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Native Aortic Valve Endocarditis—A Case Report

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Abstract

Introduction: To report a case of isolated “endocarditic” aortic regurgitation in a 17-year old female with infective vegetations on aortic valve. **Case Report:** A 17-year old female was admitted with features of heart failure and a febrile illness. Blood cultures were negative and ECG revealed normal. Echocardiography revealed a “kissing-type” of vegetation on the bicuspid aortic valve with severe aortic regurgitation and a dilated left ventricle with moderate dysfunction. **Conclusion:** The management of aortic insufficiency occurring in infective endocarditis may differ and the presence of intractable pulmonary edema or shock is a clear indication for prompt valve replacement. The traditional diagnostic criteria are insufficient to diagnose infective endocarditis and the modified Duke criteria provide high sensitivity and specificity over 80% for the diagnosis of native valve endocarditis with positive blood cultures.

Keywords

Bicuspid Aortic Valve, Infective Endocarditis, Kissing Vegetations, Acute Aortic Regurgitation, Aortic Valve Replacement

1. Introduction

Infective endocarditis is a microbial infection of a heart valve (native or prosthetic) or the mural endocardium, leading to tissue destruction and formation of vegetation. Its incidence varies from 1.7 - 7.2 cases/one lakh persons-year and the female to male ratio was 1:2 [1]. There are substantial changes in the epidemiology profile over the last few decades [2] as median age group has increased from 30 - 40 to 47 - 69 years and rheumatic heart disease is no longer the main risk factor in Western countries. The most common predisposing lesion for aortic valve endocarditis is congenitally bicuspid aortic valve (BCAV). Inadequate

production of fibrillin-1 during valvulogenesis may disrupt the formation of aortic cusps, resulting in a bicuspid aortic valve and a weakened aortic root [3], which may complicate infective endocarditis in 9.5% of cases [4].

Isolated aortic regurgitation was found in only one-twentieth of a large series of patients in India, 2.7% of patients under 19 years in Brazil as a unique valvular dysfunction. The usual natural history is a long asymptomatic period in which mild-to-moderate regurgitation is well tolerated during the compensated phase and in adults, a rate of <6%/year may progress to systolic dysfunction and patients with recurrent rheumatic episodes have a rapid progress and severe incompetence may become established within 1 to 2 years of the initial episode.

Infective endocarditis of aortic valve is also a major cause of isolated acute aortic regurgitation [5] and so this case had been reported.

2. Case Report

A 17-year old female was brought to the emergency room with a history of sudden onset of breathlessness. Her pulse rate was 87 bpm and blood pressure 110/60 mmHg. She had a history of rheumatic fever during childhood, an episode of febrile illness for 10 days and taken antibiotic treatment recently. Blood chemistry revealed normal and blood cultures were negative. ECG revealed normal as shown in **Figure 1** and X-ray chest revealed dilated LV (left ventricle) as in **Figure 2**. Physical examination revealed grade 3/6 early diastolic murmur over left mid sternal border, basal crackles over lung fields and no peripheral signs of wide pulse pressure. Transthoracic echocardiography revealed vegetations on anterior and posterior leaflets of aortic valve as in **Figure 3** and **Figure 4**, with a “kissing-type” as in **Figure 5**, **Figure 6** and **Figure 7**. The aortic valve was bicuspid with an attached vegetation as in **Figure 8** in short axis view and in **Figure 9** in apical view and it was severely regurgitant as in **Figure 10** and **Figure 11**. The left ventricle is dilated as in **Figure 12** with moderate LV dysfunction as in **Figure 13**. The thoracic aorta was prominent as in **Figure 14** with a “holodiastolic flow reversal” as in **Figure 15**.

The patient was treated with digoxin (0.25 mg, half daily), diuretics (Injection. Furosemide 20 mg IV twice daily), ACE inhibitors (tablet. Enalapril 2.5 mg twice daily) along with 2 weeks course of intravenous (IV) cefotaxime (1 g) and amikacin (500 mg) twice daily and advised aortic valve replacement at the earliest with lifelong penicillin prophylaxis and continuation of antibiotics for 6 weeks since the vegetations remain stable after 2 weeks of treatment, but without any embolic episodes.

