

VII Edition of Quincke's Scholarship: Lecture Highlights

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ABSTRACT

Introduction: Quincke's Scholarship deals with themes related to neuroimmunology and the complement system.

Objective: Describe the most recent advances of the VII Edition of Quincke's Scholarship.

Methods: Publications pertaining to Quincke's Scholarship were selected and revised from the work group of the Central Lab of Cerebrospinal fluid (LABCEL).

Results: The principal topic was the C1q protein; initiator of the classic complement pathway. From the analysis of the molecular concentration of this protein, its transference and the correlations between the concentration of C1q protein in cerebrospinal fluid (LCR) and the quotient of albumin (QAlb) between LCR and plasma it is hypothesized that an intratecal synthesis of the C1q in patients with a dysfunction of the blood-brain barrier.

The most recently discovered pathway in the activation of the complement is the lectin pathway. The diffusion of the MASP-3 protein from blood to LCR is proof that the MASP-3 is synthesized in the leptomeninges.

The reibergram is useful to evaluate the immune response in patients with: neurological manifestations caused by the dengue virus, and patients with multiple sclerosis.

Conclusions: The VII Edition of Quincke's Scholarship dealt with C1q protein and recently discovered themes of the lectin pathway and the use of the reibergram.

Keyword: Quincke's Scholarship; C1q protein; lectin pathway; reibergram.

INTRODUCTION

The study of cerebrospinal fluid began in 1891. The German Heinrich Quincke published on that date an article on lumbar puncture where he raised the possibility of its use in therapeutics and diagnosis.⁽¹⁾

In Havana in 2012 at the Central Laboratory of Cerebrospinal Fluid (LABCEL) began to develop the Quincke Scholarship in honor of the discoverer of the study of the LCR. They are called each year by the Chair of Scientific Communication, the Observatory of Science, Technology and Innovation, LABCEL, the Faculty of Medical Sciences "Dr. Miguel Enríquez" from the University of Medical Sciences of Havana.⁽²⁾

Among the objectives of the scholarship are to promote group scientific work, facilitate access to research laboratories and solve problems not yet clarified. Students and residents of Medicine and related specialties of Cuba and the world can participate. It is a

summer course with selective participation based on the research results of the aspirant's curriculum.^(1,2)

A central theme of research in basic sciences related to Neuroimmunology is addressed, particularly in the lectin pathway (complement system) and aspects of laboratory management. Conferences are given by LABCEL researchers and specialists from other universities and countries. At the request of the fellows and to give continuity to the work in the laboratory facilities in the following months with the advice of LABCEL researchers, the post-Quincke stays were created.⁽¹⁾

The aim of this paper is to describe the most recent advances of the VII Edition of Quincke's Scholarship.

METHODS

Publications pertaining to Quincke's Scholarship were selected and revised from the work group of the Central Lab of Cerebrospinal fluid (LABCEL).

DEVELOPMENT

The Central Laboratory of Cerebrospinal Fluid (LABCEL) of the University of Medical Sciences of Havana, together with the Goettigen University in Germany and the University of Aarhus in Denmark, investigate the biological role of the complement system in different situations. The Cuban working group works the role of the lectin pathway in the central nervous system in particular.⁽¹⁾

In the first edition of the Quincke Scholarships in 2012 we worked with ferritin to evaluate the diffusion of this protein to the cerebrospinal fluid and the clinical application in various neurological diseases. In 2013, the diffusion of Ficolines M and H in the cerebrospinal fluid, the different forms of aggregation found in this fluid and if intrathecal synthesis occurs, was evaluated. The third edition in 2014 studied the MASP-2, its concentration in serum and CSF as well as the possibility of its intrathecal synthesis taking into account its molecular mass.⁽¹⁾

Map 44 was addressed in 2015 from its diffusion of blood to the CSF, its intrathecal synthesis and the possible origin as protein of the leptomeninges. In 2016 we worked with the CL-LK collective. The sixth edition was dedicated to MASP-3, a protein discovered only 15 years ago. Until 2016 its function was not clarified. The C1q protein of the classic complement pathway was the theme that was worked on in 2018.⁽¹⁻³⁾

Most relevant aspects in the 2018 edition

In the context of the 2018 edition, fifth-year medical student José Alejandro Rodríguez-Pérez received the LURAP award from the American Society of Physiology for his outstanding research career in the area of neurosciences.

