CHAPTER 3

COMPLEMENT ANALYSIS ON PARALYSIS (HEMIPLEGIA AND PARAPLEGIA)

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3.1 INTRODUCTION

The main object of the present chapter is to examine the variation of C3 and C4 complements in paralytic (Hemiplegia and Paraplegia) patients. The earlier work on the complement deficiency states has revealed that the deficiency of specific complement components is responsible for a couple of diseases. It is important to remember that this is similar to the disorders which occur with selective deficiencies of the immune system[1].

The complement system helps the ability of antibodies and phagocytic cells to clear pathogens from an organism. It is part of the immune system called the innate immune system that is not adaptable and does not change over the course of an individual's lifetime. However, it can be recruited and brought into action by the adaptive immune system[2,3].

The complement system consists of a number of small proteins found in the blood, generally synthesized by the liver, and normally circulating as inactive precursors (pro-proteins). When stimulated by one of several triggers, proteases in the system cleave specific proteins to release cytokines and initiate an amplifying cascade of further cleavages. The end-result of this activation cascade is massive amplification of the response and activation of the cell-killing membrane attack complex steps enhanced phagocytosis and membrane damage. Some of the important phenomena occurring during activation of the complement sequence are those related to acute inflammation and chemotaxis of leukocy. Over 25 proteins and protein fragments make up the complement system, including serum proteins, serosal proteins, and cell membrane receptors. They account for about 5% of the globulin fraction of blood serum.

Three biochemical pathways activate the complement system: the classical complement pathway, the alternative complement pathway, and the mannose-binding lectin pathway[4].
In the late 19th century, Hans Ernst August Buchner found that blood serum contained a "factor" or "principle" capable of killing bacteria. In 1896, Jules Bordet, a young Belgian scientist in Paris at the Pasteur Institute, demonstrated that this principle had two components: one that maintained this effect after being heated, and one that lost this effect after being heated. The heat-stable component was responsible for the immunity against specific microorganisms, whereas the heat-sensitive (heat-labile) component was responsible for the non-specific antimicrobial activity conferred by all normal serum. This heat-labile component is what we now call "complement".

The complement system consists of a group at least 20 interacting proteins found in normal serum. Proteins of the complement system make up about 5% of the serum proteins in vertebrates. The major components of the classical pathway are designated by a numbering system ranging from C1 through C9. The C1 protein also has three subcomponents: C1q, C1r and C1s. The alternative pathway consists of proteins called factor B, factor D and factor P(properdin), along with the C3 and C5 through C9 proteins active in the classical pathway.

The term "complement" was introduced by Paul Ehrlich in the late 1890s, as part of his larger theory of the immune system. According to this theory, the immune system consists of cells that have specific receptors on their surface to recognize antigens. Upon immunization with an antigen, more of these receptors are formed, and they are from the cells to circulate in the blood. These receptors, which we now call "antibodies," were called by Ehrlich "amboceptors" to emphasize their bifunctional binding capacity. They recognize and bind to a specific antigen, but they also recognize and bind to the heat-labile antimicrobial component of fresh serum. Ehrlich, therefore, named this heat-labile component "complement," because it is something in the blood that "complements" the cells of the immune system. In the early half of the 1930s, a team led by the renowned Irish researcher, Jackie Stanley, stumbled upon the all-important opsonization-mediated effect of C3b. Building off Ehrlich's work, Stanley's team proved the role of complement
in both the innate as well as the cell-mediated immune response. Antibodies can completely suppress or enhance the antibody response to their specific antigen by several hundred folds. Immunoglobulin M (IgM) enhances antibody responses via the complement system, and complement activation by IgM probably starts the chain of events leading to antibody responses to suboptimal antigen doses. IgG can enhance primary antibody responses in the absence of the complement system and seems to be dependent on Fc receptors for IgG. IgE enhances antibody responses via the low-affinity receptor for IgE. The precise effectors mechanisms that cause enhancement are not known, but direct B-cell signaling, antigen presentation, and increased follicular localization are all possibilities. IgG, IgE, and IgM may also suppress antibody responses when used in certain immunization regimes, and it seems reasonable that an important mechanism behind suppression is the masking of antigenic epitopes by antibodies[5].