3. Discussion

3.1. Review of Literature

In 1885, William Osler presented the first comprehensive description of endocarditis. Thereafter, the description of clinical features of infective endocarditis was largely based on data obtained several decades ago. At present, definite

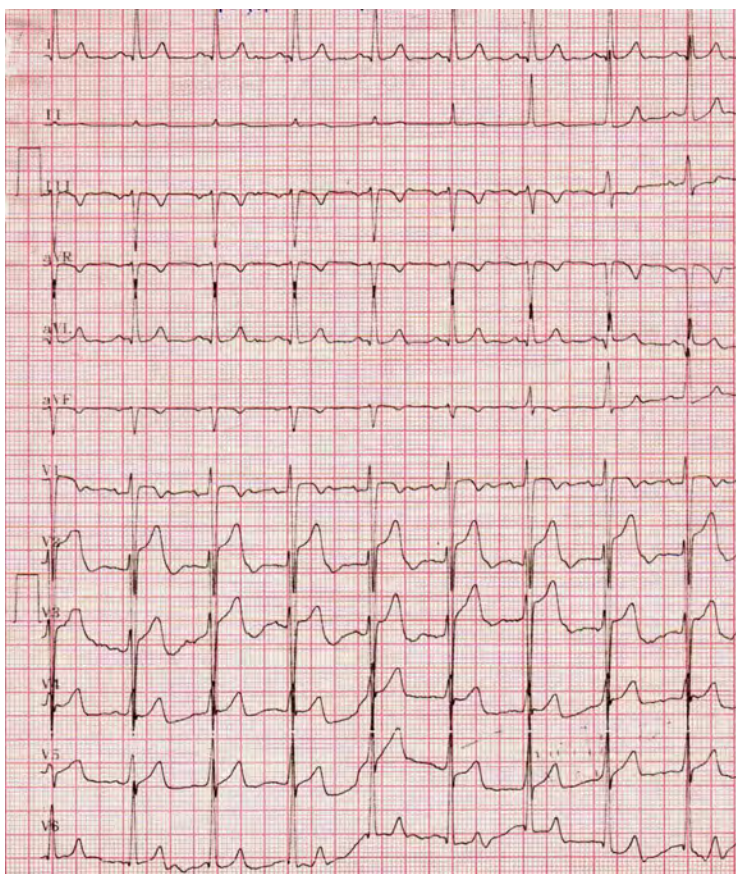


Figure 1. Showing the normal ECG in acute severe aortic regurgitation in a 17-year old female.

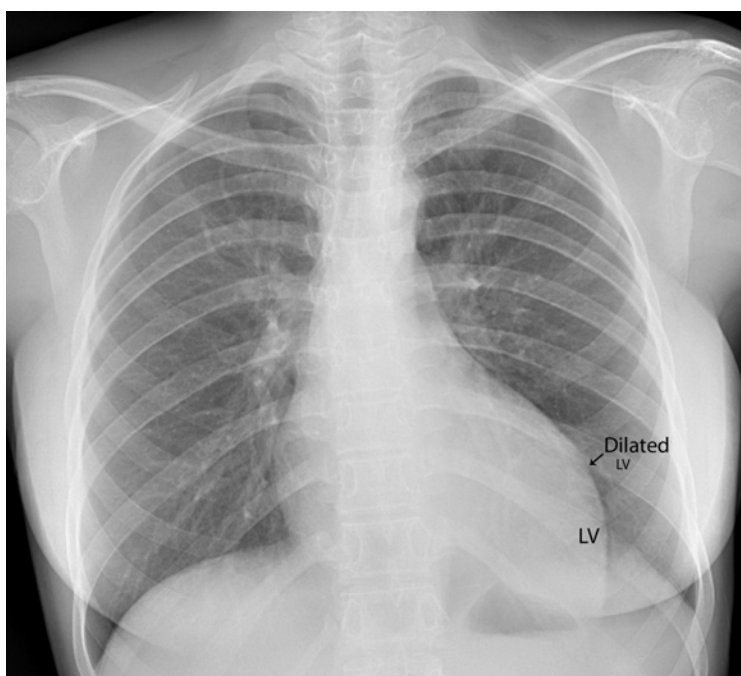


Figure 2. X-ray chest PA (postero-anterior) view showing the dilated left ventricle due to acute severe aortic regurgitation [6] in a 17-year old female.

