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CIRCULATING NEURAL AND MUSCLE PROGENITOR MONONUCLEAR CELLS IN BLOOD OF DOWN SYNDROME PATIENTS

By

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ABSTRACT

Background: Down syndrome (DS) is a genetic disorder, which is associated with various manifestations including neuromuscular defects. These defects should be compensated through other pathways for regeneration and repair, with growing evidence suggest that circulating neural and muscle progenitor cells have pivotal role in the maintenance of muscle and neural tissues integrity and repair after injury.

Objective: The aim of the present work was to determine factors and markers of muscle and neural regeneration in the blood of Down syndrome (DS) patients as well as controls and demonstrating correlation between them.

Subjects and Methods: This study was carried out on 40 DS patients and 30 apparently healthy controls. DS patients were selected from cases already diagnosed by chromosomal karyotyping in the genetic unit, pediatric department, Cairo University. Factors of regeneration were measured in terms of NGF, SDF-1 and Galectin-1 using ELISA. Markers of regeneration were measured in terms of circulating mononuclear cells expressing Nestin, CD34 and CD45 using flow cytometry.

Results: Results showed significant increase in plasma NGF,SDF-1, and Gal-1 in DS patients compared to controls. On the other hand, we demonstrated significant decrease in Nestin, CD34, and CD45 surface marker. Our results showed negative correlation between NGF and Nestin, between SDF-1 and CD34, and between Gal-1 and CD45 among DS patients.

Conclusion: The significant increase in the NGF, SDF-1 and Gal-1 accompanied by a significant decrease in number of mononuclear cells expressing, Nestin, CD34 and CD45 indicated neuromuscular degeneration in DS, which was not compensated by the regenerative mechanism.

Key words: Down syndrome, Galectin-1, stromal derived growth factor, nestin, CD45, CD 45, CD 34.

INTRODUCTION

Down syndrome (DS) is the most common known genetic disorder which causes mental retardation. It was reported from cytogenetic and molecular assays that ~95% of DS is due to 'full trisomy 21' in which an entire extra chromosome 21 is present ***(Sherman et al., 2005),*** with the consequent over expression of genes encoded within it***(Patterson and Costa, 2005).*** DS is associated with a rich variety of phenotypes, which are variable in both prevalence and expression. Two exceptions are the existence of mental retardation and hypotonia which are close

to 100% of individuals with DS ***(Korenberg et al., 1994)***. Mental retardation and hypotonia are due to neuromuscular defects ***(Vicari, 2006)***.

Evidence from several reports showed that bone marrow (BM) contains a population of tissue committed-stem cells (TCSCs) that accumulate in BM and actas a reserve pool of stem cells for regeneration. TCSCs are released into peripheral blood during stress/tissue injury in order to repair damaged tissues (***Kucia et al., 2005 and Marycz et al., 2015***). Adult BM harbors TCSCs for both neural and endothelial progenitors. Neural progenitor cells (NPC) expresses Nestin as a surface marker, while endothelial progenitor cells (EPC) expresses CD34 as a surface marker(***Kucia et al., 2006 andChang et al., 2013)***. Both NPC and EPC are important for neural regeneration (***Taguchi et al., 2009).***

Several studies have described the ability of the whole bone marrow or population enriched for hematopiotic stem cells to give rise to skeletal muscle fibers after intravenous injection***(Ferrari et al., 1998 and La Barge & Blau, 2002)***. Such cells express CD45surface markers for muscle regeneration ***(Rosu-Myles and Bhatia, 2003)***, where it is indicated that circulating muscle activity within the bone marrow, expresses the CD45 surface marker which is hematopiotic in origin **(*Camargo et al., 2003)*.**

Some chemokine factors are involved in neural and muscle regeneration. Nerve growth factor (NGF) is a chemokine neurotrophic factor that acts through its specific receptors to enhance the survival, differentiation, and maintenance of specific neurons of the peripheral and central nervous systems ***(Ye et al., 2003)*** including basal forebrain cholinergic neurons (BFCNs) ***(Marei et al., 2013).*** NGF increase in case of muscle degeneration to induce tissue repair (***Corsi et al., 2006)***.