In general, inflammation is a response of organisms to different aggressions that seek to maintain homeostasis. The innate and the acquired immune response intervene in this process. The complement system produces a wide variety of anaphylatoxic substances that intervene in the inflammatory response.⁽⁴⁾

The actions of the complement in the central nervous system have not yet been clarified. In the case of lectin pathways, some of its components participate in neurodevelopment, neuronal communication and neuroinflammation as a response to different endogenous or exogenous aggressions.⁽⁵⁾

The classical pathway is initiated by the binding of the C1q recognition molecule of pathogenic antigens, antigen-antibody complexes, and bacterial polysaccharides. Based on the cerebrospinal fluid analysis of patients with neuroinflammatory diseases and blood-brain barrier dysfunction, the reibergram was used to assess the C1q intrathecal synthesis. Interestingly Lumpuy et al found that their production in the central nervous system is possible.⁽³⁾

Further studies should be carried out to deepen further into the possible therapeutic and prognostic effects of these discoveries. Rodríguez Pérez gave a very interesting lecture on multiple sclerosis, a disease whose etiology is not yet known, although the possibility of viral causality is raised. Using the reibergram to calculate the specificity of the antibody index it is possible to establish evidences that relate the Epstein Barr virus to this disease. There were significant differences between Qspecific (Specific antibodies in

CSF / Specific antibodies in serum) between the multiple sclerosis group and the control group ($p < 0.0001$).⁽⁶⁾ Eosinophilic meningitis produced by *Angiostrongylus cantonensis* is in this moment an emerging disease in Western hemisphere. González-Losada quantified CSF and serum albumin by immunochemical nephelometry with kinetic analysis. The MBL reibergram was used in order to determine if MBL can be synthesized in the central nervous system or not. The H- and M-ficolins regressions were used in order to determine whether H- and M-ficolins could be synthesized in the central nervous system or not. Interestingly, it was found that Intrathecal activation of the lectin pathway by at least one of the quantified starters in this group of patients with eosinophilic meningitis due to *Angiostrongylus cantonensis*.⁽⁷⁾

The dengue virus continues as one of the scourges in tropical countries. Nowadays neurological manifestations associated to dengue virus are reported more frequently. Reibergram allowed to establish the incidence of intrathecal synthesis of three immunoglobulins types. Padrón González commented his results in the research developed with the objective To identify the neuroimmune response evaluated by Reibergram in patients with neurological manifestations because of dengue virus. It was shown that the use of Reibergram is important in the assessment of the immune response in patients with neurological manifestations of dengue virus.⁽⁸⁾

Dorta Contreras spoke about the results achieved by the LABCEL working group on the lectin pathways that were presented at the Experimental Biology event in San Diego, United States. Above all, he referred to the MASP-3 protein, whose functions are not fully understood. The evidence up to now allows to affirm that it is a regulating element of the lectin pathway and is able to activate the alternative pathway by activating factor D.⁽⁸⁾ Dorta commented on the diffusion of that protein to the central nervous system which can be found as complexes and its molecular weight is around 105 KDa. Blood-cerebrospinal fluid allows the protein diffusion according to molecular size and its relationship with their molecular flow. From the different inflection points of the relative frequency was found five different molecular orders and it's identified with the same number of aggregation forms. This five aggregation forms was associated with the molecular flow of this structures throughout blood-cerebrospinal barrier. It takes into account that the structure that diffuses more rapidly should be the 105 KDa native structure and it is possible to associate this aggregation with native multiple structures

and its molecular flow.^(8,9) Dorta also stated that the MASP-3 protein in CSF is predominantly brain-derived and all results pointed to the leptomeningeal cells as the source of the protein.⁽¹⁰⁾

CONCLUSIONS

The VII Edition of Quincke's Scholarship dealt with C1q protein and recently discovered themes of the lectin pathway and the use of the reibergram.