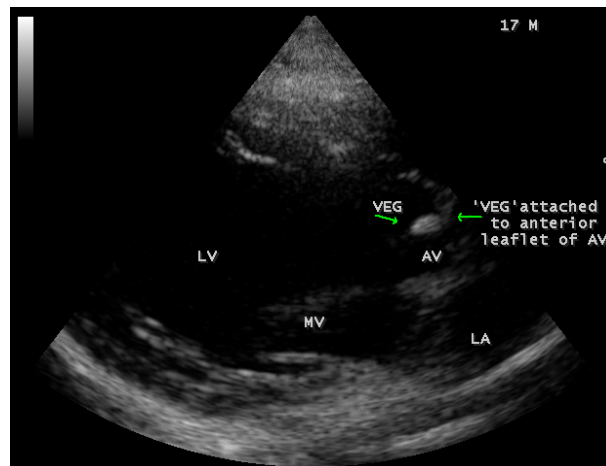


Figure 3. Parasternal long axis view showing the vegetation on the anterior leaflet of aortic valve (arrows) in a 17-year old female.

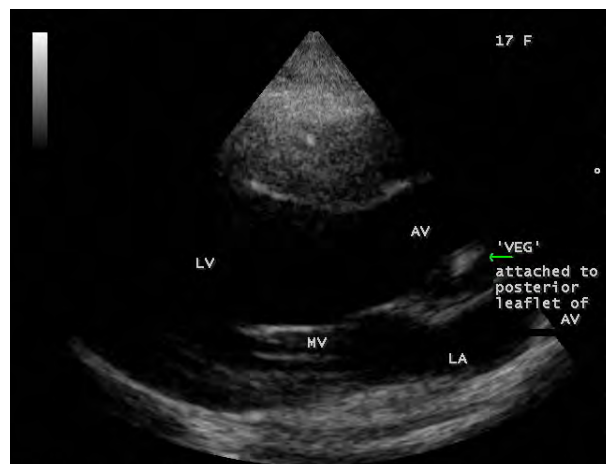


Figure 4. Parasternal long axis view showing the vegetation on the posterior leaflet of aortic valve (arrow) in a 17-year old female. AV-aortic valve.

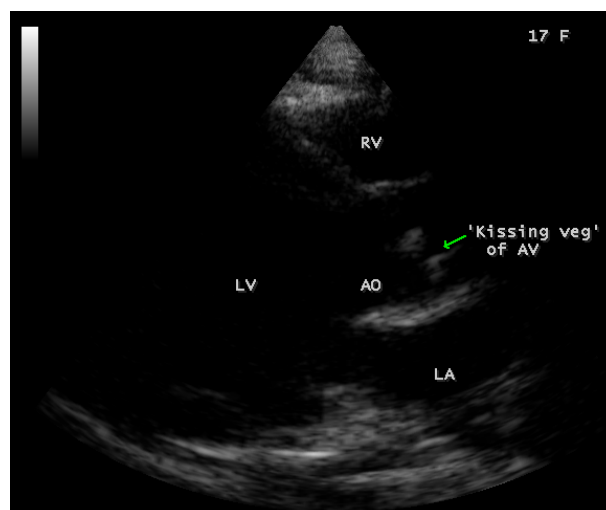


Figure 5. Parasternal long axis view showing the “kissing-type” of vegetations (arrow) on the aortic valve in a 17-year old female.

