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Streptococcus and rheumatic fever

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Abstract

Purpose of review—To give an overview of the current hypotheses of the pathogenesis of rheumatic fever and group A streptococcal autoimmune sequelae of the heart valve and brain.

Recent findings—Human monoclonal antibodies (mAbs) derived from rheumatic heart disease have provided evidence for crossreactive autoantibodies that target the dominant group A streptococcal epitope of the group A carbohydrate, N-acetyl-beta-D-glucosamine (GlcNAc), and heart valve endothelium, laminin and laminar basement membrane. T cells in peripheral blood and in rheumatic heart valves revealed the presence of T cells crossreactive with streptococcal M protein and cardiac myosin. For initiation of disease, evidence suggests a two-hit hypothesis for antibody attack on the valve endothelium with subsequent extravasation of T cells through activated endothelium into the valve to form granulomatous lesions and Aschoff bodies. Autoantibodies against the group A streptococcal carbohydrate epitope GlcNAc and cardiac myosin and its peptides appear during progression of rheumatic heart disease. However, autoantibodies against collagen that are not crossreactive may form because of the release of collagen from damaged valve or to responses to collagen bound *in vitro* by certain serotypes of streptococci. In Sydenham chorea, human mAbs derived from disease target the group A carbohydrate epitope GlcNAc and gangliosides and dopamine receptors found on the surface of neuronal cells in the brain. Human mAbs and autoantibodies in Sydenham chorea were found to signal neuronal cells and activate calcium calmodulin-dependent protein kinase II (CaMKII) in neuronal cells and recognize the intracellular protein biomarker tubulin.

Summary—To summarize, pathogenic mechanisms of crossreactive autoantibodies which target the valve in rheumatic heart disease and the neuronal cell in Sydenham chorea share a common streptococcal epitope GlcNAc and target intracellular biomarkers of disease including cardiac myosin in the myocardium and tubulin, a protein abundant in the brain. However, intracellular antigens are not believed to be the basis for disease. The theme of molecular mimicry in streptococcal autoimmune sequelae is the recognition of targeted intracellular biomarker antigens such as cardiac myosin and brain tubulin, while targeting extracellular membrane antigens such as laminin on the valve surface endothelium or lysoganglioside and dopamine receptors in the brain. Antibody binding to these cell surface antigens may lead to valve damage in rheumatic heart disease or neuropsychiatric behaviors and involuntary movements in Sydenham chorea.

Keywords

autoimmunity; molecular mimicry; rheumatic heart disease; streptococci; Sydenham chorea

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Conflicts of interest

M.W.C. has received compensation from Moleculera Labs (laboratory diagnostics for Sydenham chorea and PANDAS) and Grifols (Formerly Talecris) for support of the NIMH IVIG trial.

INTRODUCTION

Group A streptococci (*Streptococcus pyogenes*) have long been associated with the development of autoimmune sequelae associated with rheumatic fever [1,2]. The primary manifestations of rheumatic fever involve heart, joints, brain, or skin. Rheumatic carditis is the most serious of all five of the streptococcal sequelae and presents with heart murmur as a result of valve deformation. Sydenham chorea is the neurologic manifestation of rheumatic fever [3] and may present solely or in conjunction with carditis, or polymigrating arthritis, the most common manifestation [4]. Other signs of rheumatic fever include erythema marginatum and subcutaneous nodules. The Jones criteria [5] define rheumatic fever diagnosis, and these five major manifestations, any of which may be present, as well as documentation of a streptococcal infection by microbiologic culture or elevated antistreptococcal antibody titers such as elevated antistreptolysin O and anti-DNAse B which indicate previous infection with group A streptococci [1].

Mimicry between group A streptococci and host antigens has been proposed [6,7] and supported by evidence from previous studies as a mechanism for the development of the manifestations observed in acute rheumatic fever (ARF) [8,9]. Group A streptococci possess antigens [8–14] and superantigens [15,16] which stimulate B and T cells to respond to self. In studies to understand the potential mechanisms leading to postinfectious autoimmune sequelae, production of human mAbs [8,9] and human T-cell clones [17–19] have revealed evidence supporting the molecular mimicry hypothesis. Animal models of rheumatic heart disease have been important in defining mimicry in heart disease as well as defining pathogenic epitopes of the autoantigens and microbial antigens involved [20]. Although the use of animal models lead to a better understanding of the human disease [20–22,23], they are not a substitute for human studies.