Stromal derived growth factor-1 (SDF-1) is another chemokine factor. It is a chemokine coupled with CXCR receptor, which is expressed on neural, endothelial and hematopiotic progenitor cells. SDF-1 chemo-attracts various progenitor cells to the damaged tissue. SDF-1–CXCR4 axis plays an important role in regulating/ directing the circulation/trafficking of all of these cells***(Dar et al., 2011)***.Galectin-1 (Gal-1) is another chemokine factor implicated in the development of skeletal muscle (***Watt et al., 2004 and Kami &Senba, 2005)***.

The aim of the present work was to determine neural and muscle factors and markers of regeneration in the blood of DS patients compared to controls. Factors of regeneration were measured in terms of NGF, SDF-1, Gal-1. Markers of regeneration were measured in terms of mononuclear cells expressing Nestin, CD34 and CD45 in the blood of DS patients.

PATIENTS AND METHODS

Forty DS cases (23 males and 17 females) participated in our study. Their age ranged from 2-6 years (mean 3.5 ± 1.3 year). Thirty matched healthy normal children (18 males and 12 females), whose age ranged from 2-5 years (mean 3.1 ± 0.9 years) were included as control. DS patients were selected from cases already diagnosed by chromosomal karyotyping in the genetic unit, Pediatric Department, Cairo University. The selection criteria of the patients and controls were to be free from any infection and in good nutritive status and did not undergo surgical operations through the last 6 months. Height and weight were recordedfor both

groups.Blood samples were obtained after an informedconsent of the parents in accordance with the current revisionof the 1975 Helsinki Declaration,and the following parameters were determined:

1. **Determination of NGF, SDF-1 and Gal-1 plasma levels:**

We used the quantitative sandwich enzyme-linked immunosorbent assay technique (ELISA) in the determination of plasma levels of NGF(***Antonucci et al., 2009***), SDF-1(***Jin et al., 2009***)and Gal-1 (***Montiel et al., 2010***).Concentrations were determined by comparison with astandard curve, following manufacturer's instruction.

2. **Quantification of circulatingNestin, CD34 and CD45 mononuclear cells:**

Peripheral mononuclear cells were first isolated from the blood samples (0.5 mM EDTA).The isolated cells were labeled with the phycoenythrin (PE)-conjugated monoclonal Nestin antibody, phycoenythrin (PE)-conjugated CD45 and Fluorescein isothiocyanate (FITC) conjugated CD34. The stained cells were washed with phosphate buffered saline and /BSA and then analyzed by flow cytometer at the Toxicology Centre, Faculty of Medicine, Ain Shams University (***Duda et al., 2007***).

All calculations and data presentations were carried out by the use SPSS program. For the statical analysis, we calculated the arithmetic mean, standard deviation and student "t" test.

RESULTS

Results showed significant increase in plasma NGF (155.9 ± 55 pg/mL vs. 89.8 ± 35.9 pg/mL), SDF-1 (560.1 ± 65 pg/mL vs. 455 ± 85.3 pg/mL) and Gal-1 (27.2 ± 5.5ng/mL vs. 18.8 ± 4.8 ng/mL) in DS patients compared to controls. On the other hand, we demonstrated significant decrease in Nestin mononuclear cells per 10^5 cells (6.3 ± 1.4 vs.9 ± 4.4), CD34mononuclear cells per 10^5 cells (54 ± 3.4 vs. 60 ± 4.8) and CD45 mononuclear cells per 10^5cells (64 ± 3.8 vs.70 ± 4.8).Our results showed significant negative correlation between NGF and Nestin, between SDF-1 and CD34, and between Gal-1 and CD45 among DS patients.

Table (1): Mean ± SD of plasma NGF, SDF-1 and Gal-1 among Down syndrome patients compared to controls.

Groups / Parameters	Controls	Down Syndrome	p
NGF (pg/ml)	89.8 ± 35.9	155.9 ± 55	P < 0.0001 *
SDF-1 (pg/ml)	455 ± 85.3	560.1 ± 65	P < 0.0001 *
Gal-1 (ng/ml)	18.8 ± 4.8	27.2 ± 5.5	P < 0.0001 *

* significant.

