manifestation features of psychologism in Azerbaijani prose by conducting comparative analysis. And in this article research has been conducted on the subject of psychologism in L.N. Tolstoy and in the Azerbaijani prose of 1960-1980 within the comparative typological aspect. It had been considered legitimate here identification of not only similarities, but also inconsistencies during the interpretation of the analysis.
In the article, in both Azerbaijani prose and Tolstoy's creativity the heroes' spiritual world have been characterized through expression possibilities of psychologism: internal monologues, dialogues, actions and behaviors, dreams and fantasy, writer's prose, etc., and the heroes' appearance have also been shown as part of the image, to create a fuller imagination. As a result, in both Azerbaijani prose and Tolstoy's creativity, different and similar features in the expression methods of psychologism have been extensively analyzed.
Keywords: hero, psychologism, character, trait, spiritual world.

INTRODUCTION

In the second half of the twentieth century, interest to the man's spiritual world began to show itself more and more in the Azerbaijani literature. The discovery of a complex field and the disclosure from the psychological aspect with the influence of the social environment of human thoughts and feelings showed itself as the main aim in the writers' work. Prose had come to the fore in literature during this period. Stories, narratives and novels had given life to individual characters as the leading genre and had shown a high level of development of psychological imagery in Azerbaijani literature, with reflecting very interesting stories and events. While having a great importance in the works, the psychological aspect had become the main tool for the author in revealing the purpose of the work. If psychologism artistic method has reached to the high level of development in Azerbaijani literature from the second half of the twentieth century, the development of psychologism in world literature dates back to the beginning of the previous century. Thus, the development of psychologism in Azerbaijani prose associates its roots to world literature. It is more correct to evaluate the manifestation features of psychologism in Azerbaijani prose by conducting comparative analysis. And in this article research has been conducted on the subject of psychologism in L.N. Tolstoy and in the Azerbaijani prose of 1960-1980 within the comparative typological aspect. It had been considered legitimate here identification of not only similarities, but also inconsistencies during the interpretation of the analysis.
There are many artists in the world literature who write with psychologism method. Many of them can be named. But I would like to focus on the great classic writer Leo Tolstoy. He had influenced to readers' spirit and heart with his works, had an irresistible influence on the development of their personalities by cultivating in them the best human qualities, aroused love to the motherland, people, language, nature and the world. I think that Tolstoy, used the most unique methods of psychologism, also had an impact on Azerbaijani literature. Because if psychologism method is mentioned, L. Tolstoy should be mentioned in parallel. Of course, before Tolstoy, there was psychologism in literature. But, the development of psychologism began not only in Russian but also in world literature with L.N. Tolstoy. L.Tolstoy developed the inner world of heroes for the first time in literature. With this principle, that N. Chernyshevsky called "the dialectic of the soul", the inner world of the hero began to change with the influence of certain events. Thus, the writer showing the instability of human nature, spoke about the effects of the environment, nature and events took place to the spiritual world of man. The works of the author , easily using all forms of psychological description, had been studied worldwide and had been loved . Of course, L.N .Tolstoy, as a writer who skillfully used psychologism in his creativity, could not remain unaffected to Azerbaijani literature.

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Having a look at the methods of expression of psychologism in both Azerbaijani prose and Tolstoy's creativity, I would like to explore their similarities and differences and to draw a conclusion. First of all, I must say that if L. Tolstoy expresses the changing of the inner world of the hero under the influence of events, certain moments and memories arising from impressions , in Azerbaijani prose, writers took the whole logic of the actions out of the psychological state. I think that the heroes of Azerbaijani prose are happier than Tolstoy's heroes. Their tragedies and misfortunes are connected with their inner worlds and characters, but the tragedy of Tolstoy's heroes is connected with the environment, events and any influences. For example, Banovsha's misfortune is her belief in dreams and legends, Mahmud's tragedy is his purity and clearness, Tahmina's tragedy is her belief in people, Zaur's tragedy is his disbelief in Tahmina, and so on. The tragedy of Tolstoy's heroes is the environment, people and their love. Katyusha Maslova's tragedy begins with people's indifference attitude to her, Natasha's tragedy is Anatol Kuragin's deception her, and the cause of Anna Karenina's tragedy is her great love for her son and Vronsky. But Tolstoy never leaves a hopeless impression on the reader, the reader always hopes that if the situation changes, everything will turn out for the better. Tolstoy described the events in stages in such a way that, the point at which hero's psychological state came was not questionable to the reader. For example, the writer had also prepared the reader for Anna Karenina's suicide at the end by throwing herself under a train. The first impression at the end of the novel was that the ending could not be otherwise. The final is expected and clear. Because the reasons given are correct, complete and precise. The same can be said about the character of Tahmina in Azerbaijani prose. Although Tahmina's death at the end disappoints the reader, it does not surprise her (him). Because it had to be that way. She was not a man of the environment in which she lived, she could not be happy in this environment. Her thoughts, ideas , philosophy were completely different.

One of the main features of psychologism in Azerbaijani prose is to make the reader think. Events and stories are often incomplete, the ending is not clear. The writer makes the reader responsible for analyze the events and draw conclusions. As it happens in the novel "The sixth floor of a five-story house". Many points in the novel remain hidden. Zaur's suspicions are neither denied nor confirmed. To clarify the hidden points fall to reader's lot. At the same time, this form of psychologism is present in Isi Malikzadeh's creativity. Although the events and stories in the writer's narratives and stories are completed, the fate of the hero and the subsequent life remains obscure to the reader. The author commits the reader to draw conclusions about the future of the heroes. L. Tolstoy did not have this. One of the features of psychologism in his works is the details that he carefully describes, so that nothing remains hidden or obscure to the reader.

Tolstoy is a great psychologist. He always pays attention to the moral formation and development of the heroes. In the novel "War and Peace", if Natasha Rostova is a young, impulsive, lovely, happy girl at the beginning of the work, but under the influence of events in her life, she changes a lot. At the end of the novel, she is a serious, quiet, lady, full of beauty, a beautiful mother and a faithful wife. In Azerbaijani prose, the spiritual world of the heroes is unchanging and stable. At the beginning of the work, in what way the author had expressed the character to the reader, at the end of the work, his inner world remains unchanged. The impact of events is felt only in the mood of the character. Thoughts, ideas, and philosophy remain constant.

One of the forms of psychological analysis is the combination of dreams with reality. Dreams and fantasy as being one of the methods of Tolstoy's psychologism manifestation had also showed itself in Azerbaijani prose. In Tolstoy's novel "Anna Karenina", with overlap Anna's terrible dream with the moment of suicide at the end, in Azerbaijani prose, in the "Legend of Gumushgol" Banovsha's seeing Orkhan in a dream and to face with him in reality , or in "White Harbor" Nemat's dream are the same psychological description methods .

In Azerbaijani prose, the hero's inner world is expressed itself in external manifestations: by way of actions and behaviors, mimicry, facial expressions, gestures. In the novel "Deli Kur", Jahandar agha's feelings and attitude to the events were expressed itself in his actions and behavior. The pursing of the lips when Jahandar agha was angry, his losing color like bronze or the blowing of his hands can be an example of this.

The external portrait of the heroes of Azerbaijani prose is a complement to their inner world. The external appearance of the characters does not contradict the internal one. Let's have a look at Mahmud character in the novel "Mahmud and Maryam". The transparency in Mahmud's eyes clued his inner qualities of purity, fairness and clarity or can be given example Nemat character in "White harbor". But the inner worlds of Tolstoy's heroes, on the contrary often do not overlap with their appearance. The Kuragin family in the novel "War and Peace" can be example for this. If Anatol Kuragin is how beautiful and charming in appearance, his inner world is so ugly and unpleasant. Or if Elen is how beautiful and fascinating, her heart is so empty, far from human qualities.

One of the main features of Tolstoy's psychologism is the uncertainty in the characters. Tolstoy's heroes are not as they seem. They can change under the influence of an ordinary moment, and the changes in their lives affect not only their future life, but also their inner world. But in Azerbaijani prose, the characters cannot be changed in any way. They are as they are. Let's pay attention to Zaur character in the novel "The sixth floor of a five-story house". Zaur loves Tahmina very much. But his love cannot influence his thoughts. He is powerless to struggle with his doubts. And finally, his inner world triumphs over love. Because the environment that nurtured him also shaped him. Nothing can change his character. Tolstoy's heroes, on the contrary, are changeable. The writer demonstrates the impacts of the environment, that turned his beloved Katyusha into a prostitute, on her returning to life again and change of her inner world. Or Pierre Bezukhov, Natasha Rostova, Andrei Bolkonsky and others. can be shown example for this.

One of the features of Tolstoy's psychologism is the revelation of the essence of social relations and historical events through the psychology of personality. In Tolstoy's narrative “Haji Murad”, Haji Murad's inner world appears in the background of the struggle with Tsarist Russia and Sheikh Shamil. Or in the novel “War and Peace” many points of the heroes' inner world become clear in the background of the Russo-French war. This method is also widely used in Azerbaijani prose. The heroes of Farman Karimzadeh's novel "Snowy Pass" and Ismayil Shikhli's “Deli Kur” can be shown examples for this. While Karbalai Ismail was fighting against the Soviet government, all the determination and fighting spirit of his character are being skillfully demonstrated by the writer. The same can be said about Jahandar agha. Jahandar agha's struggle against the colonial regime is an indicator of the national spirit in his character.

Tolstoy used to pay special attention to the author's position, the characteristics of psychological details, correct and clear description of the hero's portrait in his creativity. Tolstoy used to note at the end the author's position not only in dialogues, but also in internal monologues. Overlapping of every psychological detail with the man's inner world, while writing artistic work, was one of the main conditions for him. And we attribute these features to Azerbaijani prose, too. All writers express the author's position in their works, and this helps the reader to understand the hero correctly. Psychological details are the same as the hero's character. The heroes' portraits resonate with their inner world.

Tolstoy analyzes in detail his heroes' all feelings and thoughts. He fully expresses their steps, way of life and how they have succeeded in life from the beginning of their childhood. The writer lovingly narrates his heroes' fate. We can observe this clearly in the characters of Nikolenka Irtenyev and Natasha Rostova. In Azerbaijani prose, this aspect is reflected only in some works. In Elchin's novel “Mahmud and Maryam”, the childhood of Mahmud's life is described through the author's speech, Ziyad khan's thoughts, Mahmud's memories. In Azerbaijani prose, the heroes are presented to the reader with their already formed, as stable, unchanging thoughts as they are. Psychologism manifests itself in the works through the heroes' experiences, psychological states, feelings and excitement, emotions, thoughts related to stories, events.

Tolstoy had also expressed the hero's inner world with dialogues, monologues, author’s speech, that these psychological description forms are widespread in Azerbaijani prose, too. In almost all stories, narratives the image of the man's inner world is reflected in the author's speech. In Elchin and Isi Melikzade's creativities this psychological description form is mainly used. Anar had used dialogues and monologues in his creativity very much. In the novel “The Sixth Floor of a Five-Story House”, Tahmina's inner world shows itself in her dialogues with Zaur. Zaur's thoughts, ideas and spiritual experiences have being expressed through monologues.