The most recent evidence in studies of rheumatic heart disease suggest that autoantibody responses against human cardiac myosin peptides localized to the S2 hinge region of the human cardiac myosin rod fragment detect carditis [24], and the disease-associated peptide epitopes can monitor the progression of rheumatic heart disease [23]. Rheumatic carditis is associated with antistreptococcal antibody and T-cell responses against cardiac myosin and anticardiac myosin antibody responses against the dominant group A carbohydrate epitope, N-acetyl-beta-D-glucosamine (GlcNAc). The autoantibodies against cardiac myosin are also in tandem with responses against collagen I [25] which could not only be because of the aggregation of collagen by certain streptococcal serotypes, but also may be because of the release of collagen from the damaged valve during rheumatic heart disease. The cardiac myosin responses are crossreactive, whereas the responses against collagen I are not crossreactive indicating that release of collagen from the valve is a probable important source of exposure of collagen to the human immune system.

Finally, a recent analysis of the crystallized group A streptococcal M protein describes how the alpha helical coiled-coil structure and epitopes are recognized in alpha helical proteins as a basis for molecular mimicry and crossreactivity between streptococcal M proteins and cardiac myosin [14]. All aspects of these mechanisms will be discussed further in the review.

In Sydenham chorea and its possible variant pediatric autoimmune neuropsychiatric disorder associated with streptococci (PANDAS), new evidence strongly supports autoantibody mimicry mechanisms [9,26–28]. Autoantibodies present in Sydenham chorea were found to signal neuronal cells and bind to brain gangliosides as well as intra-cellular tubulin. The emerging concepts of mimicry show how autoantibodies that are potentially pathogenic

recognize an intracellular biomarker such as tubulin in the brain or cardiac myosin in the heart, but target the surface of the neuronal cells or valve endothelial cells during pathogenesis by signaling pathways in the neurons or by inflammatory effects on the endothelium of the valve. These mechanisms of molecular mimicry in the brain will be described in more detail in the review.

ADVANCES IN RHEUMATIC HEART DISEASE: A MULTISTEP HYPOTHESIS

Rheumatic heart disease is characterized by the presence of high levels of antistreptococcal group A carbohydrate antibodies which have been found to persist and remain highly elevated in rheumatic valvular heart disease with a poor prognosis [29]. Even in the early days of research in group A streptococcal-induced rheumatic heart disease of the valve, Goldstein *et al.* [30] demonstrated that carbohydrates were important in binding autoantibodies against the streptococcus and the valve. More recent studies of human monoclonal antibodies (mAbs) from rheumatic heart disease show that they not only recognize cardiac myosin in the myocardium [8] as shown for antibodies previously from humans and streptococcal immunized animals [6,7,31], but also recognize valve endothelium as well. Human mAbs derived from rheumatic carditis reacted with GlcNAc and cardiac myosin [8], and these human antistreptococcal antibodies attached to the surface of valvular endothelium as well as the myocardium indicating a crossreactivity between the valve endothelium, group A streptococcal carbohydrate and cardiac myosin in the myocardium. Eventually, the crossreactive antigen on valve endothelium and in the basement membrane was determined to be laminin, but it and other cell surface proteins are also glycosylated, and the carbohydrate epitopes on the valve and streptococcus were pointed out by Goldstein *et al.* in early studies. The human mAbs which react with the valve and the heart, as well as the group A carbohydrate epitope GlcNAc, correlate with what has been described about antigroup A carbohydrate antibodies in streptococcal infections and their association with progressive valvular heart disease [29,30]. The group A carbohydrate consists of a polyrhmannose core in alternating 1,2 and 1,3 linkages, and it has been suggested that the terminal O-linked GlcNAc residue is important in the induction of cross-reactive Abs because of its structural similarity to many host glycoconjugates [32,33].