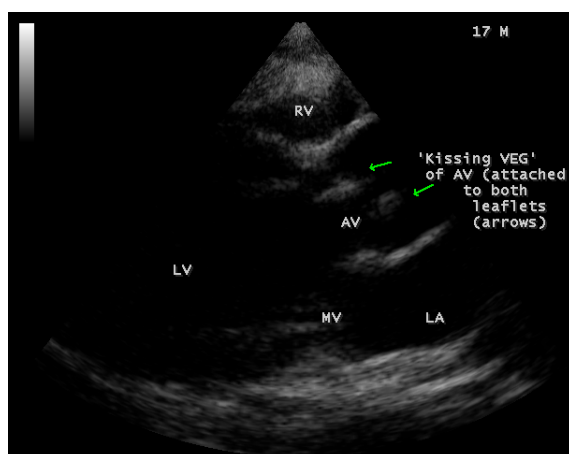


Figure 6. Parasternal long axis view showing the “kissing-type” of vegetations (arrows) on the aortic valve in a 17-year old female—large view.



Figure 7. Apical view showing the “kissing-type” of vegetations (arrow) on the aortic valve in a 17-year old female.



Figure 8. Short axis view showing the bicuspid aortic valve with vegetation (arrow) in a 17-year old female. AO—aorta, BICAV—bicuspid aortic valve, RVOT—right ventricular outflow tract, PV—pulmonary valve, LA—left atrium, VEG—vegetation.

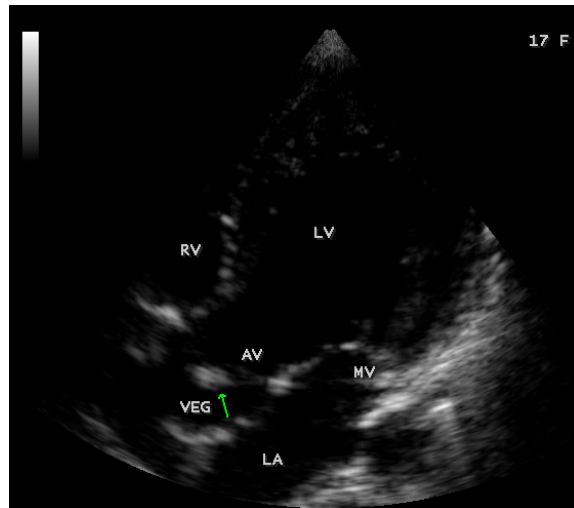


Figure 9. Apical view showing the vegetation on the aortic valve (arrow) in a 17-year old female.

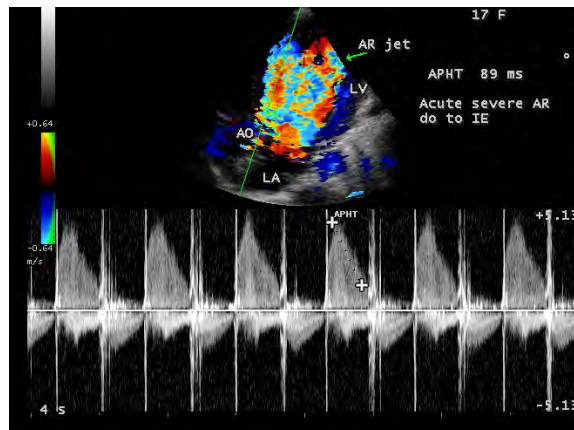


Figure 10. CW (continuous wave) Doppler showing the acute severe aortic regurgitation (arrow) jet (steep deceleration slope) in a 17-year old female. Shortened pressure half time (APHT-89 ms) is due to elevated LV diastolic pressure.