The development of Tolstoy's heroes from the psychological aspect had been presented in two stages: in the attitude of the heroes to the world and people, and in the contents aimed at analyzing their inner worlds. Psychological development is expressed so in Azerbaijani prose, too. The hero of “Snowy Pass” Karbalai Ismail. The author expresses the invisible aspects of the hero's inner world in his (her) relation to people. In his dialogue with Iman, Karbalai Ismayil can accept no way the fact that these people, who once worked on his land and needed him, now stand face to face and settle accounts with him. Or we see the respect and sympathy of Karbalai Ismail for Abbasgulu Bey, despite his complicated and conflicting relationship with him.

One of the methods to reveal the heroes' inner world used in L. Tolstoy's creativity is internal monologues. Internal monologue is one of the artistic methods of psychologism. The writer tries to create an idea of the hero's spiritual life with this tool, creates a deep image of his inner world, and the reader follows the crisis of the man's psychological state. I would like to note that in Tolstoy's works, the characters' character is revealed through the personality's psychological analysis. For example, in the novel “War and Peace” in Pierre Bezukhov's inner monologues, the hero's psychological state, moral shocks and other emotional states are skillfully expressed. I would like to pay attention to Zaur's inner monologues in the novel “The sixth floor of a five-story house” in Azerbaijani prose. The hero's psychological experiences, and doubts and thoughts that he (she) can only admit to himself (herself) had been demonstrated beautifully. As events unfold in the novel the hero's approach to events is also described through internal monologues.

L.Tolstoy always shows the strengths and weaknesses of the characters' inner world. He does not keep any secret side in his works, he clarifies every mysterious points by expressing a deep explanation of the characters' actions and behavior. A clear psychological description of the heroes' spiritual world is one of the main conditions for Tolstoy. This method was partially used in Azerbaijani prose. For example, in the novel "Mahmud and Maryam", there is no secret side of Mahmud's spiritual world that is not clear to the reader. On the contrary, many aspects related to Tahmina's inner world in the novel “The sixth floor of a five-story house" remain obscure to the reader. Because there are many contradictory points between the character's actions and behaviors and their inner world.

The main and leading method of psychologism in Azerbaijani prose is the discovery heroes' psychology by the author by characterizing characters' actions and behaviors. For example: in I.Shikhli's novel “Deli Kur” he is the author who tells us Jahandar agha's character. The hero's psychology had been expressed through his actions and behaviors. The reader understands the character's inner world, how he evaluates the events, only from his actions. His killing own sister Mrs. Shahnigar, is an indication of how much the hero's sister with her participation in the mullahs' assembly has damaged his self-respect, ego, pride, zeal, and reputation.

Conclusion: Thus, the heroes of both Tolstoy and Azerbaijani prose are people who come from within society with positive and negative qualities. In the article, in both Azerbaijani prose and Tolstoy's creativity the heroes' spiritual world have been characterized through expression possibilities of psychologism: internal monologues, dialogues, actions and

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behaviors, dreams and fantasy, writer's prose, etc., and the heroes' appearance have also been shown as part of the image, to create a fuller imagination. As a result, in both Azerbaijani prose and Tolstoy's creativity, different and similar features in the expression methods of psychologism have been extensively analyzed.

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METHODS OF BIOLOGY TEACHING IN CONNECTION WITH OTHER NATURAL SCIENCES

Vusale Hajiyeva

Doctoral student in philosophy on the Methodology of teaching biology, Azerbaijan State Pedagogical University.

Email: baku_2007@mail.ru

ABSTRACT

This article is devoted to the ways and means of establishing interdisciplinary communication between biology and natural sciences. The main purpose of the research is to explore ways to properly establish interdisciplinary communication in the learning process, as well as in the teaching of biology.
In the field of integration in education, it is impossible to achieve success in teaching different subjects, especially without the use of interdisciplinary communication. Integration has become one of the main principles of training in modern period, as well as the basis of the educational process. Teaching subjects at a coherent pace will increase the effectiveness of the perceptual process, as well as accelerate the formation of motivation in the learning process. Teaching biology in conjunction with other natural sciences will help students to form a correct worldview, as well as create a complete and holistic view of the world. However, special attention should be paid to the establishment of interdisciplinary communication in accordance with the age and individual characteristics of students. For this, the right forms and methods must be used.
The article provides information about these forms and methods, the mechanisms of their use. It is especially important to establish interdisciplinary links, as well as the form in which they are organized to increase the effectiveness of training. Form means the outward expression of the organized activity. Forms of work organized individually, in groups, in groups and in pairs are used during active learning. Depending on the level of difficulty of the topic and the interdisciplinary relationship created, as well as the age and perceptual characteristics of students, the forms of work should be chosen by the teacher at the stage of lesson planning.
In addition, the use of teaching methods in establishing interdisciplinary links is of particular importance. The use of these teaching methods will be of particular importance in the formation of logical, creative, critical thinking in students. Teaching methods include both traditionally used oral, visual, and practical methods, as well as active learning methods used in modern education. Also, the organization of out of class, out of lesson activities and nature excursions is one of the main ways to establish interdisciplinary communication. It is known that it is impossible to fully establish the connection between biology and other natural sciences in the teaching process. The best way to deal with this problem is to turn to out of lesson, out of class activities.
Significance Application: Can be used to properly organize interdisciplinary communication in biology classes in secondary schools.
Keywords: Integration, training, biology, interdisciplinary communication, method

INTRODUCTION

Current research shows that it is very difficult to succeed in the teaching of various subjects, including biology, without the use of integration, especially interdisciplinary communication, in the learning process.
Interdisciplinary integration has a special place in increasing the interest in the learning process, in the formation of students' worldview, as well as in the development of thinking. Integration, which is one of the main principles of education, is also used as a learning tool. This shows that the teacher both builds the lesson on the principles of integration and implements the learning process using integration, making the lesson more memorable.
Ways of connecting biology with other natural sciences means the forms and methods used to create interdisciplinary connections in the learning process.

Different ways of Biology teaching with other natural subjects

It is especially important to establish interdisciplinary links, as well as the form in which they are organized to increase the effectiveness of training. Form means the outward expression of the organized activity. Forms of work organized individually, in groups, in groups and in pairs are used during active learning. Depending on the level of difficulty of the topic and the interdisciplinary relationship created, as well as the age and perceptual characteristics of students, the forms of work should be chosen by the teacher at the stage of lesson planning.

Individual work - during which the student develops the ability to think freely and judge. The student, who understands the connection between the topics at a free pace, clarifies the process and explains his idea using his personal experience. When establishing interdisciplinary communication in the form of individual work, the teacher should pay attention to the coordination of information that is simple and known to students. For example, when explaining the

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"Impact of Climate Change on Plant Life," it is possible to make a geographical connection by asking students individually what seasons are in and how climates change in the seasons.
Working in pairs - In this form of training, students share responsibilities, communicate more closely, cooperate. The information is exchanged between the two students. When establishing interdisciplinary relationships in the form of work for couples, attention should be paid to the establishment of results-oriented relationships. Topics that the two students can discuss and come to a common denominator for can be co-ordinated. Experimental relationships are an example of this. For example, in explaining the "Respiratory Process in Plants", students can both experiment in pairs and clarify energy conversions and the place of oxygen and carbon dioxide in respiration.

Working in pairs - In this form of training, students share responsibilities, communicate more closely, cooperate. The information is exchanged between the two students. When establishing interdisciplinary relationships in the form of work for couples, attention should be paid to the establishment of results-oriented relationships. Topics that the two students can discuss and come to a common denominator for can be co-ordinated. Experimental relationships are an example of this. For example, in explaining the "Respiratory Process in Plants", students can both experiment in pairs and clarify energy conversions and the place of oxygen and carbon dioxide in respiration.

Group work - When organizing group work, the teacher divides the class into two, three or four groups, with 3-6 students in each group. Students discuss, exchange information, and make judgments to better understand the topic. At this time, students develop communication skills, the ability to listen carefully to each other's opinions and to express their opinions. In this form of work, the teacher must create opportunities for students to explore controversial facts and resolve these controversial situations as a result of the interdependence of subjects.

Teamwork - When working with a team, the student focueses to teamwork and gets into habit. They develop respect for each other's opinions and listening skills. When using this form of work, the teacher should be able to comment on difficult issues that he or she will be trying to explain, and be able to incorporate them into the communication process by supporting the team's views in this area. For example: It is known that living things are exposed to various physical influences from the day they are created. Students should be asked what these effects are. For example, temperature, sound, gravitational field, pressure, various rays, magnetic and electric fields. A deeper explanation of these effects should be given by the teacher. What is the gravitational, electric and magnetic fields, the conversion of internal energy into potential and kinetic energy, and so on. should be explained.
Research shows that teachers mainly use individual and collective forms of work when creating interdisciplinary connections. In this case, either information is obtained by contacting the student and a link is established, or the general idea of the team, the way of looking at the topic and the issue is used. Although these forms, in turn, are important, relationships with couples and groups in the form of work create a common denominator for the exchange of information.
The most important way to establish interdisciplinary communication is to choose the right methods. The method is one of the main elements of the teaching process. It is impossible to set up a lesson without using any method. Research is derived from the Greek word methodos, meaning search. Method- A way and method followed to achieve a goal. According to MA Danilov, the method is such a logical rule applied by the teacher that with its help students consciously acquire knowledge, acquire skills and habits. The method, which is a broader concept than methods and tools, is in fact similar to these concepts. It is incorrect to draw boundaries between methods, techniques and tools.

Two main methods in teaching and learning process
In modern times, two forms of methods are used in the learning process. These are
traditional and modern methods. The main objectives of this set of methods are without answering the following questions: What to teach? Whom to teach? How to teach? Müasir dövrdə təlim prosesində iki metod formasından istifadə edilir. Bunlar
Active learning methods used in modern teaching and making the process of lesson building more interesting and interactive, which is the basis of curriculum training, are also of special importance for interdisciplinary communication. These methods are called "Active", "Interactive" and "Active" methods, and all three names are used as synonyms with the same meaning. Active learning methods are built in accordance with teacher-student, student-student interaction schemes. In this process, not only the teacher involves children in the learning process, but also students themselves motivate each other and are in the process of mutual exchange. , the student tries to understand and master the topic by working independently in that direction.
The information is analyzed and synthesized by the pupil, divided into parts and summarized. In the end, a result is obtained. In this process, the teacher simply observes, redirects in dark places, and tries not to make mistakes. The main task of the teacher in this case is to "teach students" to learn. There are many active learning methods to organize active learning. Some of these methods can be devided into some groups as follows:

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1.	Brainstorming methods.	(Braing storming), Auksiyom(Auction), (Kluster), BİBÖ(KWL), (Questioning).
2.	Discussion methods.	(Discussion), (Debate), (Forums)
3.	Role-playing methods (in drama)	(Role play), (Simulation), (Dramatize, Dramas)
4.	Presentation methods.	(Demonstration), (Panels), Esse (Esse)
5.	Research methods.	(Problems solving), (The cube), Venn diaqramı (Venn diagram), (Projects design), (İnterviw)
6.	Təşkilatı metodlar.	(Jigsaw puzzle), (Carousel)

Let's review some examples of these methods:
Brainstorming - the main purpose of these methods is to teach students to explore ways to solve problems, to develop in them the ability to think independently, freedom. During the application of the method, ideas are put forward, those ideas are discussed, and finally the best idea is selected. Students' hypotheses are accepted without criticism. 5-10 minutes are allotted for the method.
This method can be used to create an interdisciplinary link between the environment and the organism. The teacher writes the main question on the board:
How do environmental factors affect human health?
Students note the positive and negative effects of environmental factors on the body. These notes are then collectively analyzed and all suggested ideas are reviewed and summarized. Thus, the impact of these factors on the human body is studied by integrating geography.
Discussion method - in other words, discussion. The main purpose of this method is to discuss conflicting topics between students on the basis of one topic. For this, the teacher creates two groups. These two groups first analyze the different aspects of the topic among themselves. The research is then shared with the team, and both sides try to prove the positive aspects of their research. For example, this method can be used to connect chemistry with topics such as the use of medicines and herbs. Students note the positive and negative effects of drugs on the body. Emphasizes the role of biochemical processes in the body. It seeks to clarify the human effects of chemical compounds in medicinal plants. For example, both the harms of tobacco and its use as a medicine in small doses can be discussed.
One of the methods of role-playing games is modeling. In this method, a small model of any event, process, or area is created, and the topic is explained based on it. This method also plays an important role in the formation of creative ability, as well as in the formation of the final idea about the process or area. For example, by creating models of small water bodies, the deaf will not only study the living things living there, but also observe the geographical structure, landscape, and the influence of the sun on these structures. In this way, the teacher also creates an interdisciplinary connection by recalling geographical knowledge.