Figure 1 [34] shows the antibody and T-cell mechanisms in a two-hit hypothesis of rheumatic heart disease, in which the autoantibodies target the activated valve endothelium. Figure 2 [34,35] is a comprehensive diagram indicating the multistep process of rheumatic heart disease including damage to the internal valve and exposure of collagen. Step 1 shown involves the crossreactive anticardiac myosin and antigroup A carbohydrate antibody attacking the endothelium (Fig. 1) at the valve surface and the exposure of laminin and collagen (Fig. 2) to the immune system. Antibodies that form against exposed collagen or to group A streptococci that bind to collagen *in vitro* [13,24,36] target the collagen in the damaged internal valve. Neovascularization predisposes the previously immunoprivileged and protected valve to damage from antibodies that get into the internal valve directly.

Valve endothelium is an infiltration site for lymphocyte extravasation into the immunoprivileged valve [37]. Studies show clearly that infiltration of T cells is because of the upregulation of vascular cell adhesion molecule-1 (VCAM-1) on valvular surface endothelium [37]. Waves of CD4⁺ T cells, the most prominent T-cell subset in the valve during rheumatic carditis, and the granulomatous reaction are evident with the presence of gamma IFN in the valve [38]. Infiltrates are observed at and directly below the valve endothelium as well as endocardium covering the papillary muscle which does contain cardiac myosin within the cardiomyocytes in the muscle, where valve attaches into the myocardium [37]. Anticardiac myosin antibodies and crossreactive T cells may target this region attached to the valve.

Crossreactive T-cell clones that respond to group A streptococcal M protein and cardiac myosin epitopes have been derived from both peripheral blood [17] and heart valves [18] of rheumatic carditis. The avidity of the T-cell clones indicated antigen response profiles for streptococcal M protein > cardiac myosin > laminin > tropomyosin in gamma IFN Elispot and proliferation assays *in vitro* [17]. The study of human T-cell clones from rheumatic heart disease revealed potential sites of T-cell mimicry between streptococcal M protein and human cardiac myosin, and represents some of the most well defined T-cell mimicry in human autoimmune disease. The crossreactive human T-cell clones proliferated to peptides B2 and B3A, dominant peptide epitopes in the B repeat region of group A streptococcal M protein serotype 5. In human cardiac myosin, epitopes were demonstrated in the S2 and light meromyosin regions. Crossreactive T cells extravasate into the valve through valvular endothelium, and T cells isolated from valves responded to M protein peptides as well as human cardiac myosin peptides in the S2 and LMM regions of the cardiac myosin rod. Similar results were found for T cells in the Lewis rat model of valvulitis [20,39].

The explanation for antistreptococcal antibody crossreactivity with the valve endothelium and its role as an infiltration site for lymphocyte extravasation into the immuno-privileged valve [31] is the antibody recognition of laminin and glycosylated proteins at the valve surface and within the basement membrane [8]. T cells recognize laminin within the basement membrane and surface of the valve [17]. Laminin is a large 900-kDa alpha-helical coiled-coil molecule composed of three chains, A, B1 or B2, which contain domains that are highly homologous with streptococcal M proteins and cardiac myosins. Shared amino acid sequences in the protein laminin were highly homologous with human cardiac myosin and form the basis for the crossreactivity between the myocardium and the valve. Further evidence demonstrated that the laminin sequence HTQNT was found to inhibit the binding of rheumatic-derived mAbs to valve endothelium and basement membrane [8]. Rheumatic carditis derived mAb was found to be cytotoxic for human endothelial cells in the presence of complement [8]. Suggested mechanisms for antibody deposition on the valve would indicate that laminin or some other similar cross-reactive protein or glycosylation of laminin or other extracellular matrix proteins exposed at the valve surface and within the basement membrane may trap antibody on the valve surface. Laminin or other crossreactive proteins on the valve surface or in the basement membrane would contribute to the deposition of antibody on the valve as well as enhance the upregulation of proinflammatory signals by the endothelium. Targeted crossreactive antibodies may bind directly to valve endothelium or basement membrane of the valve and be further damaged by shear stress on the endothelium. Lymphocytes appeared to extravasate into the valve directly through endothelium expressing VCAM-1 [37]. An animal model of similar histological valvular heart disease was established in Lewis rats immunized with streptococcal M6 protein [20]. This model has been confirmed and expanded by Ketheesan and colleagues [21]. In humans, the rheumatic heart disease model requires that the endothelium become activated in order for M-protein-specific T cells to enter the valve and produce disease. As valvular injury is the most serious consequence of rheumatic carditis, the understanding of pathogenic mechanisms in valvular inflammation is crucial to understanding the basis of rheumatic heart disease.