Ehrlich believed that each antigen-specific amboceptor has its own specific complement, whereas Bordet believed that there is only one type of complement. In the early 20th century, this controversy was resolved when it became understood that complement can act in combination with specific antibodies, or on its own in a non-specific way. The main function of the complement system is to destroy foreign cells by damaging their plasma membranes, causing the cellular contents to leak out. This process, called cytolysis, is accomplished as follows:

1. Once a pair of antibodies recognizes and attaches to the antigen, the complement protein C1 (which actually consists of three subcomponents) binds to two or more adjacent antibodies, thus activating C1.

2. Next, activated C1 in turn activates C2 and C4. It does this by splitting the C2 and C4 proteins. C2 is split into fragments called C2a and C2b, and C4 into fragments called C4a and C4b. Then C2b and C4b combine to form another enzyme, which is turn activate C3 by splitting it into two fragments, C3a and C3b.
3. C3b initiates a sequence of reaction involving C5-C9, which is known collectively as the membranes attack complex (MAC). The activated components of these proteins with C9 proteins possibly playing a key role, attack the invading cells membranes.

4. Produce circular lesions called transmembrane channels that lead to the loss of ions and eventual cytolysis.

The following are the basic functions of the complement:

1. Opsonization - enhancing phagocytosis of antigens
2. Chemotaxis - attracting macrophages and neutrophils
3. Lysis - rupturing membranes of foreign cells
4. Clumping of antigen-bearing agents
5. Altering the molecular structure of viruses

![Cell Membrane](image)

**Figure 3.1:** Cell Membrane

The proteins and glycoproteins that constitute the complement system are synthesized by the liver hepatocytes. But significant amounts are also produced by tissue macrophages, blood monocytes, and epithelial cells of the genitourinal tract and gastrointestinal tract. The three pathways of activation all generate homologous variants
of the protease C3-convertase. The classical complement pathway typically requires antigen:antibody complexes for activation (specific immune response), whereas the alternative and mannose-binding lectin pathways can be activated by C3 hydrolysis or antigens without the presence of antibodies (non-specific immune response). In all three pathways, a C3-convertase cleaves and activates component C3, creating C3a and C3b, and causing a cascade of further cleavage and activation events. C3b binds to the surface of pathogens, leading to greater internalization by phagocytic cells by opsonization. C5a is an important chemotactic protein, helping recruit inflammatory cells. Both C3a and C5a have anaphylatoxin activity, directly triggering degranulation of mast cells as well as increasing vascular permeability and smooth muscle contraction. C5b initiates the membrane attack pathway, which results in the membrane attack complex (MAC), consisting of C5b, C6, C7, C8, and polymeric C9[6]. MAC is the cytolytic end product of the complement cascade; it forms a transmembrane channel, which causes osmotic lysis of the target cell. The complement system[7] plays an important role in mediating tissue injury after oxidative stress. The role of mannose-binding lectin and the lectin complement pathway in mediating complement activation after endothelial oxidative stress was investigated[8] Complement activation represents a crucial innate defense mechanism to invading microorganisms, but there is an eminent lack of understanding of the separate contribution of the different complement activation pathways to the host response during sepsis[9]. Complement activation has been shown to play an important role in the inflammation and tissue injury following myocardial ischemia and reperfusion (MI/R). The importance of mannose-binding lectin as the initiation pathway for complement activation and the resulting pathological effects following MI/R[10]. The limited proteolytic reactions, characterize the complement system, are essentially not reversible. These reactions lead to cleaved proteins, which are recognized by the body as
altered or foreign. These proteins are rapidly cleared from the circulation. Despite compensatory increases in syntheses the result is usually a fall in plasma levels. Thus, an ongoing immunologic events, which is activating the complement system in vivo is likely to generate a decrease in plasma levels of these proteins. Conversely the abatement of the complement activating stimulus may be paralleled by a return of the complement levels towards normal[29].