REFERENCES

1. Padrón-González AA, Dorta-Contreras AJ, Rodríguez-Pérez JA, Castillo González, González-Losada C. Becas Quincke: siete años multiplicando la experiencia. *Inmunología* [Internet]. 2018 [consultado 23 Abr 2019];37(4):46-49. Disponible en: <https://issuu.com/seinmunologia/docs/sei-v37-n4-2018>
2. Lumpuy-Castillo J, Jiménez-Hernández E, González-Losada C, Rodríguez-Pérez JA and Dorta-Contreras AJ. Teaching immunology based on open science's principles. Conference Abstract: XII Congress of the Latin American Association of Immunology & XXIII Congress of the Mexican Society of Immunology.
3. Lumpuy-Castillo J, González-Losada C, Schmitz M, Gudmann Hansen A, Jensenius JC, Dorta-Contreras AJ. C1q Intrathecal Synthesis in Patients Without Inflammatory Diseases with Blood-Brain Dysfunction. *FASEB J* 2018[Consultado Agosto 22, 2018]; 32, 1_supplement: 741.3. Disponible en: https://www.fasebj.org/toc/fasebj/32/1_supplement
4. González-Costa M, Padrón González AA. La inflamación desde una perspectiva inmunológica: desafío a la Medicina en el siglo XXI. *Rev haban cienc méd* [Internet]. 2018 [consultado 20 Mar 2019]; 18(1):30-44. Disponible en: <http://www.revhabanera.sld.cu/index.php/rhab/article/view/2445>

5. Padrón-González A, Dorta-Contreras J. Vía de las lectinas, una ruta del complemento en construcción. Archivos de alergia e inmunología clínica. [Internet]. 2018. [citado 28 Ago 2018]. (1):5-12. Disponible en:
<http://www.archivos.org.ar/contenido/art.php?recordID=MTA5MQ>
6. Rodriguez-Pérez JA, Pérez-Vallín V, Mirabal-Viel A, Padrón-González AA, Castillo-González W, González-Losada C, Dorta-Contreras AJ. Epstein Barr Virus and Multiple Sclerosis. FASEB J 2018[Consultado Agosto 22, 2018]; 32, 1_supplement: 617.3. Disponible en: https://www.fasebj.org/toc/fasebj/32/1_supplement
7. González-Losada C, Padrón-González AA, Lumpuy-Castillo J, Rodriguez-Pérez A, Castillo-González W, Dorta-Contreras AJ. Intrathecal Activation of the Lectin Pathway in Patients with Eosinophilic Meningitis by *Angiostrongylus cantonensis*. FASEB J 2018; 32, 1_supplement: 741.2. Disponible en:
https://www.fasebj.org/toc/fasebj/32/1_supplement, Abstract 741.2 ;Consultado Abril 22, 2018.
8. Padrón-González AA, González-Losada C, Dorta-Contreras J. Empleo del Reibergrama en manifestaciones neurológicas del dengue. Rev Hab. [Internet]. 2017.[citado 28 Ago 2018] Disponible en:
<http://www.revhabanera.sld.cu/index.php/rhab/article/view/2004/1863>
9. Dorta-Contreras A J, Padrón-González A A, González-Losada C, Lumpuy-Castillo J, Rodriguez-Pérez J A, Ramos-Robledo A, Martínez-Reyes J, et al. MASP-3: a new leptomeningeal protein in the lectin pathway. The FASEB Journal 2018 32:1_supplement, 741.5-741.5
10. Padrón-González A A, González-Losada C, Lumpuy-Castillo J, Rodriguez-Pérez J A, Ramos-Robledo A, Castillo-González W, Dorta-Contreras A J. MASP-3 aggregation and its blood to cerebrospinal fluid diffusion. The FASEB Journal 2018 32:1_supplement, 741.1-741.1