As mitral regurgitation is most commonly seen in rheumatic carditis, it is reported to be caused by annular dilation and chordal elongation, which prevents adequate surface coaptation of the valve leaflets [40]. Troponin levels are not elevated indicating that myocardial function is not compromised. Cardiac myosin is not present in the valve. However, antibodies or T cells specific to cardiac myosin react with the valve in rheumatic carditis because they crossreact with the valve proteins laminin and vimentin [8,39]. The similarity of cardiac myosin with proteins in the valve may be the basis of crossreactivity with the valve. Mimicry may result in initial damage to the valve, while release of collagen I

from damaged valve may lead to the immune response observed against collagen I in rheumatic heart disease [25]. Martins *et al.* [25] have shown that collagen I in the valve may serve as an important target antigen associated with internal valve damage. Anticollagen I antibody was found to be elevated in patients with ARF and was significantly higher in patients with carditis than in those without carditis. Although antibodies to collagen I were not found to be crossreactive, they may be generated because of exposure of collagen I to the immune system from the damaged valve. These investigators also found elevated antibody to cardiac myosin in patients with ARF, compared with that in patients with pharyngitis and in healthy control individuals. Antistreptococcal crossreactive anticardiac myosin antibodies initially may cause valve inflammation at the endothelium, leading to edema, cellular infiltration, and fibrinous vegetations in the rough zone of the anterior leaflet. Scarring of the leaflets appears after chordal elongation, which is the cause of mitral regurgitation. Valve endocardium and laminar basement membrane would be targeted by the first wave of autoantibodies in rheumatic carditis, and the chordae tendinae are the most susceptible to attack by the antibody.

Repetitive streptococcal infections would lead to lymphocyte infiltration through neovascularized regions in the scar tissue of the valve leading to perpetuation of the disease. As the rheumatic heart disease progresses, immune responses in the valve would advance to epitope spreading and recognition of other components of the valve such as vimentin and collagen. In previous studies [13,36], certain group A streptococcal strains have been shown to aggregate collagen *in vitro* and induce responses against collagen. These events may add to the insults to the valve through induction of collagen-specific antibodies which are not crossreactive and target the internal valve.

Most recent studies have utilized human cardiac myosin peptides to study antibody epitopes recognized in rheumatic heart disease as well as pharyngitis and normal individuals [24■■]. Figure 3 illustrates the human cardiac myosin S2 rod region epitopes recognized by rheumatic carditis sera from the United States. Our study identified disease-specific epitopes of human cardiac myosin recognized by IgG in rheumatic carditis in humans. Immune responses to cardiac myosin were strikingly similar in rheumatic carditis among a small sample of worldwide populations [U.S. mainland (Fig. 3), Hawaii (not shown) and India (not shown)], in which immunoglobulin G targeted similar human cardiac myosin epitopes in the S2 subfragment hinge region within human cardiac myosin S2 subfragment (amino acid residues 842–992 and 1164–1272). This recent report suggests that cardiac myosin epitopes in rheumatic carditis target the S2 region of cardiac myosin and are similar among populations with rheumatic carditis worldwide, regardless of the infecting group A streptococcal M serotype [24■■].

To understand the molecular interactions of crossreactive streptococcal and host epitopes, human mAbs which target the group A carbohydrate epitope GlcNAc also react with alpha-helical coiled-coil molecules and very well defined peptide epitopes that suggest hydrophobic and aromatic amino acids are important in the interaction with crossreactive antibody molecules [41]. More recently, the crystal structure of streptococcal M protein was solved [14], and M protein mutants explained the alpha helical structure related to virulence and crossreactivity. The alpha-helical coiled-coil streptococcal M protein structure is well known for its crossreactive properties with antibodies against cardiac myosin [1]. The alpha helical structure in M1 protein was observed to exhibit substantial irregularities and instabilities of a non-idealized alpha helix [14]. Mutations in the M1 protein, which dictated an idealized alpha helix, stabilized the alpha helical structure and diminished the virulent proinflammatory and cardiac myosin crossreactive properties of the streptococcal M1 protein but maintained its ability to induce protective opsonic antibody [14].