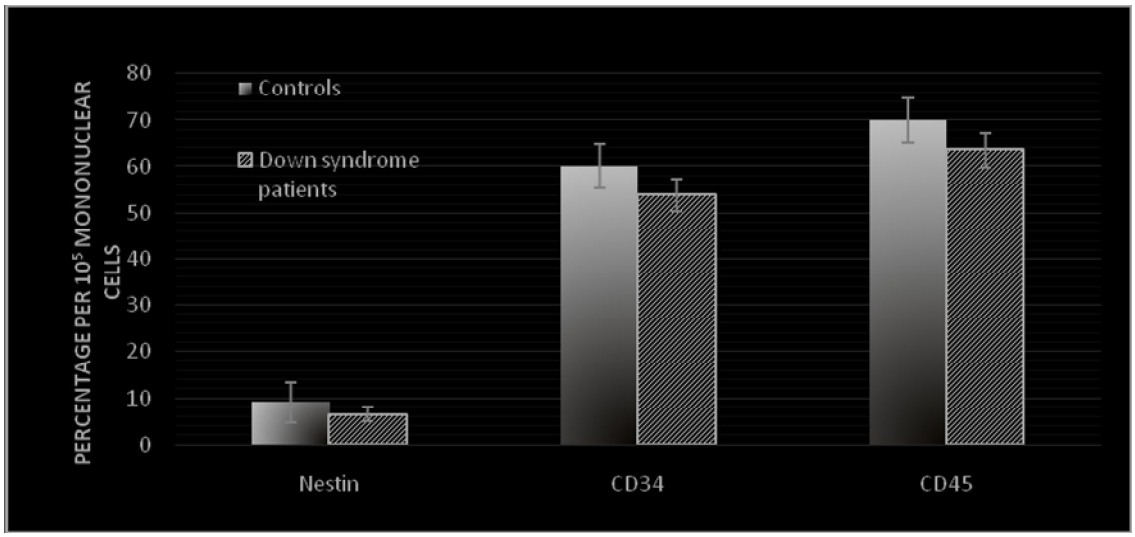

Figure (1): Mean and SD of circulating mononuclear cells expressing Nestin, CD45 and CD34 among Down syndrome patients compared to controls.

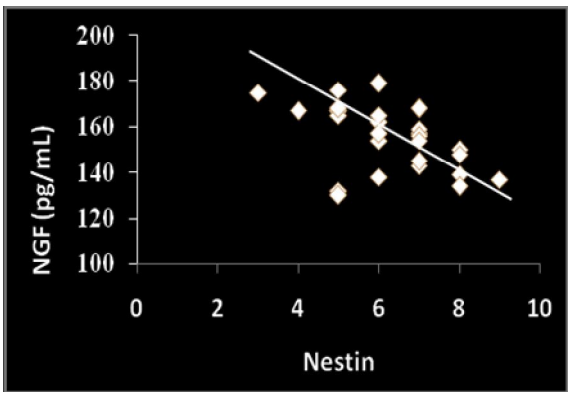

Figure (2): Correlation between NGF and Nestin surface marker on circulating mononuclear cells in blood of Down syndrome patients.

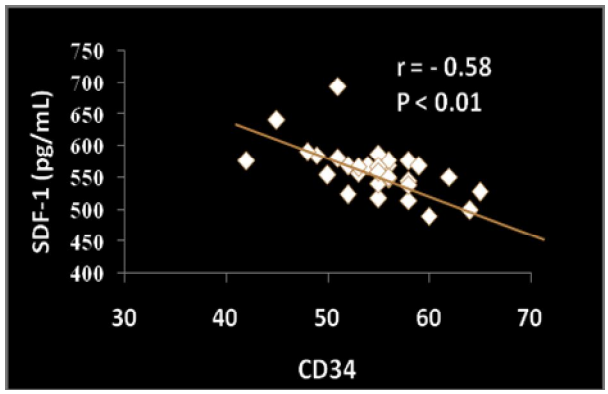

Figure (3): Correlation between SDF-1 and CD34 surface marker on circulating mononuclear cells in blood of Down syndrome patients.

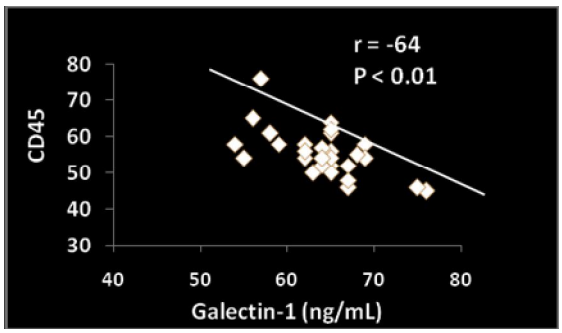

Figure (4): Correlation between Galactin-1 and CD45 surface marker on circulating mononuclear cells in blood of Down syndrome patients.