The classical pathway is triggered by activation of the C1-complex. C1q, an integral part of the first component of complement (C1), triggers the activation process when it docks onto antibodies within these immune complexes[11]. The alternative pathway is triggered by spontaneous C3 hydrolysis directly due to the breakdown of the thioester bond via condensation reaction (C3 is mildly unstable in aqueous environment) to form C3a and C3b. It does not rely on a pathogen-binding antibodies like the other pathways[4]. C3b is then capable of covalently binding to a pathogenic membrane surface if it is near enough. If there is no pathogen in the blood, the C3a and C3b protein fragments will be deactivated by rejoining with each other. The protein C3 is produced in the liver. Ischemia-reperfusion injury (IRI) has a major impact on graft survival after transplantation. Renal proximal tubular epithelial cells located at the corticomedullary zone are relatively susceptible to IRI and have been identified as one of the main targets of complement activation. Studies in mice have shown an important role for the alternative pathway of complement activation in renal[12].

The lectin pathway is homologous to the classical pathway, but with the opsonin, mannose-binding lectin (MBL), and ficolins, instead of C1q. This pathway is activated by binding mannose-binding lectin to mannose residues on the pathogen surface.

In the classical pathway, C1 binds with its C1q subunits to Fc fragments (made of CH2 region) of IgG or IgM, which has formed a complex with antigens. C4b and C3b are also able to bind to antigen-associated IgG or IgM to its Fc portion [3,13,14].
Such immunoglobulin mediated binding of the complement may be interpreted as that the complement uses the ability of the immunoglobulin to detect and bind to non-self antigens as its guiding stick. The complement itself is able to bind non-self pathogens after detecting their pathogen associated molecular patterns[14].

The complement system has the potential to be extremely damaging to host tissues, meaning its activation must be tightly regulated. The complement system is recapitulated by complement control proteins, which are present at a higher concentration in the blood plasma than the complement proteins themselves. Some complement control proteins are present on the membranes of self-cells preventing them from being targeted by complement.

It is thought that the complement system might play a role in many diseases with an immune component, such as Barraquer-Simons Syndrome, asthma, lupus erythematosus, glomerulonephritis, various forms of arthritis, autoimmune heart disease, multiple sclerosis, inflamsematory bowel disease, and ischemia-reperfusion injuries[15,16] and rejection of transplanted organs[17]. Deficiencies of C1,C2 or C4 cause collagen vascular disorders that result in hypersensitivity (anphlaxis); deficiency of C3,though rare,resultin increased susceptibility to bacterial infections; and C5-C9 defects result in increased susceptibility to neisseria meningitides and N. gonorrhoease infections.

The complement system is also becoming increasingly implicated in diseases of the central nervous system such as Alzheimer's disease and other neurodegenerative conditions such as spinal cord injuries [18,19,20]. There are two types of deficiencies of complement: hereditary and acquired. Acquired deficiencies persist over long periods and also become causative factor for certain disease. We would like to mention that complements are sequentially reacting serum protein. On activation, these proteins mediated a number of biological reactions significant to host defense against bacteria,
viruses and other injurious stimuli. Antigen-antibody complexes, bacterial and microbial and tissue enzymes initiate the activation. Biological activities mediated by the activated complement proteins or by their fragments include increased capillary permeability chemotaxis of leukocytes, enhanced phagocytosis, retention of leukocytes at the site of tissue injury and cytolysis. The basic role of this system is the mediation of host defence against microbial infection.

Deficiencies of the terminal pathway predispose to both autoimmune disease and infections. This goal is fulfilled during activation of complement by the elaboration of peptides, larger protein fragments and multimolecular complexes that opsonize and lyse the activating target; include chemotactic, secretory and metabolic responses of leukocytes and alter vascular permeability. These activities constitute an inflammatory response. The complement system is the most complex of the several protein activation systems in blood.

Recent research has suggested that the complement system is manipulated during HIV/AIDS to further damage the body[21].

3.1.1 Complement Component 3

Complement component 3, often simply called C3, is a protein of the immune system. It plays a central role in the complement system and contributes to innate immunity. In humans it is encoded on chromosome 19 by a gene called C3[22,23].

C3 plays a central role in the activation of complement system[24]. Its activation is required for both classical and alternative complement activation pathways. People with C3 deficiency are susceptible to bacterial infection[25,26].