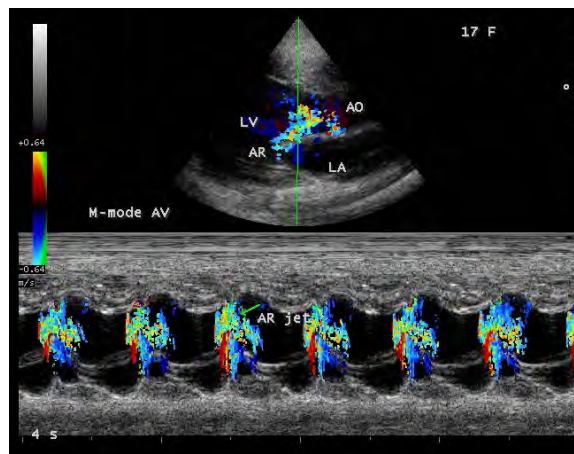


Figure 11. Color M-mode (green line) showing the acute severe aortic regurgitation (arrow-AR jet) in a 17-year old female.

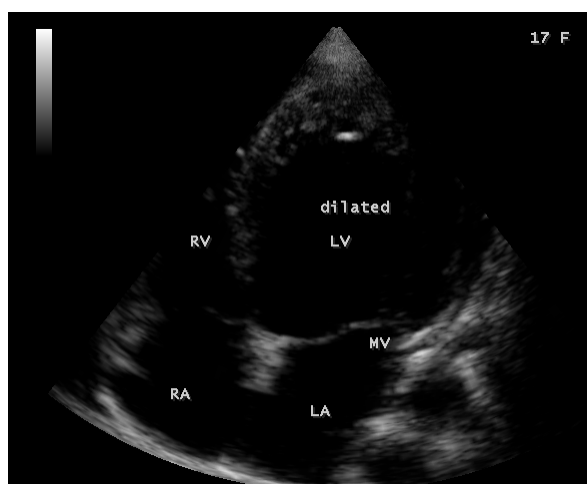


Figure 12. Apical view showing the dilated left ventricle and a normal left atrium in a 17-year old female in acute severe aortic regurgitation.

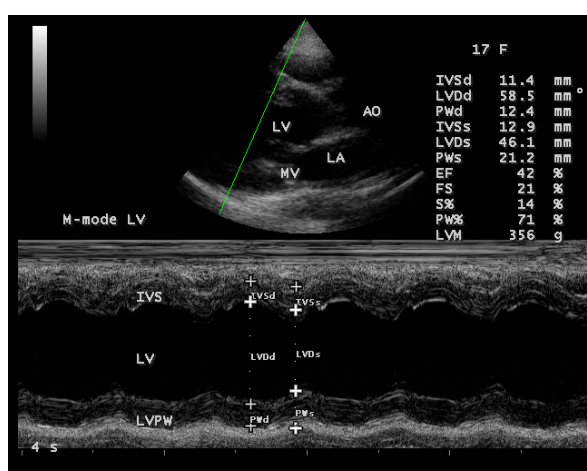


Figure 13. M-mode LV study (green line) showing moderate LV dysfunction with an ejection fraction of 42% in a 17-year old female in acute severe aortic regurgitation.

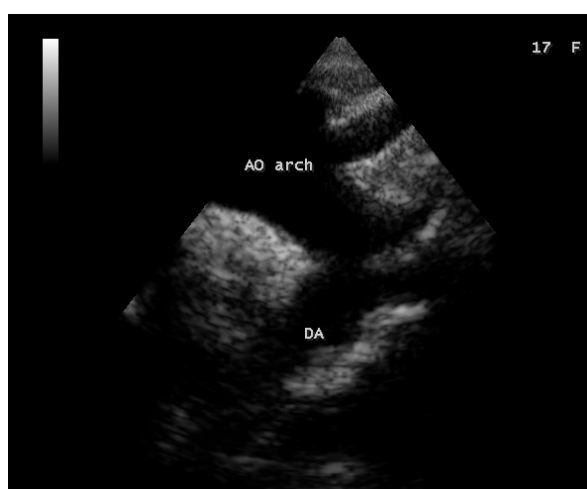


Figure 14. Suprasternal view showing the prominent aortic arch in a 17-year old female in acute severe aortic regurgitation.