DISCUSSION

DS is a genetic disorder associated with several manifestations including neuromuscular defects. In our study, we estimated NGF,SDF-1 and Gal-1as factors involved in neural and muscle regeneration. Our results showed significant increase in plasma levels of NGF,SDF-1 and Gal-1 among DS patients compared to controls.

Results of our present study showed an increase in NGF level in blood of DS patients which acts as a protective mechanism to reverse neural degeneration. This is in agreement with ***Corsi et al.(2006***) who showed that plasma levels of NGF were higher in children, adult and old DS subjects than in controls. It has been demonstrated that βAPP over expression in Ts65Dn mice impairs the retrograde transport of nerve growth factor (NGF) from the hippocampus to the basal forebrain, causing degeneration of basal forebrain cholinergic neurons (BFCN) (***Salehi et al., 2006)***.

In the present study, the mean ± SD of SDF-1 in blood of Down syndrome patients was significantly higher compared to controls. The significant increase in SDF-1 indicated the presence of damage since the secretion of SDF-1 increases during tissue damage to enhance repairing and induce mobilization of progenitor cells (***Yamaguchi et al., 2003)***. It has been reported that plasma elevation of SDF-1 induced mobilization of mature and immature hematopoietic progenitors and stem cells including EPCs. It was found that the responsiveness of progenitor cells towards SDF-1 changes somewhat during murine development in which cells isolated from younger mice (1–2 months old) respond better to SDF-1, cells from older animals (2–6 months old)(***Kucia et al., 2006)*.** Results of the present study were contradictory with a more recent study that showed decreased plasma SDF-1 levels in DS individuals (***Costa et al., 2010)***. The latter discrepancy can be attributed to the difference in age of the present study population 3.5 ± 1.3,which was extremely much younger compared the other studies, whose mean of age was 28 ± 9 (***Costa et al., 2010***). Decreased levels in SDF-1 have been shown to decrease with ageing due to increased fat deposition associated with ageing (***Tuljapurkar et al., 2011)***.

In the present study, high levels of Gal-1 was detected in blood of DS patients compared to controls. This was in agreement with a previous studyin which it demonstrates that Gal-1 levels increases during muscle degeneration *in vivo,* along with changes in its cellular localization, followed by decreased expression during regenerative stages (***Cerri et al., 2008)***.

The results of present work demonstrated a significant decrease in Nestin surface marker on mononuclear cells among DS patients compared to control**.** This was in agreement with a previous study that have investigated the characteristics of adult neurogenesis in the Ts1Cje brain and determined that the numbers of self-renewing neural progenitor colonies are reduced, and the number of neurons produced by adult Ts1Cje neurogenic progenitors shows a striking reduction to less than one half (***Hewitt et al., 2010)***. It has been shown that the number of neurons generated from trisomy 21 human Neural Progenitor Cells (hNPC) lines decreases dramatically with increased time in culture while age-matched euploid hNPCs continue to generate 20–30% neurons. Therefore, trisomy 21 hNPCs exhibits a developmentally regulated defect in neurogenesis that can be delineated in culture (***Bhattacharyyaet al., 2009***).

In the present study, mononuclear cells expressing CD34 were significantly lower among DS patients compared to controls.

This was in agreement with a previous study that detected a marked decrease of progenitors' number in young DS individuals compared to controls (***Costa et al., 2010).*** A decrease in vitro growth capacity of bone marrow CD34+ cells in DS mouse model Ts65Dn (***Jablonska et al., 2006)*** and a reduced number of CD34+ in DS fetuses and children were also reported (***Holmes et al., 2006)***.

Mononuclear cells expressing CD45 surface marker were significantly lower among DS patients compared to control. This indicated defective myogenesis and muscle regeneration in Down syndrome patients. Analysis of hematopoietic progenitor populations showed that Ts65Dn mice possessed fewer functional hematopoietic stem cells and a significantly decreased percentage of bone marrow lymphoid progenitors (***Lorenzo et al., 2011)***.

Our results showed negative correlation between NGF and Nestin, between SDF-1 and CD34, and between Gal-1 and CD45 among DS patients. This indicated the presence of degeneration, which was not compensated by regenerative mechanisms.