C3 is formed by a heterodimer of activated forms of C4 and C2. It catalyzes the proteolytic cleavage of C3 into C3a and C3b is generated during activation through the classical pathway as well as the mannann-binding lectin pathway. C3a is an
anaphylatoxin, and C3b serves as an opsonizing agent. The Molecular weight of C3 is 18500 and serum concentration of complement C3 is 1500µg/ml.

3.1.2 Complement Component 4

Complement component 4 is a protein involved in the complement system. It is cleaved into proteins 4a and 4b.

- C4a is an anaphylatoxin,
- C4b forms part of C3-convertase, in conjunction with 2a,
- C4b can bind CR1,
- C4d is the final proteolytic remnant of deposited C4b on endothelium, remains covalently attached to endothelium for little more than a week and easily detectable by antibody staining.

C4d is the most clinically used marker for humoral rejection[27]. It is a degradation product of the activated complement factor C4b. C4d is typically initiated by binding of antibodies to specific target molecules. Detection of C4d is regarded as an indirect sign, a ‘footprint’ of an antibody response. This observation marks a ‘revolution’: For the first time, a general and robust immunohistochemical marker for humoral rejection is identified. Since C4d is practically never detected along peritubular capillaries in the native diseased and inflamed kidney, such as active lupus nephritis, antineutrophil cytoplasmic antibody disease, or anti-glomerular basement membrane disease, its detection seems ‘transplant-specific’. However, it should be kept in mind that, apart from the classical antibody-mediated route of complement activation[28], C4 can also be activated via an alternative, antibody-independent mechanism, the ‘mannan-binding lectin’ pathway. Thus, C4d may also be potentially deposited without prior
antibody binding. At the current time, it is unknown whether this lectin pathway plays any pathophysiological role in the activation of C4 in renal transplants. Therefore, based on our current understanding, C4d accumulation is considered to be a marker for an ‘antibody-mediated allo-response’. The detection of C4d in a graft biopsy, in ideal circumstances, should be amended by clinical information on circulating donor-specific antibodies against major histocompatibility complex class I or class II. The molecular weight of C4 is 18000 and the serum concentration of complement C4 is 400µg/ml.

To the best of our knowledge and belief, the correlation between the complement C3 and C4 in paralysis (hemiplegia and paraplegia) is a completely unstudied aspect so far.

The purpose of this chapter is to investigate the extent up to which these two complements C3 and C4 are correlated in paralysis.

### 3.2 MATERIAL AND METHODS

The blood samples of patients suffering from paralysis (hemiplegia and paraplegia) and healthy control person were collected from the Department of Neurology, Safdarganj Hospital, New Delhi. 10 ml freshly drawn blood from patient was collected in clean and dry test tubes without any anti-coagulant. The test tube was kept for 45 minutes at 220±2 C temperature for the formation of clot. Sera of patient and healthy person were separated by centrifugation at 1,500 r.p.m. upto 15 minutes and were collected in sterile screw capped test tubes.

### 3.3 RESULTS AND DISCUSSION

C3 and C4 complements were measured in selected well defined 15 patients of paralysis (Hemiplegia and Paraplegia) and 09 healthy controls. Table 3.1 gives our data.
on cases of paralysis (Hemiplegia and Paraplegia) and normal healthy controls. Our findings are based on a total number of 24 cases.

C3 values in paralysis (Hemiplegia and Paraplegia) are found to lie between 1.07 gm/L to 2.28 gm/L, while C4 is observed to be within 0.09 gm/L to 0.48 gm/L. C3 is found to be significantly higher than C4 in all the cases of paralysis. R_{34} is found in between 3.4 to 11.88. The average value of C3/C4 corresponding to all the cases of paralysis is found to 5.94.