Presentation method - These methods help teachers to prepare a lesson in a short time. The lesson is demonstrated using different slides. Another type of this method is the essay method. On the basis of any topic given by the teacher, students enter through independent research, write a free text of 400-600 words consisting of the main part and the result. When teaching the subject of stress in biology, the teacher can ask students to write an essay entitled "Chemical and environmental causes of stress", which can be integrated into chemistry and geography, as well as develop students' research skills.

Interview method - First of all, it is worth noting that at the present time children almost lose their communication skills. In order to partially overcome the current situation, the teacher must be able to partially restore oral speech in the classroom. It is advisable to use the interview method for this. An interview is a conversation in a general sense.
Teachers and students talk about the topic by asking various questions. The main purpose of creating this method is to involve students in the teaching process. Thus, the topic is first explained by the teacher. However, the teacher calls the intentional explanation of some parts, or simply explains it in a simple way. This requires the student to listen more carefully to the lesson. Because the questions to be asked are from the parts that remain obscure and need explanation. At the end, students are asked questions on the topic, either individually or in groups. The questions are recorded on a sheet of paper and collected by the teaching assistants. Questions related to the topic that allow for interesting, interdisciplinary communication and better understanding of the lesson are selected and answered by the teacher. Questions are answered during the lesson, and some questions are given as homework for research. This method can be used to apply interdisciplinary communication. For example, when the teacher explains the digestive system, digestive topics in the stomach and intestines, he simply mentions the names that exist in the lesson and does not explain the

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concepts of chemistry and physics. These concepts, which are not fully understood by the students or are only partially mentioned, are asked by the interviewer to the teacher as a question, and the teacher explains the concept by emphasizing the subject to which the concept belongs. For example: During the explanation of the topic, the teacher notes that there are some enzymes in the stomach. However, it does not explain the concept of enzymes. He then explains the concept of an enzyme based on a question. Note that the enzyme is a biological catalyst of a protein nature. It is involved in biochemical reactions and speeds up the process. The enzymes in the stomach are pepsin, chymosin and lipase. Each of them breaks down different substances. As an interesting fact, the teacher can point out that in most cases, the names of enzymes are corrected by adding the suffix "aza" to the end of the substance they affect.

For example, the enzyme that affects lipids is called lipase, and the enzyme that affects lactose is called lactose. The teacher then notes that during digestion in the small intestine, only the breakdown substances diffuse into the blood. It does not reveal the essence of diffusion. Based on the questions, it clarifies this physical process once again. The process by which particles penetrate each other is called diffusion. Diffusion occurs in gases, liquids and solids. Changes in the state of these aggregates also affect the rate of diffusion. The teacher also notes that diffusion in liquids and gases occurs due to Brownian motion. Brownian motion is an event that confirms that matter is made up of atoms and molecules. The regular motion of small particles of snake suspended in liquids is called Brownian motion. Organizational methods are methods in which the teacher divides students into several groups and coordinates the class. One of the organizational methods is the zigzag method. In this method, which serves to learn the lesson more comprehensively in a short period of time, students are actively involved in solving the problem, they develop a sense of self-confidence. In the zigzag method, the class is divided into 4 groups.

At the same time, each member of the group is numbered 1, 2,3,4. The topic is divided into 4 parts and one part is given to each of the 4 members in the groups. The teacher explains that the students in groups 1,2,3,4 are expert students and must read, understand and learn the given text. To do this, all students with the same number should come together, read and discuss the topic, and then return to their groups and inform the other students about it. Finally, the topic should be generalized and logically combined. This method should be used when explaining more difficult and extensive topics. For example, this method can be used to teach geography and to make the lesson easier and more interesting. After dividing the students into groups according to the above procedure, each expert student is given a series of sections on the struggle for survival and intensive reproduction, intraspecific struggle, interspecific struggle and struggle with unfavorable environmental conditions. They are also instructed to find new patterns for each part at a free speed. Based on the information provided, students find new examples and, when they return to their groups, introduce them to those parts and teach them. In the end, the information is summarized. And the final conclusion is prepared. Another way to establish interdisciplinary communication is to integrate in extracurricular, after classes activities and excursions (field trips).

As the natural sciences are difficult subjects, their full integration into the teaching process will make it difficult to use both lessons and time efficiently, and will lead to deviations from the program. For this purpose, it would be expedient to create integration in extracurricular activities and excursions. In these forms of work, more emphasis should be placed on practical material, topics that are difficult to master, interesting and relevant in modern times. These can be about global environmental problems, food shortages, chemical and biological weapons, and so on.

Excursions have a special place in biology classes. When organizing a trip, the teacher must determine the purpose of the tour and prepare a special plan. Excursions are a universal form for all school subjects. During the organization of excursions to "food" factories, as well as to greenhouses, students will clearly see the inter-connection and commitment of physical, biological and chemical processes.

Result: The above information suggests that there are many ways to integrate biology with other natural sciences. These ways are as follows:

1. Forms of work - individual, pair, group, collective.
2. Traditional and active learning methods.
3. Extracurricular, extracurricular activities.
4. Excursions.

These ways, methods have an important role in organization learning process and implementation of integration, it is important to use these paths and tools properly. First of all the teacher should do the followings:

1. Be able to choose the right forms and methods of work;
2. The tools chosen should be appropriate to the age and individual characteristics of the students;
3. The complexity and breadth of the topic should be taken into account.

The information provided will be of great importance in the construction of the teaching process by teachers in secondary schools and will facilitate the process.

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BIOLOGICAL AGENTS DURING ATOPIC DERMATITIS THERAPEUTICAL MANAGEMENT

Maia Matoshvili, Davit Tophuria, Inga Kakhniashvili

Dermato-Venerology Department, Human Normal Anatomy Department Tbilisi State Medical University.

Email: mmatoshvili@hotmail.com; datotopuria1981@yahoo.com

ABSTRACT

The complicated form of atopic dermatitis, which affects adults so children, is a debilitating disease with a significant decline of patients' quality of life. Etiological factors are currently a topic of study and interpretation, the main features of atopic eczema are skin barrier disturbance and immune dysregulation. Severe refractory disease that fails to improve with conventional therapy may benefit from biologic therapy. Progress in understanding immunopathology of atopic dermatitis have allowed identification of therapeutic molecular targets in the field of biological therapy. Our reviewe is about different biological treatments with a focus on novel targeted agents: Systemic immunotherapy (Omalizumab, Dupilumab, Lebrikizumab, Tralokinumab, Nemolizumab, Ustekinumab, Fezakinumab, Tezepelumab, Apremilast, allergen specific immunotherapy), and topical agents (Tofacitinib, Crisaborole).
Keywords: Dermatitis, atopic; Biological agents.

INTRODUCTION

Atopic dermatitis (AD), also known as atopic eczema is a common chronic or recurrent inflammatory skin disorder with a significant social and economic impact worldwide, affecting 2.1–4.9% of adult population, and 15–20% of children (1,2). An increasing prevalence of AD has been reported, especially in low-income countries (3). Furthermore, the past decades brought a 2–3-fold increase in prevalence in industrialized countries (3). Generally AD onset is in early childhood, as one of the first steps of the 'atopic march', which describes the natural history of atopic manifestations, and it is characterized by xerotic skin and acute flare-ups of intensely pruritic eczematous lesions (4). Recent studies recognize a predilection of AD for persistence in adulthood, with a lifetime prevalence accounting for 34.1% Recent years brought significant improvement in elucidating the complex interactions between skin barrier, genetic and environmental factors. The better understanding of pathologic pathways is a stepping-stone to improved management for AD patients. The goal of this review is to summarize the topic of severe refractory atopic dermatitis from the perspective of novel therapeutic immunomodulatory methods: IgE directed therapy (Omalizumab), anti IL-4 (Dupilumab) and anti IL-4/IL-13 agents (Lebrikizumab, Tralokinumab), IL-31 directed therapy (Nemolizumab), anti IL-12/23 (Ustekinumab), IL-22 blockade(Fezakinumab), thymic stromal lymphopoietin directed therapy (Tezepelumab), phosphodiesterase inhibitors (Apremilast, Crisaborole), and JAK inhibitors (Tofacitinib).

Methodology: Mepolizumab, a humanized monoclonal anti-IL-5 antibody, Rituximab, a chimeric monoclonal antibody against CD20, a pan marker of B lymphocytes, as well as inhibitors of tumour necrosis-α factor/receptor (TNF-α), such as Infliximab, Etanercept, and Adalimumab, brought moderate and intermittent improvement of AD. High-dose intravenous immunoglobulins (IVIGs) were investigated for their immunodulatory effects in moderate to severe AD, and failed to bring significant improvements. Earlier studies on recombinant human interferon-γ (rhIFN-γ) proved its efficacy in reducing clinical severity of AD. However, rhIFN-γ is not currently approved by the FDA for AD. T-cell modulating agents, such as Efalizumab and Alefacept failed to bring spectacular results in adult patients with moderate to severe AD. In addition, Efalizumab was voluntarily withdrawn from the market because of the risk of severe neurological adverse reactions caused by reactivation of the John Cunningham human polyoma virus .

Allergen-specific immunotherapy: There is still controversy regarding the use of allergen immunotherapy (AIT) in AD patients. Data suggests that AIT improves the clinical course of AD, pleading for its potential form of treatment. Case reports and small cohort studies showed effectiveness of AIT on AD. A multi-centre randomized study that enrolled 89 adult patients with AD and sensitization to house dust mites, of whom 51 completed the study, assessing the usefulness of AIT, observed the improvement of disease and a reduction in the need for topical corticosteroids. A meta-analysis of eight randomized trials that included 225 patients brought moderate-level evidence for the efficacy of AIT in AD. As shown by a prospective placebo-controlled study that included 168 patients with AD, AIT is beneficial only in severe AD, with a SCORAD score greater than 50. A systematic review using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach reported improvement of clinical symptoms of AD. However, the study also noted the strength of recommendation for use of SIT in patients with AD as weak, pinpointing the need for high-quality evidence to support AIT in AD. Several studies on sublingual immunotherapy in AD patients bring arguments in favour of AIT as a safe and effective strategy. There are no contraindications for AIT in AD; AIT does not worsen AD.