Changes in stem and progenitor cells may be of great importance for the aging process, because any decline with age in the numbers and functional integrity of stem cells could potentially lead to progressive deterioration of functional and proliferative homeostasis in organs (***Van Zant and Liang, 2003)***. The significant decline in the circulating muscle and neural progenitors may explain the signs of accelerated aging, which is manifested in DS cases.

In conclusion: Although NGF , SDF-1 and Gal-1 are factors for regeneration, their increase in the blood of DS patients act as sign of degeneration as they respond to injury to enhance repairing. The significant increase in the NGF, SDF-1 and Gal-1 accompanied by a significant decrease in number of mononuclear cells expressing, Nestin, CD34 and CD45 indicate neuromuscular degeneration in DS which is not compensated by the regenerative mechanism. This provides an evidence for the impairment in neuro-muscular regenerative capacity in DS individuals.

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خلفية البحث: يرتبط وجود متلازمة داون بمجموعة من الظواهر المتعددة، والتي تختلف في الإنتشار والظهور، بإستثناء التخلف العقلي وإنخفاض التوتر العضلي الذي يوجد في 100% من الحالات.والسبب في وجود التخلف العقلي وإنخفاض التوتر العضلي هو الخلل العصبي العضلي.وهذا الخلل يتضمن صعوبة في التعلم والتحدث والتذكر والسلوك الحركي. وتشترك العديد من الجينات في حدوث الخلل العصبي العضلي لدى مرضى الداون، وهذا الخلل ينبغي تعويضه من خلال عدة طرق لتجديد الخلايا وإصلاحها.

الهدف من البحث: قياس عوامل ودلالات التجديد العصبي العضلي في دم مرضى متلازمة داون وفى المجموعة الضابطة.

طرق وأدوات البحث:

أجريت الدراسة على أربعين طفلا مصابا بمتلازمة داون مقارنة بثلاثين طفلا سليما. تم قياس الخلايا المهيئة للأعصاب والأوعية من خلال دلالات النيستين والسي دي 34 والتي تظهر على سطح خلايا أحادية النواة، بالإضافة إلى الجاذبات الكيميائية ن ج ف وإس دي إف 1.كما تم قياس الخلايا مجددة الدم والتي تملك قدرة على تجديد العضلات من خلال دلالة (السي دي 45) بالإضافة إلى الجاذب الكيميائي جالكتين -1.وقد تم قياس الخلايا أحادية النواة الحاملة للدلالات النيستين والسي دي 34 والسي دي 45 في الدم باستخدام التدفق الخلوي، وتم أيضا قياس الجاذبات الكيميائية ن ج ف وإس دي إف 1 وجالكتين -1 في البلازما بإستخدام المقايسة المناعية المرتبط بالإنزيم (إليزا).

نتائج البحث:أظهرت الدراسة الحالية زيادة مؤثرة في متوسط الجاذبات الكيميائية ن ج ف، إس دي إف –1 وجالاكتين -1في دم مرضى متلازمة داون مقارنة بالمجموعة الضابطة،بينما أظهرت الخلايا أحادية النواة الحاملة للدلالات النيستين والسي دي 34 والسي دي 45إنخفاضامؤثرا في الدم مقارنة

بالمجموعة الضابطة.وأظهرت النتائج أيضا علاقة مضادة بين ن ج ف والنيستين، وبين إس دي إف – 1 والسي دي 34، وبين جالاكتين -1 والسي دي 45.

الاستنتاج: بالرغم من كون ن ج ف، إس دي إف – 1و جالاكتين -1عوامل مساعدة على تجديد الخلايا إلا أن زيادتها في دم مرضى الداون تعتبر علامات على كثرة الهدم لأنها تزيد استجابةً للتلف لتحفيز التجديد.كما أن الزيادة المؤثرة في ن ج ف، إس دي إف – 1والجالاكتين -1 المصاحبة للانخفاض المؤثر في الخلايا أحادية النواة الحاملة للدلالات النيستين والسي دي 34 و(السي دي 45) تدل على وجود تلف عصبي عضلي في مرضى متلازمة داون والذي لا يعوض بآلية للتجديد.

ونتائج هذه الدراسة توضح الإنخفاض الواضح في الخلايا المنشئة للأعصاب والعضلات لدى مرضى متلازمة داون. كما أن قلة توفر هذه الخلايا ربما تفسر سرعة ظهور علامات الشيخوخة التي تظهر في حالات متلازمة الداون، كما تعد دليلا على ضعف القدرة على تجديد الخلايا.