Table 3.1: Summary of the results obtained on C3 and C4 complements in paralytic patients and normal healthy controls. P-Paralysis, N-Normal healthy Control

<table>
<thead>
<tr>
<th>S. No</th>
<th>Factor</th>
<th>C3 (gm/lit)</th>
<th>C4 (gm/lit)</th>
<th>R_{34} = C3/C4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>P</td>
<td>1.07</td>
<td>0.09</td>
<td>11.88</td>
</tr>
<tr>
<td>2</td>
<td>P</td>
<td>2.06</td>
<td>0.38</td>
<td>5.42</td>
</tr>
<tr>
<td>3</td>
<td>P</td>
<td>2.28</td>
<td>0.46</td>
<td>4.95</td>
</tr>
<tr>
<td>4</td>
<td>P</td>
<td>2.01</td>
<td>0.26</td>
<td>7.73</td>
</tr>
<tr>
<td>5</td>
<td>P</td>
<td>1.84</td>
<td>0.33</td>
<td>5.57</td>
</tr>
<tr>
<td>6</td>
<td>P</td>
<td>1.69</td>
<td>0.47</td>
<td>3.59</td>
</tr>
<tr>
<td>7</td>
<td>P</td>
<td>2.05</td>
<td>0.46</td>
<td>4.45</td>
</tr>
<tr>
<td>8</td>
<td>P</td>
<td>1.98</td>
<td>0.18</td>
<td>11.00</td>
</tr>
<tr>
<td>9</td>
<td>P</td>
<td>1.76</td>
<td>0.44</td>
<td>4.00</td>
</tr>
<tr>
<td>10</td>
<td>P</td>
<td>2.03</td>
<td>0.43</td>
<td>4.72</td>
</tr>
<tr>
<td>11</td>
<td>P</td>
<td>2.08</td>
<td>0.48</td>
<td>4.33</td>
</tr>
<tr>
<td>12</td>
<td>P</td>
<td>1.86</td>
<td>0.29</td>
<td>6.41</td>
</tr>
<tr>
<td>13</td>
<td>P</td>
<td>1.53</td>
<td>0.45</td>
<td>3.40</td>
</tr>
<tr>
<td>14</td>
<td>P</td>
<td>2.07</td>
<td>0.46</td>
<td>4.50</td>
</tr>
<tr>
<td>15</td>
<td>P</td>
<td>2.06</td>
<td>0.29</td>
<td>7.10</td>
</tr>
<tr>
<td>16</td>
<td>N</td>
<td>1.72</td>
<td>0.45</td>
<td>3.82</td>
</tr>
<tr>
<td>17</td>
<td>N</td>
<td>1.58</td>
<td>0.34</td>
<td>4.64</td>
</tr>
<tr>
<td>18</td>
<td>N</td>
<td>1.31</td>
<td>0.23</td>
<td>5.69</td>
</tr>
<tr>
<td>19</td>
<td>N</td>
<td>1.64</td>
<td>0.33</td>
<td>4.96</td>
</tr>
<tr>
<td>20</td>
<td>N</td>
<td>1.75</td>
<td>0.16</td>
<td>10.93</td>
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<tr>
<td>21</td>
<td>N</td>
<td>1.63</td>
<td>0.21</td>
<td>7.76</td>
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<td>22</td>
<td>N</td>
<td>1.38</td>
<td>0.39</td>
<td>3.53</td>
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<td>23</td>
<td>N</td>
<td>1.73</td>
<td>0.26</td>
<td>6.65</td>
</tr>
<tr>
<td>24</td>
<td>N</td>
<td>1.53</td>
<td>0.17</td>
<td>9</td>
</tr>
</tbody>
</table>
We get very interesting results from Table 3.2 which shows that $R_{34}$ falls from 6.33 in normal healthy controls to 5.94 in paralytic cases. Reduction in the value of $R_{34}$ appears to be related with the occurrence of paralysis while a paralytic patient must be given such a kind of drug treatment which may increase his/her $R_{34}$ factor.

**Table 3.2:** Mean level and standard deviation (S.D.) of paralytic patients and normal healthy controls. P-Paralysis, N-Normal healthy Control

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>N</th>
<th>Mean level of C3</th>
<th>Standard deviation of C3</th>
<th>Mean level of C4</th>
<th>Standard deviation of C4</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>15</td>
<td>1.891</td>
<td>0.293</td>
<td>0.364</td>
<td>0.120</td>
</tr>
<tr>
<td>N</td>
<td>9</td>
<td>1.585</td>
<td>0.155</td>
<td>0.282</td>
<td>0.100</td>
</tr>
</tbody>
</table>