Novel topical agents for AD:1.Tofacitinib-Initially approved for the treatment of rheumatoid arthritis, Tofacitinib, an oral small-molecule JAK inhibitor that acts by blocking several Th2 cytokine signalling (IL-4, −5 and −13), shows promise in AD. Many of the cytokines involved in AD use JAK biological pathways. The latter encompasses several tyrosine kinase proteins that interact with the common γ-chain of cytokine receptors to initiate cytokine mediated responses.
Crisaborole-A topical PDE inhibitor ointment, has been approved by the FDA in the topical treatment of AD patients of at least 2 years of age. It proved to reduce skin inflammation and pruritus, as compared to controls, with the disadvantage of being less effective than low potency topical corticosteroids (10). In contrast to topical corticosteroids, topical PDE inhibitors do not pose the risk for telangiectasia and skin atrophy.
CONCLUSION: Atopic dermatitis poses a challenge for clinicians and patients alike, particularly in severe forms of disease. Recent progresses in understanding the pathophysiology of atopic dermatitis underlie its multiple facets and allow the introduction of novel substances for the systemic and topical treatment of severe atopic dermatitis. New therapeutic strategies brought tremendous advances in the management of refractory to conventional treatment, severe atopic dermatitis. Robust evidence pleads for efficacy of Dupliumab, while other immunomodulatory agents, such as Nemolizumab, Lebrikizumab, Tralokinumab, Ustekinumab and Apremilast show promise, but further data are needed to confirm their usefulness and safety in atopic dermatitis. Allergen specific immunotherapy may be of use in selected cases of atopic dermatitis.

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DEVELOPMENT AND APPLICATION OF STEM CELL TECHNOLOGIES DURING SKIN WOUNDS HEALING

Maia Matoshvili, Davit Tophuria, Nino Adamia

Dermato-Venerology Department, Human Normal Anatomy Department, Pediatrics Department. Tbilisi State Medical University.

Email: mmatoshvili@hotmail.com; datotopuria1981@yahoo.com

Abstract

The main clinical focus of stem cell application in wound care is to target improved quality of wound healing. The medical practitioner would anticipate achieving acceleration in healing, prevention of wound contracture and scar formation, earlier wound closure, and ideally regeneration of the skin and its appendages using stem cells.]. Stem cells, defined based on the findings obtained by McCulloch and Till, are characterized by their capacity for self-renewal, asymmetric replication, and differentiation to other cells building different tissues and organs.
Keywords: Stem Cells, wound Healing, regeneration

Background Stem cells replenish lost cells throughout an organism's lifespan. They have the capacity for unlimited replication providing a population of "sister" SCs. These cells are responsible for self-renewal and differentiate tissue-specific cells. This process maintains the constant number of aging somatic cells, which have become apoptotic. Their therapeutic potential is largely due to their capability to secrete pro-regenerative cytokines, causing them to be an attractive choice for the treatment of chronic wounds [1]. Among the main sources of cells that might be used for wound healing and regeneration of injured skin are embryonic stem cells (ESCs), induced pluripotent stem cells (iPS), and adult stem cells [2]. However, the remaining challenge of stem cell application for skin regeneration is still to describe the optimum source and the method of processing and administration from a clinical standpoint and to define the roles of stem cells in the real clinical situation [3-5]. Table 1 shows stem cells used for wound therapeutic. Embryonic stem cells (ESCs)-the ESCs were first established from the inner cell mass (ICM) of mouse blastocysts in 1981, and the term "embryonic stem (ES) cell" was coined. ES cells are pluripotent stem cells derived from the inner cell mass of the preimplantation blastocyst (35-day-old embryo) and obtained from mice, humans, and nonhuman primates. ES cells have the ability to differentiate cell types, including neural cells, blood cells, adipocytes, chondrocytes, muscle cells, and skin cells. In an attempt to utilize the remarkable regenerative potential of ESCs for cutaneous repair, Guenou et al. showed that human embryonic stem cells growing in induction medium containing BMP4 (bone morphogenetic protein-4) and ascorbic acid could differentiate between basal keratinocytes, which were subsequently used to reconstitute the epidermis composed of multiple layers of differentiated cells. These tissues were also successfully transplanted into nude mice to facilitate wound healing. In another report, Shroff et al. evaluated the effect of human embryonic stem cell (hESC) therapy in six patients with non-healing wounds. It showed that the wounds of all the patients healed after receiving hESC therapy. Reduction in the size of wounds and granulation was observed among all the patients [5.6]. Despite these promising findings, the use of embryonic stem cells has remained controversial. The cells could be the most suitable ones over adult stem cells for skin tissue regeneration owing to their capacity of self-renewal and the unlimited supply of differentiated keratinocytes or keratinocyte progenitors for treating cutaneous injuries [7]. In addition to the widespread clinical use of ESCs, which is currently elusive due to the potential for immunogenicity and tumorigenicity, another major limitation of using ESC-derived cells for regenerative wound healing is ethical controversy and substantial legal restrictions [8]. Induced pluripotent stem cells (iPS cells)-The iPS cells are the newest class of pluripotent stem cells, which potentially combines the advantages of MSCs and ESCs, ushering in a new era of regenerative medicine [6]. In 2006, Yamanaka et al. at Kyoto University in Japan observed that the introduction of four genes (Oct-3/4, Sox2, c- Myc, and KLF4) into cells from the mouse tail could reprogram the cell back to an embryonic state. In 2007, iPS cells were produced from human cells These induced pluripotent stem cells were shown to be remarkably similar to ESCs in morphology, proliferation potential, gene expression pattern, pluripotency, and telomerase activity. Like ESCs, iPSCs can differentiate between all types of cells from the skin to nerve and muscle [7]. This revolutionary technology allows for generation of autologous pluripotent stem cell populations, thereby circumventing the major limitations of ESC, including ethical concerns and potential for immunological rejection. Taking advantage of these characteristics, significant progress has been made in the differentiation of iPSCs into skin cells—including folliculogenic human epithelial stem cells, fibroblasts, and keratinocytes—to engineer skin substitutes [10]. Bilousova et al. induced iPS cells in vitro to differentiate skin-like cell lines and to form multi-differentiated epidermis, hair follicles, and sebaceous glands. Additionally, Itoh et al. generated in vitro 3-D skin equivalents exclusively composed of human iPSC-derived keratinocytes and fibroblasts. Two recent studies conducted by Umegaki-Arao et al. and Sebastiano et al. have further proven this concept. One of the most recent studies in this regard suggested that exosomes derived from human-induced pluripotent stem cell-derived mesenchymal stem

cells (hiPSC-MSCs) facilitated cutaneous wound healing in rats by promoting collagen synthesis and angiogenesis [9]. However, despite experimental evidence supporting the therapeutic benefits of iPSCs, there are still numerous issues such as associated cancer risk development through using retroviral vectors, epigenetic memory retained from parent cells, genetic instability, inefficient cell re-programming yielding low cell numbers with high processing costs, and potential immunogenicity [10].

Methodology: Therefore, iPSC-based therapies for wound-healing applications require further extensive analyses for safety and reliability of the reprogramming technology. Adult stem cell-the most stem cells used in skin regeneration and wound healing are adult stem cells owing to containing significant proliferative capacity, long-term self-renewal potential, and having the ability to differentiate into other lineages. They are found in various tissues, including the skin, heart, liver, brain, and bone marrow. Among the different types of adult stem cell, mesenchymal stem cells (MSCs) and adipose-derived stromal cells (ASCs) have gained considerable attention as a suitable candidate to enhance tissue regeneration. Mesenchymal stem cells (MSCs)-MSCs harvested from various sites (bone marrow, adipose tissue, amniotic fluid, and dermis) are considered a source for therapeutic approaches owing to their multilineage differentiation, high frequency, facility of isolation and characterization, and the ability of MSCs to migrate to injury sites in the body. These cells are involved in all three phases during the wound-healing process. They also enhance wound healing by immune modulation, production of growth factors, which enhance neovascularization and re-epithelialization, stimulate angiogenesis, and accelerate wound closure. One case study has reported that increased wound closure occurs when MSCs are administrated and accelerated dermal fibroblast and keratinocyte migration . Furthermore, Nakagawa et al. suggested that the combination of hMSCs with bFGF in a skin defect model improved cutaneous wound healing as the hMSCs transdifferentiate into the epithelium. Smith et as showed that MSCs secreted soluble factors inducing dermal fibroblast proliferation, migration, and chemotaxis. Endogenous bone marrow-derived mesenchymal stem cells in the dermis may provide an important early signal for dermal fibroblast responses to cutaneous injury. Li et al. demonstrated that activated MSCs promoted wound healing in acute incisional wounds, as reflected in regained tensile strength. A clinical study was performed to test a new technique for the treatment of chronic non-healing wound (diabetic ulcer) using autologous graft composed of autologous skin fibroblasts on biodegradable collagen membrane (Coladerm) in combination with autologous MSC derived from the patient's bone marrow. The wound showed a steady overall decrease in wound size and an increase in the vascularity of the dermis and in the dermal thickness of the wound bed after 29 days of combined treatment. The treatment of burn injuries, especially severe ones, has always been a challenging issue, but the use of MSCs had beneficial therapeutic effects on burns wound healing. A case report of radiation burns has indicated the efficiency of a new therapeutic approach combining surgery and local cellular therapy using autologous MSCs, which this benefit of the local cell therapy could be linked to the "drug cell" activity of MSC by modulating radiation inflammatory processes. During the normal wound-healing process, angiogenesis is one of the most important stages in which MSCs secret various pro-angiogenic factors such as VEGF to promote endothelial cell proliferation and form new vessels. There is evidence that suggests topical VEGF accelerates diabetic wound healing through increased angiogenesis as well as mobilizing and recruiting bone marrow-derived cells. likely by regulating most a network of several angiogenic molecules. Experimental studies established that MSCs could orchestrate the inflammatory response following tissue injury. Transplantation of human umbilical cord MSCs into cutaneous rat wounds significantly accelerated wound healing and remarkably decreased the quantity of infiltrated inflammatory cells and levels of IL-1, IL-6, and TNF-a and increased levels of IL-10 and TSG-6 in wounds.

Conclusion: Bone marrow-derived stem cells (BM-SCs)- BM-SCs are considered the primary source of MSCs in adults and a good candidate for the treatment of different types of wounds. Preclinical studies using autologous BM-MSC have reported the potential therapeutic effect of these cells in dermal rebuilding and scarring reduction in chronic wound Although BM-MSC is successfully implemented in clinical treatment, other limitations in therapeutic efficacy are challenges that need to be addressed through an extensive investigation of BM-MSC. The risks of BM-MSC during clinical translation are harvesting invasiveness, in vitro culture, and further cost-time resource.

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FACTORS RELATED TO DERMAL REGENERATION

Maia Matoshvili, Davit Tophuria, Natia Kvizhinadze

Dermato-Venerology Department, Human Normal Anatomy Department, Pharmacy Department. Tbilisi State Medical University. Georgia.