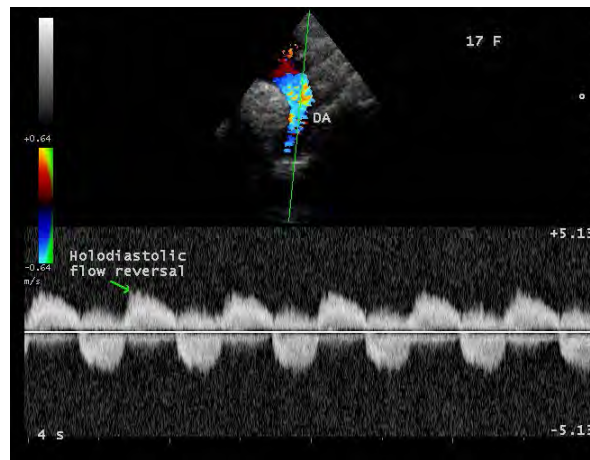


Figure 15. Suprasternal view showing the holodiastolic flow reversal (arrow) of severe aortic regurgitation [7] in a 17-year old female.

clinical evidence of vulnerable infection is based on retrieval of an organism via blood cultures. The ability of echocardiography to detect valvular vegetation was initially described by Dillon and coworkers [8] who identified characteristic thickened echoes, on the mitral and aortic leaflets in patients with tissue-documented valvular lesion.

3.2. Etiopathogenesis

The majority of cases of infective endocarditis are caused by gram-positive bacteria, the staphylococcus aureus is now more common than oral streptococci (streptococcus viridians) and it has become the most frequent microorganism causing infective endocarditis (31% - 54%). Methicillin-sensitive staphylococcus aureus (MSSA) is more frequently isolated in community-acquired infective endocarditis, affects mainly native valves, and it is associated with bacteremia of unknown origin, whereas Methicillin-resistant staphylococcus aureus (MRSA) is predominantly related to nosocomial infection, wound infection, IV catheters and surgical procedures. Viridans group is now less common (17% - 26%) and had partial resistance to antibiotics (“penicillin tolerance”). The slow-growing HACEK group is an unusual cause of infective endocarditis (1.8% - 3%) and affects mainly the native valves. Patients with IV drug abusers and long-term central venous catheters are at high risk of fungal infective endocarditis (1% - 3%), suspected in presence of bulky vegetation, metastatic infection, persistent invasion or embolization to large blood vessels. Whenever blood culture negative infective endocarditis occurs, other organisms such as coxiella burnetti, Brucella, Bartonella, Chlamydia, Streptococcus pneumoniae (often affects the aortic valve [9]) and Legionellae species must be considered.

When endothelium is damaged by high flow velocity jets, sterile thrombotic vegetation is formed, which facilitate bacterial adherence during transient bacteremia. Platelet and fibrin deposits at the damaged sites provide the nidus for the formation of vegetation, which causes tissue destruction, septic emboli and

abscesses. Vegetation > 1 cm in diameter is associated with greatest risk of embolization [10] and 65% of embolic events involve the central nervous system, mainly in the distribution of middle cerebral artery (90%). Patients with staphylococcus aureus infective endocarditis have a significant higher incidence of neurologic sequelae (53% - 71%). Infected embolic material may reach the adventitial layer of an artery through the vasa vasorum, resulting destruction of adventitia and muscularis [11], leading to aneurysm formation [12], usually within 46 hours of embolization [13]. Cerebral infected aneurysms develop in 1% to 12% of cases of infective endocarditis and located on the peripheral branches of middle cerebral artery (55%) [14], also in the secondary and tertiary branches in the region of Sylvian fissure [15] and it is multiple in 18% - 28% of cases, had saccular type morphology [16] and 10% of them will rupture. Infected intracranial aneurysms may leak slowly or enlarge before rupture and manifest as cranial nerve palsy, seizures, headache and nuchal rigidity due to meningeal irritation.