ANTINEURONAL ANTIBODIES OF SYDENHAM CHOREA

Sydenham chorea is a disorder of the central nervous system which is characterized by involuntary movements preceded by neuropsychiatric symptoms and emotional lability [42]. Human mAbs derived from Sydenham chorea have advanced our understanding of the potential role of antibody in movement and behavioral disorders [9]. The chorea-derived human mAbs or acute chorea serum IgG reacted with the surface of neuronal cells and demonstrated antibody crossreactivity with the group A carbohydrate epitope GlcNAc and lysoganglioside [9]. The human mAb study as well as study of IgG in the sera from Sydenham chorea shows that specific neuronal cell directed IgG causes activation and induction of elevated CaMKII levels in a human neuronal cell line SK-N-SH. Subsequent study of acute and convalescent Sydenham chorea sera led to the discovery that antibodies in the acute sera also induced similar neuronal cell signaling as well as increased dopamine release from the neuronal cell line [28]. Removal of IgG from serum leads to a loss of antibody-mediated neuronal cell signaling activity. Antibody-mediated neuronal cell signaling was induced by IgG antibodies in serum or cerebrospinal fluid from Sydenham chorea, and the presence of these signaling autoantibodies were associated with symptoms. The autoantibodies decreased when symptoms improved [9,33]. Further study indicated the chorea-derived, mAb-induced tyrosine hydroxylase activity in dopaminergic neurons after intrathecal transfer of purified human chorea-derived mAb into Lewis rat brain [28] (Fig. 4). In addition, in a mouse model of behavior following streptococcal immunization, passive transfer of antistreptococcal antibodies into mice led to autoantibody deposits in the brain as well as behavior changes [43,44]. Most recent studies demonstrate that the dopamine D1 and D2 receptors are the targets of the autoantibodies in Sydenham chorea and PANDAS [45■■]. This new animal model in the Lewis rat demonstrates that exposure to group A streptococcal antigens during immunization leads to behaviors characteristic of Sydenham chorea and PANDAS. The altered behaviours appear concomitantly with antibody deposits in the brain as well as elevated antibody responses in the animal model that activate the CaMKII in neuronal cells after streptococcal exposure [45■■]. The collective data from humans and animal models over the past 15 years suggest that in Sydenham chorea, the neurologic manifestation of rheumatic fever, antibodies are produced which cross the blood-brain barrier and trigger antibody-mediated neuronal cell signaling and dopamine release in the caudate putamen region of the brain which would lead to the movement disorder (Fig. 5). Most recently, we expressed the immunoglobulin human V gene-mouse IgG1 chimera of the chorea-derived human mAb which signals human neuronal cells *in vitro* in transgenic mice and found that the humanized autoantibody targeted dopaminergic neurons *in vivo* (Cox *et al.*, in revision, *Journal of Immunology*). Effective treatment including plasmapheresis or intravenous immunoglobulin leads to improvement in disease and suggests that autoantibodies play a role in chorea or neuropsychiatric and behavioral disorders [46].

CONCLUSION

Molecular mimicry is proposed to be an important mechanism in the pathogenesis of ARF. The investigation of human mAbs from rheumatic carditis and Sydenham chorea has supported the hypothesis that antibodies against group A streptococcal carbohydrate epitope GlcNAc recognize crossreactive structures on the heart valve and on neuronal cells in the brain which may lead to the initiation of carditis and rheumatic heart disease and Sydenham chorea, respectively. Further studies suggest that anticollagen antibodies in addition to anticardiac myosin antibodies are present in rheumatic heart disease. T cells present in the rheumatic valve recognize cardiac myosin and streptococcal M protein epitopes, and enter the valve through activated endothelium leading to a Th1 response in the valve. In the brain,

antibody-mediated neuronal cell signaling of neuronal cells may be a mechanism of antibody pathogenesis in Sydenham chorea.

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 438).