Email: mmatoshvili@hotmail.com; datotopuria1981@yahoo.com

ABSTRACT
Normal wound healing is a dynamic and complex multiple phase process involving coordinated interactions between growth factors, cytokines, chemokines, and various cells. Any failure in these phases may lead wounds to become chronic and have abnormal scar formation. Chronic wounds affect patients' quality of life, since they require repetitive treatments.
Keywords: Growth factors, Interleukins, wounds

Background: For develop better substitutional medical approaches to improvement of injured skin tissues, regenerative medicine applications have been widely investigated. Regenerative therapies consist of different technological approaches such as gene targeting, stem cell treatment, soluble molecules, cell reprogramming, and tissue engineering [1]. In particular, a basic principle for these applications is using engineering techniques to facilitate a natural wound-healing cascade by providing proper physicochemical and biochemical factors [3]. A number of bioactive factors, including growth factors and cytokines, are involved in various tissue repair stages and are necessary to promote dermal regeneration. Cytokines are extracellular signaling proteins secreted by many cell types affecting the activity of other cells, including immune cells. They include interleukins, lymphokines, interferons, and tumor necrosis factor. The study of cytokines in wound healing is challenging, since examination of isolated cytokine responses in the human body usually represents an oversimplification of the phenomena. Additionally, modifying the healing process by regulating the cytokine milieu is a considerable challenge, since cytokine responses depend on time and concentration in the wound bed [2]. Growth factors are signaling proteins that release at the wound site and are required for communication between various cells such as smooth muscle cells, fibroblasts, myofibroblast, keratinocytes, endothelial cells, and immune cells. They can induce angiogenesis supplying oxygen and nutrients to cells transplanted for organ substitution to maintain their biological functions [4]. Different studies on human patients have confirmed that growth factors such as PDGF are involved in enhancing the wound-healing rate in acute wounds and even provide complete healing in chronic wounds [5]. Therefore, the development of regenerative medicine applications with the aid of exogenous growth factors could be an alternative clinical solution for skin regeneration. Transforming growth factor beta (TGFβ)-the TGF-β superfamily consists of 33 members. In mammals, mainly TGF-β1, β2 and β3 isoforms are found, but TGF-β1 predominates in cutaneous wound healing. They are produced by macrophages, keratinocytes, fibroblasts, and platelets].

Methodology: These three isoforms share 60–80% homology and are encoded by different genes. All three isoforms are believed to bind and signal through the two TGF-β receptors (TβRI and TβRII). TβRI activates the SMAD intracellular signaling pathway through Phosphorylation of Smad2 and Smad3 binding to Smad4, translocates into the nucleus, and activates transcription of target genes [65]. TGF-β can also activate a number of nonSmad signaling pathways, including ras/MEK/ERK, which requires the heparan sulfate-containing proteoglycan (HSPG) syndecan 4; p38, which requires the HSPG β-glycan; and c-Jun N-terminal kinase (JNK), which requires focal adhesion kinase and TGF-β-activated kinase (TAK) [66]. Much of the current knowledge on TGF-β action in wound healing has been obtained from animal studies using incisional and/or excisional wound models [6]. Preclinical studies indicated a significant reduction in scarring and considerably improved dermal architecture after intradermal injection of avotermin (TGF-β3) in adult rats. In adult mammals, high levels of TGFβ1 and TGFβ2 and low levels of TGFβ3 facilitate scar-forming healing, while in fetal mammals, high levels of TGFβ3 and low levels of TGFβ1 and TGFβ2 favor scar-free healing [7]. Other evidence support the involvement of TGFβ in regeneration, including using the potent small molecule inhibitor [8] and experiments with zebrafish [69]. Overall, these experimental observations support the role of TGFβ signaling in wound healing, including both non-specific scar formation and tissue-specific regeneration [7]. Vascular endothelial growth factor (VEGF)-the VEGF is the most important signaling growth factor in angiogenesis and vasculogenesis. VEGF is involved in wound healing and is secreted by platelets, macrophages, fibroblasts, and keratinocytes [59]. The VEGF family consists of VEGF-A, VEGF-B, VEGF-C, VEGF-D, and VEGF-E and placental growth factor. VEGF-A is one of the most potent proangiogenic molecules in the skin. It has been widely investigated as an exogenous cargo growth factor for skin tissue regeneration [60]. VEGF-A is a 45 kDa heterodimeric heparin-binding protein. Multiple isoforms of VEGF-A can be generated through alternative splicing. VEGF-A interacts with multiple receptors, including VEGF receptor-1 (VEGFR-1) and VEGF receptor-2 (VEGFR-2). These are tyrosine kinase receptors that differ in their ligand binding properties and tyrosine kinase activity. Although VEGF-A binds VEGFR1 with a higher affinity than VEGFR-2, VEGFR-2 exhibits stronger inherent tyrosine kinase activity. VEGFR-2 is believed to be more important than the two receptors in terms of controlling endothelial cell function and regulating angiogenesis based on its superior ability to stimulate downstream signaling cascades. On ligand binding,

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VEGFR-2 dimerizes, resulting in kinase activation and autophosphorylation of tyrosine residues. Phosphorylation of these residues leads to activation of protein kinase B (inhibits apoptosis), the mitogen-activated protein kinase (MAPK) pathway (induces proliferation), Src kinase, focal adhesion kinase, and p38 MAPK (leads to cell migration). It has been demonstrated that VEGF acts as an important regulator of angiogenesis (physiological and pathological) by inducing proliferation of fibroblasts and endothelial cells as well as by promoting neovascularization, re-epithelialization, and collagen deposition. Artificial three-dimensional scaffolds have been used as efficient dermal regeneration templates f to treat skin defects created by burns, trauma, and chronic diseases in regenerative medicine. Inadequate angiogenesis is often caused during application of such scaffolds. Tan et al. used collagen scaffolds with VEGF in a diabetic rat wound model and found that the treatment resulted in an enhanced healing rate, improved vascularization, and increased level of VEGF in the granulation tissue. Using plasmid DNA encoding activated VEGF-165 in collagen-chitosan dermal equivalents to treat the full-thickness burns could result in a significantly higher number of newly formed and mature blood vessels, enabling fast regeneration of the dermis. Platelet-derived growth factor (PDGF)-the PDGF is an important biochemical mediator of wound healing and promotes cellular reactions throughout all phases of the wound-healing process. PDGF is known to improve dermal regeneration, promote local protein and collagen synthesis, and cause angiogenesis. PDGF comprises a family of homodimeric or heterodimeric growth factors: PDGF-AA, PDGF-AB, PDGF-BB, PDGF-CC, and PDGF-DD. It is mainly secreted from the α-granules of the platelet, but it is also released by different cells such as keratinocytes, macrophages, fibroblasts, and endothelial cells [6]. There are two PDGF receptors (PDGFR), PDGFR-alpha (PDGFRA) and PDGFR-beta (PDGFRB), engaging several well-characterized signaling pathways such as Ras-MAPK, PI3K, and PLC- γ, which are known to be involved in multiple cellular and developmental responses [7]. Dermal fibroblasts are one of the major target cells of PDGF in initiation and propagation of skin tissue repair. They secrete PDGF-BB and express PDGFRB receptor. PDGF-BB stimulates Wnt2 and Wnt4 mRNA expression. In terms of its relevance to wound healing and skin tissue regeneration, PDGF-BB exhibits chemotactic, mitogenic, angiogenic, and stimulatory effects, leading to modification of the extracellular matrix by stimulating collagen, collagenase, and glycosaminoglycan synthesis [8]. PDGFRB targeted deletion studies into dermal fibroblasts have demonstrated its role in transducing wound-healing signals accounting for an 85% reduction of granulation tissue mass [9]. Therefore, wound treatment using exogenous PDGF has been studied by developing a cellular collagen-chitosan temporary matrix of a wound site for in vivo dermal regeneration. This study suggested that PDGF supplementation could have altering effects on oxidative events depending on the duration of the wound-healing process [8]. In another study, a combination of AMD3100 (which mobilizes marrow-derived progenitor cell) and PDGF-BB therapy has been synergistically shown to improve progenitor mobilization and trafficking, resulting in significantly improved diabetic wound closure and neovascularization [10]. Fibroblast growth factor (FGF)-the FGFs include a family of polypeptides growth factors which have been demonstrated to have considerable capability in tissue repair and regeneration. It was originally identified to induce proliferation and differentiation in various types of the cell. The interaction of FGFs with their receptor tyrosine kinases (FGFRs) in the presence of heparin/heparan sulfate (HS) proteoglycans (HSPG) as a cofactor results in activation of FGFRs by phosphorylation of tyrosine residues. Activated FGFRs lead to triggering a number of signaling pathways such as the RAS/MAP kinase pathway, PI3 kinase/AKT pathway, and PLCγ pathway, resulting in specific cellular responses. Regeneration is controlled by a different type of growth factors among which FGFs are the key players in tissue regeneration, including the neural, liver, bone, skin, intestine, cardiac, and muscle. According to the amino acid sequence, the FGF family is divided into seven subfamilies. However, FGF2 (basic FGF) is indicated to be widely applied for scarless wound healing and skin wound regenerative therapy. It has been reported that the sustained release of basic FGF from a chitosan film as a delivery vehicle could accelerate wound healing in full-thickness skin wounds made on the backs of genetically diabetic mice and promote proliferation of fibroblasts and granulation tissue formation. In another study, incorporation of bFGF with gelatin microspheres significantly accelerated dermal tissue regeneration. Furthermore, studies have identified that FGFs are key regulators of keratinocyte migration in wounded skin, as the loss of FGFR1 and FGFR2 in keratinocytes results in a wound-healing defect [10]. Hepatocyte growth factor (HGF)-the HGF was originally discovered as a mitogen of hepatocytes to be produced by stromal cells. HGF stimulates many properties of the epithelial cell, including proliferation, motility, morphogenesis, and angiogenesis via tyrosine phosphorylation of its receptor, tyrosine-protein kinase Met (c-Met) [9]. The mature form of HGF is composed of α/β heterodimers linked by a disulfide bond. The α-chain contains an N-terminal hairdomain and first Kringle domain and exhibits a high-affinity binding site for Met, and the β-chain has a serine protease-like structure; although the α-chain is required for Met binding, it is not able to activate Met and the β-chain induces the activation of Met and biological responses [9]. The binding of HGF to its receptor, c-Met, results in structural changes in c-Met and phosphorylation of protein tyrosine kinase (PTK) domain. Subsequently, two other phosphotyrosines in the carboxy-terminal multifunctional docking domain recruit intracellular signaling molecules Grb2 (growth factor-receptor-bound protein 2), Gab1 (Grb2-associated binder 1), phosphoinositol 3-kinase (PI3K), MAPK, PLCγ (phospholipase Cγ) and Shp2 (SH2-domain-containing protein tyrosine phosphatase 2), signal transducer and activator of transcription factor (STAT) pathway. Therefore, c-Met and its related signaling pathways play a crucial role in the diverse process, including embryogenesis, wound healing, organ regeneration, and mature tissue survival. It promotes mitogenic, morphogenic, and mitogenic activity in various cell types. HGF/Met contributes to immune regulation by modulation of DC migration and activation of monocytes and macrophages. HGF is a cytokine known to play multiple roles during the various stages of wound healing and accelerates wound healing by promoting the dedifferentiation of epidermal

cells through1-integrin/ILK pathway [9]. According to this study, HGF increased the expressions of the cell adhesion molecules 1-integrin and the cytoskeleton remodeling protein integrin-linked kinase (ILK) in epidermal cells in vivo and in vitro. Baek et al. [98] demonstrated that Met signaling in skin-resident DCs was essential for their emigration toward draining lymph nodes upon inflammation-induced activation. These findings were supported using a conditional Met-deficient mouse model where activated skin resident DCs failed to migrate toward the skin-draining lymph nodes despite an activated phenotype. Epidermal growth factor (EGF)-the EGF is primarily secreted by platelets, macrophages, fibroblasts, and keratinocyte and is present during dermal wound healing and facilitates skin regeneration. The binding of EGF to EGFR activates EFGR through ligand-induced dimerization, leading to a downstream signaling cascade, including Ras/MAPK, PLCγ/PKC, PI3K/Akt, and STAT [9,10].