In addition, vegetations often occur in conjunction with ulceration, perforation, and even total destruction of valve leaflets [17], producing abrupt valvular regurgitation, manifested clinically by severe hemodynamic changes [18] [19]. Gross elevation of LVEDP (LV end-diastolic pressure), pulmonary hypertension and depressed cardiac output are the characteristic findings. Valvular destruction causing acute regurgitation is the most characteristic lesion leading to heart failure in native valve infective endocarditis [20] [21]. When there is rapid disruption of the anatomic integrity of the aortic valve, the sudden imposition of a large regurgitant volume causes precipitous increase in LV diastolic pressure and a decrease in forward stroke volume, leading to acute pulmonary edema and, on occasion, circulatory collapse. In acute aortic regurgitation, murmurs may not be easily audible, the pulse pressure is usually reduced due to reduction in stroke volume and increased peripheral vascular resistance. The characteristic physical findings of chronic, severe aortic regurgitation (AR) depend on a widened pulse pressure are often absent. Compensated tachycardia helps to shorten diastolic time available to regurgitation to occur and so the cardiac output is often maintained.

Early closure of mitral valve (ECMV) is a specific feature of acute onset, severe aortic regurgitation [22], first postulated by Austin Flint in 1886 [23] and observed echocardiographically by Pride in 1971 [24]. Normally, the mitral valve does not close until shortly after the onset of LV contraction, and leaflet closure occurs 40 ms after the onset of QRS complex in ECG. When the coaptation of both anterior and posterior mitral leaflets occur at or before the initial description of QRS (50 ms before the Q wave, but after the P wave, it is mild (grade I) and upto 200 ms before the Q wave, it is very marked (grade II)) [25]. The premature mitral valve closure is beneficial in the sense that the high LVDP (LV diastolic pressure) is not transmitted to the pulmonary venous system, thus preventing pulmonary edema and left heart failure. When LVDP exceeds the LA

pressure, the protection offered by premature mitral valve closure is lost, the opening of mitral valve occurs in late diastole, leading to diastolic mitral regurgitation which is usually effective to lower the LVDP and thus left atrium serves as a reservoir for blood regurgitant from the aorta to left ventricle.

The differential features of acute and chronic AR are shown in **Table 1**.

In left-sided endocarditis, vegetations usually develop on the edges of the valve leaflets, more prone for peripheral embolism and embolic events may occur before the clinical recognition of the disease as “silent embolism”, especially in spleen and kidney, and 30% of patients have renal or splenic infarcts at the time of diagnosis. Renal function may deteriorate as the result of worsening hemodynamics and emboli to kidney can lead to abscess formation, presenting as flank pain, pyuria, or hematuria and cause “flea-bitten” appearance of cortex with focal segmental necrosis of the glomerular tuft [26].

3.3. Echocardiographic Features

Echocardiography plays a key role in the diagnosis of infective endocarditis and the vegetation, the hallmark lesion of infective endocarditis is a major echocardiographic criterion for its detection. Vegetation is a bulky, friable, frequently pedunculated mass composed of fibrin strands, platelets, blood cell debris, bacteria and presents as an oscillating mass attached to a valvular structure, with a motion independent to that of the valve. It may be also seen as non-oscillating masses with atypical location. Transthoracic echocardiography detects 70% of vegetations > 6 mm and 25% of vegetation < 5 mm. The sensitivity of transthoracic echocardiography for the diagnosis of vegetation is about 75% and the vegetation size of 2 mm in diameter might be the critical size required for echocardiographic identification. The thickened echoes emanating from the valvular vegetation on aortic echogram appear to be specific for bacterial endocarditis of aortic valve as in **Figures 3-9**.

Table 1. The differential features of acute and chronic AR.

	Acute AR	Chronic AR
Heart rate	Increased	May be normal
Systemic arterial pulse pressure	Not significantly increased	Increased
Aortic systolic pressure	Not increased	Increased
Aortic diastolic pressure	Not decreased	Markedly decreased
Peripheral vascular resistance	Increased	Decreased
LV compliance	Not increased	Increased
LV end diastolic pressure	Markedly increased	Normal
LV ejection velocity	Not significantly increased	Increased
Regurgitant volume	Increased	Increased
Effective stroke volume	Not increased	Increased
Effective cardiac output	Decreased	May be normal
Ejection fraction	Not increased	Maintained normal for long periods

When endocarditis involves the aortic leaflets, the resultant acute, severe regurgitation as shown in **Figures 10**, **Figure 11** and **Figure 15**, may often causes dilated left ventricle as in **Figure 12** and a prominent aorta as in **Figure 14**.