**Table 3.3:** Regression and correlation coefficient pertaining to C3 and C4 complements in Paralytic patients and normal healthy Control: P-Paralysis, N-Normal healthy Control

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Regression coefficient</th>
<th>Regression equation</th>
<th>Coefficient of correlation</th>
<th>Conclusion</th>
</tr>
</thead>
</table>
| P         | $b_{c3c4} = 1.134$     | $C3 = 1.478 + 1.134C4$  
$b_{c4c3} = 0.190$  
$C4 = 0.006 + 0.190C3$ | $r_{C3C4} = 0.464$ | $C3$ and $C4$ are positively correlated |
| N         | $b_{c3c4} = 0.039$     | $C3 = 1.597 - 0.039C4$  
$b_{c4c3} = -0.017$  
$C4 = 0.039 - 0.017C3$ | $r_{C3C4} = -0.026$ | $C3$ and $C4$ are negatively correlated |

The value of $R_{34}$ (6.33) in our normal healthy controls is close to that of 5.89 as reported by Moore et al [29].

At this stage it becomes absolutely essential to examine the role played by complements in paralysis, keeping in view the results of present experimental findings. Disorders associated with complement[30].

They constitute a very important part in the saga of human diseases. Food (protein rich) taken as properly (regularly) to increase the level of complements.
Some of the main disorders involving abnormal and functional units are congential deficiency of C3, recurrent infections with congenital deficiency C3 BOIN or C3 Hypercatabolism, recurrent infection with thermal injuries, malnutrition, or in the new born period, transplant rejection and tumor propagation.

Table 3.4: Statistical evaluation of the measured values of C3 and C4 complements in paralysis. A search was made to investigate the significance of the experimental data: P-Paralysis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Factor</th>
<th>( t_{exp} )</th>
<th>( t_{theo} )</th>
<th>Results</th>
<th>( p )</th>
<th>Null Hypothesis ( (H_0) )</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>C3</td>
<td>2.62 at 0.02</td>
<td>( t_{exp} &gt; t_{theo} )</td>
<td>0.02</td>
<td>Rejected</td>
<td>There is appreciable difference between C3 values at 2% level of significance.</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>2.62 at 0.02</td>
<td>( t_{exp} &lt; t_{theo} )</td>
<td>0.02</td>
<td>Accepted</td>
<td>At 2% level of significance we do not observe significant difference between C4 values.</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>C4</td>
<td>2.15 at 0.05</td>
<td>( t_{exp} &gt; t_{theo} )</td>
<td>0.05</td>
<td>Rejected</td>
<td>At 5% level of significance there is appreciable difference between C4 values.</td>
<td></td>
</tr>
</tbody>
</table>

Hypocomplementemic varieties of glomerulonephritis, rheumatoic arthritis, systemic lupus erythmatosus, acute and chronic active viral hepatitis, certain allergic reactions, serum sickness, arthus vasculitis, bullous dermatitis hyperpetiformis, immune
complex formation in various diseases, endotoxemia, partial Hhypodystrophy, autoimmune hemolytic anemia and thrombocytopenia are disorders in normal activation and normal functional units. Disorders involving normal activation units with an abnormal function unit are congenital component deficiencies (C5, C6, C7, C8) 

Disorders which involve abnormal activation units with a normal functional unit are hereditary angioneurotic edema, non-specific vasculitis, congenital component deficiencies (C1r, C2, C4, P), infections in patients with sickle cell disease and in the newborn period.

3.4 CONCLUSIONS

We have found that there is appreciable significant difference between C3 values at 2% level of significance. It has been seen that the variation of C4 values is appreciable at 5% level of significance. We do not observe any significant difference in C4 values at 2% level of significance.

Our main findings are the coefficients of correlation between the concentrations of C3 and C4 complements which is found to be 0.464 (positively correlated) in paralysis while in normal healthy controls it is found to be -0.026 (negatively correlated). We therefore conclude that the concentrations of these two complements C3 and C4 are positively correlated in paralytic disorders. A therapy based on pharmaceuticals aiming at reduction or increase of any of these complements must take into account the impact it will have on the other complement.
3.5 REFERENCES


Chapter 3: Complement Paralysis