Conclusion: These signaling pathways are classified into four different categories: migration, proliferation, cytoprotection, and EMT among which migration and proliferation pathways have been required for wound healing [10]. EGF is influenced by different components of the keratinocyte migration machinery and induces contraction of keratinocytes, which are critical to wound re-epithelialization. Despite extensive progress in the exogenous EGF in the treatment of acute wounds, its efficacy in chronic wound therapy is limited owing to their short half-life in vivo and poor transdermal permeability. To overcome these restrictions, EGF was conjugated to an efficient delivery system to extend the residence time of EGF in the wound area and significantly regenerated skin tissue.

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NOVEL AND DEVELOPING THERAPIES FOR ATOPIC DERMATITIS

Maia Matoshvili, Davit Tophuria

Dermato-Venerology Department, Human Normal Anatomy Department, Tbilisi State Medical University

Email: mmatoshvili@hotmail.com; datotopuria1981@yahoo.com

ABSTRACT
The number of promising new medications for treatment of atopic dermatitis (AD) are in developmental stage. Novel topical medicines can be especially helpful for children, providing an alternative to the need for chronic topical corticosteroid use. While many patients with mild or moderate disease can be managed with topical treatments, there are unmet needs for recalcitrant and severe cases. New and developing therapies promisiong for real advances in management of the disease.
Keywords: Dermatitis, atopic; Eczema; Phosphodiesterase inhibitors; Novel Therapeutics

INTRODUCTION

Atopic dermatitis (AD) is a very common, chronic inflammatory skin disease affecting up to 20% of children and 10% ofadults in industrialized countries.1 Clinical features of AD include erythema, edema, lichenification, excoriations, oozing, and crusting. Pruritus is a crucial and dominant feature of AD and generates comorbidities such as sleep loss and psychological distress, creating a continuing disease burden for patients, parents and siblings, pathogenesis is not clearly elucidated, though skin barrier defects and altered immune responses are accepted as key components in disease development. Genetic and environmental factors strongly affect AD expression{1,3}. Disease prevalence is increasing in developing countries, especially in urban regions. 1. MILD ATOPIC DERMATITIS usually successfully managed with a combination of TCS and general recommendations such as moisturizing, preventing heat and sweating and reducing psychological stresses{2.4}. 2. MODERATE ATOPIC DERMATITISUsually requires topical therapy with TCS, possibly supplemented with topical calcineurin inhibitors. In patients with moderate. 3.SEVERE ATOPIC DERMATITIS Current guidelines recommend the use of traditional immunosuppressant medications including cyclosporin (CYA), methotrexate (MTX), mycophenolate mofetil (MMF), and azathioprine (AZA) in patients who fail conventional topical therapy or phototherapy. {5.6}Traditional immunosuppressive therapies can show effectiveness in AD, their routine use is limited by often inadequate disease responses and by adverse effects. Biologic therapy holds promise for providing those patients who suffer from severe disease with effective, long-term options by virtue of their targeted effects on the dysregulated inflammatory responses that cause chronic and recalcitrant disease. As our specificunderstanding of the complex pathogenesis of AD improves, including immune and molecular pathways, a variety of experimental biologics are targeting these pathways with the hope of less toxicity and greater efficacy. Novel therapies: Phosphodiesterase (PDE) inhibitors (Crisaborole) Patients with AD showed significantly elevated leucocyte PDE activity compared to non-atopic normal individuals or to patients with allergic contact dermatitis {8}. NEW AND EMERGING SYSTEMIC THERAPIES Anti IL-4 and IL-13 (Dupilumab) is a fully-humanized, monoclonal antibody targeting the alpha subunit of the IL-4 receptor to block signaling of IL-4 and IL-13. Early phase I and II trials demonstrated its effectiveness in improving the symptoms of adult patients with AD in a dose dependent manner.{9,10}It is has proven that suppressed mRNA expressionin lesional skin of genes related to activation of T cells, dendriticcells, eosinophils, inflammatory pathways, and type 2 cytokines, potential to reverse multiple molecular defects in patients with AD. Although adverse effects were relatively few, conjunctivitis, injection-site reactions, nasopharyngitis, and upper respiratory tract infection are worth mentioning.{7} Topical ophthalmic anti-inflammatory medications were typically needed to control eye symptoms while other cases resolved spontaneously. Nemolizumab subcutaneous injections were well-tolerated with adverse effects mostly in AD exacerbations, to provide significant itch relief in patients with AD in a dose-dependent manner. Further studies are warranted to better clarify the effects on skin inflammatory lesions and to further understand the side effects.

Conclusions: Therapies for AD have long been relatively stagnant with few dramatic breakthroughs. While new topical therapies are emerging, none has yet matched the efficacy of mid-strength TCS. That approach has been hampered by “steroid phobias” and misleading claims of “steroid addiction”, in part a consequence of over-prescribing by physicians, but also from emotion-based internet-generated fears. Clearly there remains a need to find more potent topical agents with fewer side effects. The most gratifying advances in AD therapy have come from better understanding of immune and inflammatory mechanisms. The shining example is the development of dupilumab which has shown remarkable reduction in clinical severity with relatively few adverse effects. The many other new compounds in the pipeline should continue to provide real advances in management of this severe, common and complex diseases.

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SYSTEMIC IMMUNOTHERAPY IN ATOPIC DERMATITIS (AD)

[1]Maia Matoshvili, [2]Davit Tophuria, [3]Natia Kvizhinadze

[1,2,3]Dermato-Venerology Department, Human Normal Anatomy Department, Pharmacy Department. Tbilisi State Medical University.

Email: mmatoshvili@hotmail.com; datotopuria1981@yahoo.com

ABSTRACT

The atopic dermatitis, which affects nearly all aged population worldwide, which affects mark able decline of patients' quality of life. Etiological factors are currently a topic of study and interpretation, the main features of atopic eczema are skin barrier disturbance and immune dysregulation. Pharmaceutical progress in understanding immunopathology of atopic dermatitis have allowed identification of therapeutic molecular targets in the field of biological therapy and Systemic immunotherapy.
Keywords: Atopic Dematitis, Immunotherapy, Interleukins

Introduction: Atopic dermatitis is a chronic, itchy skin condition that is very common in children but may occur at any age. It is also known as eczema and atopic eczema and was formerly known as Besnier prurigo. It is the most common form of dermatitis. Atopic dermatitis usually occurs in people who have an 'atopic tendency'. This means they may develop any or all of three closely linked conditions; atopic dermatitis, asthma and hay fever (allergic rhinitis). Often these conditions run within families with a parent, child or sibling also affected. A family history of asthma, eczema or hay fever is particularly useful in diagnosing atopic dermatitis in infants. Atopic dermatitis arises because of a complex interaction of genetic and environmental factors. These include defects in skin barrier function making the skin more susceptible to irritation by soap and other contact irritants, the weather, temperature and non-specific triggers: see Causes of atopic dermatitis.

Methodology: Immunotherapeutical agents:T-helper 1 (Th1)/Th2 imbalance and their associated cytokines are one facet of the pathological processes of AD. Several experimental agents have been investigated for their potential beneficial effects in the treatment of AD, by modulating Th1/Th2 homeostasis.
Omalizumab-Blocking the consequences of mast cells and basophil activation during the allergic inflammatory cascade has been a major therapeutic goal, and the use of Omalizumab has inaugurated a new era in the treatment of atopic disease. Initially, Omalizumab was approved by the FDA for the treatment of moderate to severe persistent asthma that is uncontrolled with a combination of a medium to high-dose inhaled corticosteroid and a long-acting β2-agonist, in adults and patients of 6 years and older who are sensitized to perennial aeroallergens. In 2014, FDA also approved Omalizumab for the treatment of chronic spontaneous urticaria in adults and children over 12 years of age who exhibit severe symptoms, inadequately controlled by high doses of H1 antihistamines. In addition, Omalizumab was proven to bring favourable results in patients with different subtypes of chronic inducible urticaria, allergic rhinitis, eosinophilic esophagitis, food allergy and anaphylaxis, as well as premedication in allergen specific immunotherapy, Churg-Strauss disease, eosinophilic otitis media, allergic bronchopulmonary aspergillosis, chronic rhinosinusitis, bullous pemphigoid, contact dermatitis and atopic dermatitis (1–5).
Mechanism of action; Omalizumab is a recombinant humanized monoclonal IgG1 antibody composed of 5% murine and 95% human sequence. It prevents the interaction of IgE with its receptors by recognizing and binding to the Fc portion (the CH3 domain) of free serum or membrane-bound on B cells immunoglobulin E molecule, but not IgE bound to its high (FcεRI) or low (CD23) affinity receptors. The CH3 domain serves as the site by which IgE binds to its receptors. Binding of Omalizumab to free, soluble IgE blocks the binding of IgE to its receptors, and subsequently blunts allergen-induced mediator release. Once Omalizumab is administered, it results in the formation of soluble immune complexes with free IgE, typically trimers, which are cleared by the reticuloendothelial system(2). Administration of Omalizumab dramatically reduces the serum levels of free IgE (by 99% in the first two hours after administration), which subsequently downregulates the expression of IgE high-affinity receptors on immune cells. Expression of FcεRI facilitates antigen presentation by DCs. The latter cells appear to be crucial in the phenotypic development of Th1/Th2 cells and have a documented overexpression of FcεRI on the surface of DCs in allergic individuals. Moreover, IgE neutralization therapy decreases the serum expression of several cytokines (such as IL-5, −8, −13) and negatively regulates the recruitment of immune cells (T-cells, eosinophils, and macrophages) to inflammatory sites. Thus, Omalizumab decreases both the immediate and the late phase allergic inflammation. Another mechanism of action involves mast cells and eosinophils' apoptosis in allergic patients treated with Omalizumab compared to controls. Omalizumab - Anti-IgE therapy in AD brought conflicting results. Although most data from small randomized trials, case series and case reports documented clinical benefit and resolution of eczema, a small number of studies showed no improvement of disease with Omalizumab. The response variation to treatment helped to pinpoint patients that are most likely to respond to anti-IgE therapy. Lack of filaggrin mutations and lower elevations of total serum IgE are factors associated with a likely favourable response to