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KEY POINTS

- Evidence from human mAbs derived from rheumatic carditis has advanced our understanding of mimicry between the group A streptococcal group A carbohydrate epitope GlcNAc and valve endothelium which may lead to infiltration of the valve by T cells crossreactive with streptococcal M protein and cardiac myosin.
- Anticollagen antibodies in rheumatic carditis are not crossreactive and may be a result of exposure of collagen from the valve or a response to streptococci which aggregate collagen.
- Human mAbs derived from Sydenham chorea have advanced our understanding of the potential role of antineuronal autoantibodies in movement and behavioral disorders.
- Antineuronal antibodies in Sydenham chorea may cross the blood–brain barrier and trigger antibody-mediated neuronal cell signaling induction of calcium calmodulin-dependent protein kinase II (CaMKII) and subsequent dopamine release in the caudate putamen region of the brain which may lead to the movement disorder.
- Human cardiac myosin epitopes identified in rheumatic carditis are localized to the S2 hinge region of the myosin rod.

FIGURE 1.

Two-hit hypothesis of initiation of rheumatic carditis. Group A streptococcal infection leads to the production of antigroup A carbohydrate antibody (B cells) which crossreacts with the valve endothelium and upregulates vascular cell adhesion molecule-1 (VCAM-1) on the valve endothelium in Step 1. In Step 2, T cells responsive to streptococcal M protein epitopes adhere to the VCAM-1 on activated valve surface endothelium and extravasate into the valve. The diagram illustrates the first two initial steps of rheumatic heart disease.

Source: Similar but slightly different from figure in [34].

FIGURE 2.

Multistep hypothesis of development of rheumatic carditis and heart disease. Diagram illustrating the process of initial mimicry which leads to granuloma formation, gamma interferon production and scarring in the valve. After the initial process of inflammation has developed in the valve, other proteins in the valve may then be recognized by the immune system leading potentially to epitope spreading and responses against other valve proteins such as vimentin and collagen. *Source:* Similar but wording on figure different from figure in [35]. Similar but slightly different from figure in [34].

FIGURE 3.

Reactivity of serum IgG from rheumatic heart disease with human cardiac myosin peptides from the S2 and LMM rod regions in the enzyme-linked immunosorbent assay. (a) Mean reactivity of normal serum IgG from control donors with no evidence of streptococcal infection or heart disease on the U.S. mainland against S2 and LMM peptides. (b) Mean reactivity of serum IgG from patients with streptococcal pharyngitis on the US mainland against S2 and LMM peptides. (c) Serum IgG from patients with rheumatic carditis reacted with peptides S2-1, S2-4, S2-5, S2-8, S2-9, S2-17, and S2-30, compared with the reactivity of serum IgG from patients with pharyngitis against those same peptides (b). Unadjusted Mann-Whitney P values for the comparison between carditis and pharyngitis from the U.S. mainland are shown in panel (c). The comparison for S2-4 is statistically significant on the basis of a two-sided alpha level adjusted to preserve the false-discovery rate at 5% (1 : 100 dilution of serum). Data from [24■].

FIGURE 4.

Sydenham chorea-derived human monoclonal antibody (mAb) stimulated an increase in tyrosine hydroxylase synthesis in rat brain neurons. Sydenham chorea-derived mAb 24.3.1 was passively transferred intrathecally into rat brain and the increase in tyrosine hydroxylase was determined by immunohistochemistry. Chorea-derived mAb (24.3.1) induced higher levels of tyrosine hydroxylase (left figures – pink) in neurons compared with isotype control (right figures – blue). Insets show negative (blue) regions of the rat brain. The ability of chorea antibodies to alter neurotransmitter synthesis and release may explain the efficacy of dopamine receptor blockers such as haloperidol in the treatment of Sydenham's chorea. Data from [28].

FIGURE 5.

Simplified illustration of a potential pathogenic mechanism in Sydenham chorea. Antineuronal antibody (IgG) may bind to receptors on neuronal cells and trigger the signaling cascade of CaMKII, tyrosine hydroxylase and dopamine release which may potentially lead to excess dopamine and the manifestations of Sydenham chorea. Source: Similar but slightly different from figure in [34].