Omalizumab. All of the studies noted the safety profile in both adult and paediatric population treated with Omalizumab. However, the wide variability of response to treatment remains largely obscure, while lack of standardized protocols regarding dosing is currently an unanswered task. Another notable conclusion of placebo-controlled studies showed that the improvement in clinical outcome of patients treated with Omalizumab was similar to improvements in control groups. In the authors' experience, in a case series of three patients with severe refractory atopic dermatitis with atopic diathesis (sensitization to house dust mites, and moderate serum levels of total IgE in all three cases, co-existing asthma and rhinitis in one patient), Omalizumab, 300 mg monthly, brought a significant disease improvement, which occurred within the first three months of treatment. Dupilumab-the FDA approved Dupilumab for the treatment of adult patients with moderate to severe atopic refractory dermatitis, clinical studies proving concomitant efficacy in other atopic disorders, such as asthma and nasal polyposis In addition, Dupilumab efficacy is under investigation for eosinophilic esophagitis and atopic dermatitis in paediatric patients .Mechanism of action- Dupilumab is a fully human monoclonal antibody directed against interleukin-4 (IL-4) receptor-α (IL-4Rα) that blocks the synergistic effects of IL-4 and IL-13 on allergic inflammation. Atopy is the inappropriate secretion of immunoglobulin of E isotype in response to allergen exposure. IL-4 and IL-13 are key drivers of the Th2 allergic inflammation and of consecutive production of IgE. Both IL-4 and IL-13 signal through a common receptor, IL-4Rα, to activate the signalling proteins [signal transducer and activator of transcription 6 (STAT6) and Janus kinase-1 (JAK1)] (8). IL-4 is a crucial positive regulator of allergic inflammation. It induces the immunoglobulin isotype class switch to IgE, promotes the Th2 phenotype, prevents T-cell apoptosis, renders the refractory status of T-cells to corticosteroids, and induces the expression of VCAM-1 on endothelial cells, subsequently promoting the recruitment of cells characteristic to the allergic inflammation (T-cells, eosinophils, basophils and monocytes) (9). Gene polymorphisms in IL-4, −13 and IL-4Rα have been associated with AD in certain populations (10). Additionally, IL-4 and −13 regulate expression of genes encoding proteins involved in skin susceptibility to skin pathogens . IL-4 receptors that function to stimulate the IgE receptors expression and cysteinyl leukotriene synthesis are also expressed on mast cells.
Dupilumab-Targeting Th2 polarization with Dupilumab brought unprecedented advances in the treatment of moderate to severe refractory AD. Dupilumab mono-therapy or combined therapy is associated with effective control of disease, improvement in skin lesions, significant reduction in pruritus and a substantial contribution to the reduced quality of life of affected patients (6). Dupilumab proved to reduce the expression of Th2 biomarker levels and of genes associated with the activation of T-cells, and to favour a genetic profile involved in skin barrier function. Data regarding the molecular signature showed that after 4 weeks of treatment with Dupilumab, the transcriptome of skin lesions of AD resembled that of non-lesional skin (7). A collection of clinical trials that included large number of patients with moderate to severe AD vs. control groups investigated the efficacy and safety of Dupilumab in AD (6–9). With no exception, evidence proved a rapid and marked improvement of disease activity, to the placebo group, and a safe profile of administration.IL-22 promotes epidermal hyperplasia and skin barrier dysfunction in AD.

Conclusion: Atopic dermatitis poses a challenge for clinicians and patients alike, particularly in severe forms of disease. Recent progresses in understanding the pathophysiology of atopic dermatitis underlie its multiple facets and allow the introduction of novel substances for the systemic and topical treatment of severe atopic dermatitis. New therapeutic strategies brought tremendous advances in the management of refractory to conventional treatment, severe atopic dermatitis. Robust evidence pleads for efficacy of Dupliumab, while other immunomodulatory agents, such as Nemolizumab, Lebrikizumab, Tralokinumab, Ustekinumab and Apremilast show promise, but further data are needed to confirm their usefulness and safety in atopic dermatitis. Allergen specific immunotherapy may be of use in selected cases of atopic dermatitis.

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CREATIVE THINKING, INNOVATION AND IDEA GENERATION IN MODERN MANAGEMENT

[1]Larisa Takalandze, [2]Eliso Lanchava

[1]PhD in Economics, Professor, [2]PhD in Economics, Assistant Professor

[1,2]Sokhumi State University (Tbilisi, Georgia)

Email: Larok2706@gmail.com

ABSTRACT

During the XXI century management has faced new significant problems. Today modern management aims to support innovative thinking and to remove the isolation of creative approaches. Creative management, which at the same time is a part of innovative management, helps people working in the organization to maximize their creative ability, accumulated knowledge to create new, competitive ideas that will be used to successfully operate the organization. Because organizations have to take into account the influence of various factors and creative flows, this in itself requires changes within organization and the ability to adapt to ever-changing conditions, which should be done not based on dogmas, but on new forms and methods. Modern management must ensure not only efficiency, but also creativity, innovative development. Creativity becomes part of success-oriented companies, which helps to avoid stagnation and see the issue from the new perspective. Creativity means exactly that – discover a unique opportunity in a problem, be able to perceive risk, break down patterns and create something valuable, different. This is exactly what the news brings.
Keywords: Creativity, Innovation, Creative thinking, Creative management, Innovative thinking,

Today, in the world of business and corporations, creativity is seen as the primary driver of specific benefits. Being a creative company, having a special product or service, and at the same time maintaining a competitive edge is imperative in order to survive. So, organizations need innovation to survive, finding new solutions, new ideas. In modern reality, management depends on abilities, motivations, theoretical and practical knowledge {1}. Modern management includes all spheres of human activity and, one might say, all forms and types of activity. Accordingly, it is legal that the efficiency, competitiveness of activities, productivity and services, as well as the growth of new opportunities and processes, depend on the management object, process and content. In general, it is an ongoing process that controls all resources. The functionality of political, economic, social, ecological processes, dangers or other important issues depends on it {2}. Accordingly, the result of management, as a product of the main acting factor, is reflected in everything and everyone. In such an environment, radical and legitimate differences between many factors are at the root of the problem. The principles of traditional management models, which looked effective during a slow and predictable economic process, were ineffective in modern conditions. Success requires a hybrid combination of new and collected knowledge, which in the end must be manifested to ensure stable competitiveness. Decisions adopted in the management process as a product of intellectual labor become special and competitive only when they are transformed in one unity of the collected knowledge, or when such a detail is added to the knowledge, as a result of which it shows the best abilities. Accordingly, the role of the manager in achieving a specific goal is manifested as a decisive factor. The main source of all benefits, that is, the driving force is the person. While managing an organization, formulating and solving strategic and marketing tasks, the effectiveness of a potential result depends on such factors as the level of creativity of administrations and creative groups. Creativity is the main source of society's development. What does creativity imply? This is a person who thinks creatively, always especially because of individual thoughts, reflections and actions. It can somehow react quickly during problem situations and finds a non-standard, on the one hand, easy and most accurate way out, with which he surprises and excites people around him. Creativity is the most important factor in creating innovation. An innovative idea is a new (creative) idea implemented in practice, which, as a rule, comes out as a result of creative thinking {3}. Thinking is the hallmark of a person. Logical thinking works in only one direction. Conversely, creative thinking does not limit, but goes beyond. It uses thinking resources according to rules that do not obey logic. It is the idea, courage and unity by the impulse of thinking that unites in a person an artist, a creative person, a successful, intelligent, intelligent, innovator, that is, a person who creates epochs. Objects were not created for uniformity, and especially a person's goal cannot be one-time and unchanging. Thinking and its development represents the road to liberating mechanical impulses, obsessions, often incorrect beliefs and monotony. Creativity is a phenomenon through which the creation of something new and, in particular, special, is carried out. The created product can be both intangible (idea, piece of music) and a physical object (drawing, literary work, invention) {4}. Creativity is critical to running a business, especially in a technologically advanced field that is directly knowledge-based. Innovative thinking and intelligence provokes creativity in employees. Namely, the purpose of creative management is to identify creative opportunities in people when traditional administration is based on the activities of people with well-established rules and denies their initiative. Creative management implies such management of people in organizations, the goal of which is to maximize their capabilities, so that the basis for the manifestation of competitive ideas in various spheres of human activity is embedded. The goal is to generate new ideas,

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make non-standard decisions, both for the successful development of the company (organizations) and the country. It is imperative that the original ideas of the employees are heard. Make sure to hold meetings where employees personally provide ideas to leaders. The creativity of employees, one might say, depends not only on internal factors, but also on the organizational culture, on the working environment, on the forms of management. Accordingly, provoking creativity is possible by many methods, if the leader has the desire and willingness to consider different methods that will help the development of creative thinking in organizations {3}. Creative management must ensure that costs are minimized and that potential future benefits are maximized while building intellectual capital. Its main task is the creation of human capital activity and motivation, the activity of creative potential. We present several types of creative thinking and creative management:

- **Brainstorming -** This technique is based on an environment that the value of ideas can constrain our thinking when looking for new ideas. This often happens when a normal idea comes along and the thinking process stops automatically. Not after the manifestation of the idea, but the flow of the manifested ideas stops. Each team member subconsciously filters those ideas, after which he thinks that this idea is similar and not inappropriate and cannot express it. The main purpose of brainstorming is to separate the process of evaluating and communicating ideas. People present ideas without any judgment or thought. These ideas are written (on the board, on paper), and after that their assessment and debate begins around them. At the end, the most optimal idea is chosen.

- **Checking by the method of assumptions -** When we have to think about a question, several ideas are so grounded in our minds that they deny the opposite. When thinking creatively, you don't need to run away from the opposite assumptions. On the contrary, you always need to find alternatives, test assumptions. Once the question to be verified has been selected, a small group or individual members should start looking for the possibility of different opposing assumptions and highlight the dominant ideas. All assumptions are verified. This process takes place visually, preferably on a board. All possible results and benefits of assumptions and alternatives must be analyzed. The final result will be presented by the whole group (or one member) {5}. Within companies, creativity should not be imposed on one individual. Management must create an appropriate creative environment for the team and give incentive to each employee.

Great changes are taking place in the world today. Humanity still faces instability and uncertainty. The new revolution in sciences, technologies and industries has given the development of mankind new opportunities and also unprecedented challenges. In order to achieve general well-being, maintaining connections and communication, coordinated development is a legitimate choice. Transformation and innovation are the driving forces for the success and development of society. Anyone who denies changes and news is lagging behind the times and disconnected from activity. The innovativeness of the socio-economic development of the country must be considered as a form for the implementation of non-standard, creative ideas, both in economics and politics, in public life and art. Internal competition and the national innovation system are an important foundation for a competitive economy, economic security and, accordingly, the state's competitiveness on a global scale. Innovation plays an important role in a country's economic well-being. It is of particular importance for the development of the business sector. It promotes high competitiveness, which contributes to the development of business and economy {6}. Various studies show that where innovation is developed, the standard of living of society is high. And this is a clear indicator of a developed economy. Innovation represents a chance for developing countries to keep up with the developed world and improve living standards through a sustainable development path. Today, in world practice, there is a wealth of experience in the transition of economic development to an innovative regime, which is used in different economic and political conditions. Georgia, despite a number of problems, we can say that it retains scientific and technical potential, has important natural resources and another important resource - the high potential of entrepreneurs.

The main task lies in the fact that all its resources should be directed to the development of the country's economy {6}. In this regard, the development of the innovation sphere is of particular importance, since mainly in this area, on the basis of fundamental and using research, products are created that have high user characteristics.

The main condition for the development of the innovation sphere is the issue of training and education of working personnel in this area. Modern businessmen and managers operate in a completely different environment than 10-20 years ago. Based on this, it is imperative, taking into account the characteristics of the Georgian environment, to develop local employees and activate attention to development and establish a modern management culture. It should be taken into account that the effectiveness of management, its forms are directly related to the social, economic, and cultural traditions of the country. So, it is imperative, taking these factors into account, to organize the training of managers and the training system in accordance with the requirements of a modern market economy, attract the costs of domestic and international financial organizations, develop specific training programs and implement them. These programs need to be created taking into account international experience. In the area of increasing entrepreneurial skills, the non-governmental sector and international organizations can make a great contribution. It should be noted that there is some progress in this direction. Grant financing mechanisms have been created in Georgia, the Innovation and Technology Agency of Georgia has been created, which participates in the commercialization of the results of knowledge, innovation and research from the public and private sectors and in supporting innovative entrepreneurship. The first technology park was created, where

large and small companies can work together. For representatives of the creative and engineering industries, such an ecosystem will provide an opportunity to initiate projects of higher value and interests in the global market. Over the past 11 years, the level of innovation in different countries has been measured by the Global Index (GII) and is annually prepared by Corneli University, the INSEAD business school and the World Intellectual Property Organization (WIPO). In 2018, in the research of the global innovation index, Georgia acquired the 9th position and with 35.05 points it takes 59th place. In the research, Georgia is among those 20 countries that, in contrast to the country's development, in terms of the development of innovations, shows high results. This is all good, although it should be noted that the country faces important challenges, which needs an integrated approach and solutions {6}. Small and medium-sized entrepreneurs invest less money in research and development, which hinders the creation of innovations and in the end, a less desirable result occurs. It is important that the results of this study are correctly understood and analyzed by the competent authorities in order to plan and implement those actions that will improve the situation and contribute to the development of the country, which, accordingly, will be reflected in economic growth. It is desirable that actions for the integration of Georgian scientists and the education system in a single European space be carried out in stages, also with the aim of developing cooperation in the field of research activities with neighboring countries of the region. With the creation of new technologies, industries, models, there is support for the development of globalizations in an open, inclusive, universal and profitable direction {7}. The government must ensure that the people living in the country have a sense of success, slavery and security. It is important for Georgia to study the theoretical achievements and practical experience of the civilized economic world and to establish and use them in economic management activities, which must be implemented in the near future.

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ACUTE DISSEMINATED ENCEPHALOMYELITIS IN A 5 YEARS OLD BOY, A CASE REPORT

Learta Alili Ademi, Blerim Ademi MD

University clinic for pediatric diseases, department of neurology, MD, Skopje, North Macedonia.

University clinic of neurology, Dr.Spec.,MD, Skopje, North Macedonia.

Email: Dr.learta.alili@gmail.com, Dr.blerim.ademi@gmail.com

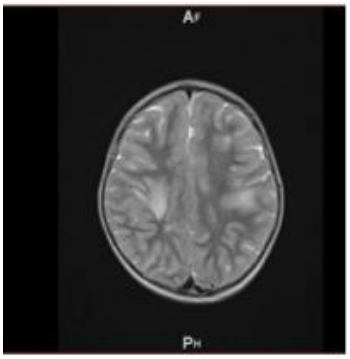
ABSTRACT
Acute disseminated encephalomyelitis (ADEM) is uncommon demyelinating disease of the central nervous system (CNS) usually following a viral infection or vaccination represented with combination of motor, sensory, visual and cognitive symptoms. In this paper is reported a case of a five years old boy who was diagnosed and finally labeled as ADEM. The case is presented through clinical features, diagnostic investigations, outcome and effective treatment.
Keywords: acute disseminated encephalomyelitis, white matter, multiple sclerosis, magnetic resonance imaging

Introduction

Acute disseminated encephalomyelitis (ADEM) is a multifocal autoimmune demyelinating disease of the CNS usually following a viral infection or vaccination. It is an uncommon poly-symptomatic disorder that manifests as an acute-onset encephalopathy associated with polyfocal neurologic deficits and is typically self-limiting. The disorder usually is represented with combination of motor, sensory, visual and cognitive symptoms. Sometimes because of to the clinical presentation, the diagnosis is a dilemma, due to which many studies may be done with no confirmed conclusion. In addition, there have always been and will be present debates regarding the diagnosis of ADEM due to different clinical presentations in different cases. More than 80% of cases are reported to occur in children under 10 years old with a slightly male predominance, and a mean age range of 5 to 8 years old. In approximately 57-92% of patients total recovery is reported to occur while in 4-30 % is reported the persisting of residual focal neurologic deficits. Clinically and pathologically ADEM resembles Multiple sclerosis (MS).

Case report

We report a five years old boy who was admitted with acute onset of symptoms of weakness and pain in the lower limbs and backbone and difficulty to stand on his feet and inability of walking. The patient is a relatively healthy child with a regular immunization status and with no family history. There was a lack of febrile illness or vaccination prior to the present illness. On admission he was conscious, afebrile, hypotonic, and with gait disturbance. During neurological examination verbal and visual contact was established, cranial nerve examination revealed normal findings, muscular strength and tone was normal, tendon reflexes were preserved with a hyperactivity in the lower limbs and positive Babinski sign on both sides, superficial and deep sensibility were preserved and there were no meningeal signs. Laboratory evaluation and diagnostic procedures were performed. Initial laboratory tests such as CBC, CRP, basic metabolic panel, and liver panel revealed normal findings. Additional laboratory studies were done, all with normal findings. There was a positive Epstein-Barr virus (EBV) IgG and Cytomegalovirus (CMV) IgG serology. Pneumoslide test showed positive Mycoplasma pneumonia IgM. Fundoscopic examination and CT scan of the brain revealed normal findings. MRI of brain showed multiple hyperintense focal lesions in subcortical white matter in fronto-temporo-parietal region bilaterally and left occipital region in T2 weighted images and FLAIR (Figure 1,2,3 and 4).



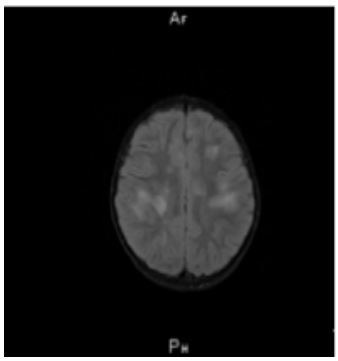


Figure 1 and Figure 2: Patient's brain MRI T2 weighted image sample

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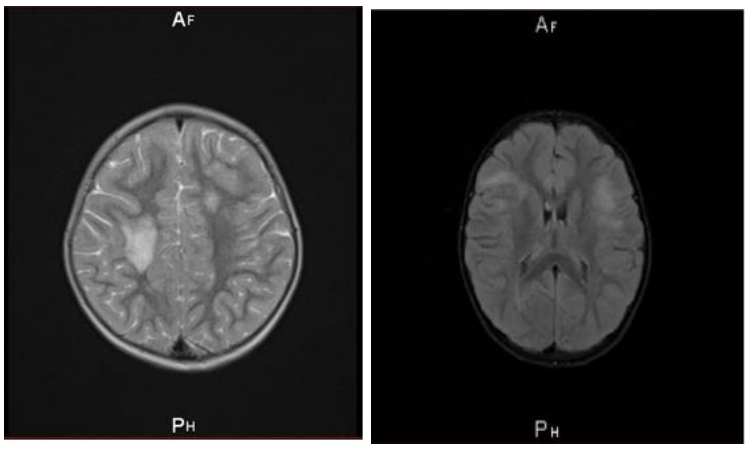

Figure 3 and Figure 4: Patient's brain MRI T2 weighted image sample

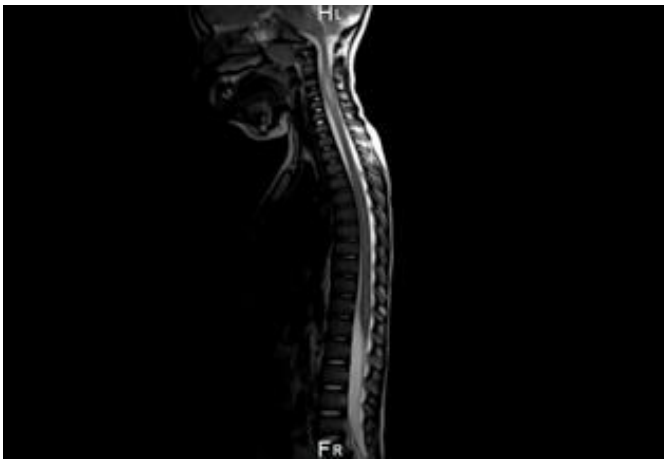

Figure 5: Patient's MRI of spinal cord T2 weighted image sample

MRI of spinal cord revealed hyperintense lesion in T2 weighted images from C2-C5 localized central with a widening of the central spinal canal upwards and downwards from the change (Figure 5).
EEG showed main activity of 7c/s and exhibited spikes of high amplitude in the right side some of which are spike wave complexes. Lumbar puncture was performed and cerebrospinal fluid (CSF) analysis showed CSF with normal pressure, lymphocytic pleocytosis and a glucose content of 2,81 mmol/l (reference value 2.5 – 4.4 mmol/l), protein content of 38,9 mg/dl (reference value 15 - 45 mg/dl) and lactate of 1,6 mg/dl (reference value <35 mg/dl). Electrophoretic separation of CSF proteins showed a total proteins content of 0,39 g/l, albumin content of 226 mg/l and Immunoglobulin: IgG = 25,6 mg/l with an IgG index of 0,42 and IgG synthesis in CNS was 0 mg/24 h, as seen in the Table 1 below. According to the characteristics of the electrophoregram there is an immunological activity in the brain that corresponds to an acute inflammatory process (Figure 6).

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Table 1: Electrophoregram

	Results	Reference value
Total proteins (g/l)	0,39	0,15-0,45
Albumins (mg/l)	226	50-250
IgG (mg/l)	25,6	3-30
Albumin coefficient	5,51	2,8-7,4
IgG index	0,42	<0,7
IgG synthesis in CNS (mg/24 h)	0	<5

Figure 6. The clinical picture and the MRI scan findings as well as CSF lymphocytic pleocytosis were suggestive of ADEM.

Treatment was implemented with high-dose intravenous corticosteroids (Methylprednisolone) with a dosage of 30 mg/kg/d during 4 days. He made a dramatic improvement over the next few days and was able to walk well at the end of the first week.

Conclusion

Short duration of illness prior to admission, widespread multifocal involvement on MRI brain scan and the response to steroids favor the diagnosis of ADEM. CMV, EBV and Mycoplasma pneumoniae infections are associated with ADEM. CSF lymphocytic pleocytosis is a feature of ADEM. His CSF analysis, done during the recovery phase, showed 20 Lymphocytes and a protein content of 39 mg/dl. The type of electrophoregram of cerebrospinal fluid is a gamma globulin type, also favoring the diagnosis of ADEM. MRI brain scan is the investigation of choice that shows high intensity lesions on T2WIs most commonly in the subcortical white matter. However, there are no generally accepted diagnostic criteria for ADEM. The predominant white matter involvement suggests demyelination, which is the hallmark of the disease. Bilateral subcortical white matter involvement on MRI brain scan is typical of ADEM, while 98% of MS cases show periventricular white matter involvement, which was not seen in this patient. Even though, distinguishing ADEM from MS with a single MRI brain scan is impossible, first episode of MS needs to be taken in consideration.

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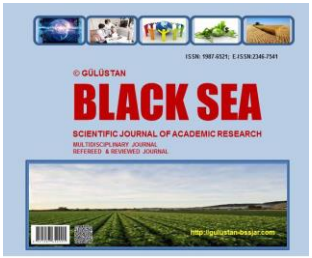

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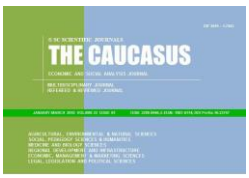

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