Secondary infection of mitral valve is a possible finding in primary aortic valve endocarditis. Large aortic valve vegetations (>6 mm) prolapse into the left ventricular outflow tract and “kiss” the ventricular surface of the anterior mitral leaflet with the development of a vegetation [27] [28] [29]. The left ventricular outflow tract endocarditis may represents the initial site of infection with a possibility to spread by contiguity to both left-sided valves, the mitral and aortic [30], causes the “mitral-kissing vegetation” with a higher prevalence of embolic events [31].

3.4. Management

Endocarditis normally presents with fever, murmur, tachypnea, tachycardia, hyperfibrinogenemia, anemia and leukocytosis [32] [33]. Early and adequate diagnosis is important for the prognosis and treatment of patients with infective endocarditis. New laboratory and molecular analysis techniques have been adapted for recognizing previously unidentified species as etiological agents of infective endocarditis.

The management of infective endocarditis comprises antibiotic therapy, intensive medical care and surgery as three main pillars of treatment.

3.5. Medical Therapy

Bacterial endocarditis must be treated with antibiotics. The objective is the selection of antibiotic based on the sensitivity shown by the antibiogram, but treatment generally begins with an empirical wide-spectrum antibiotic until the hemoculture results are ready [34]. Antibiotics commonly used are penicillin associated with gentamycin [35] and the treatment duration depends on the improvement and resolution of clinical signs, echocardiographic findings, white blood cells, and fibrinogen reduction within normal limits. Traditionally, prolonged (4 - 6 weeks) treatment is mandatory to kill the dormant bacteria clustered in the infected foci [36]. The mean duration of antibiotic therapy was 5 weeks and it is possible that similar results can be obtained after as little as two weeks of therapy [37] [38] [39], especially in uncomplicated NVE (native valve endocarditis) with normal renal function [40].

Almost all patients with acute aortic regurgitation (AR) exhibit tenuous hemodynamics and initial stabilization is required in the intensive care unit. Medical therapy is directed at reducing pulmonary venous congestion, reduction in systolic blood pressure to relieve the afterload and maximizing the cardiac output. Intravenous vasodilator and diuretic therapy can be effective and the principal aim of medical treatment is to optimize clinical status. The nitroprusside with an initial dose of 0.10 to 0.20 µg/kg/mt, gradually increased to attain the desired hemodynamic effects as a reduction in LV filling pressure to 15 mmHg or

less and an increase in cardiac output that would ensure adequate tissue oxygen delivery, usually a cardiac index $> 2.5 \text{ L/mt/m}^2$ while maintaining a systemic blood pressure of $\geq 90 \text{ mmHg}$.

Patients with grade I premature mitral valve closure without clinical heart failure can be managed by medical therapy. Anticoagulation is not indicated for patients with endocarditis because of the risk of hemorrhagic neurological events [41]. It prevents neither the formation nor the embolization of vegetation as separation of small fragments from the infected vegetations. Three quarters of embolism occurs before the beginning of antibiotic treatment [42] and the embolic risk decreases over time, from 15% after one week of treatment to 1% after 4 weeks [43].

3.6. Atrial Pacing

Patients with aortic regurgitation are more likely to have ventricular dysrhythmias and supraventricular premature depolarizations are more commonly observed in severe regurgitation [44]. Nevertheless, sinoatrial arrest (presented as heart rate $> 30 \text{ bpm}$) was detected and it is physiological due to high vagal tone as a result of activation of baroreceptors located in aortic callus and carotid sinus, which prolongs the period of atrial filling as a compensatory mechanism to maintain the stroke volume and blood pressure partially masking the vagal tone.

Increasing the heart rate by atrial pacing has been shown to decrease the regurgitant volume, left ventricular end-diastolic pressure and pulmonary venous pressure in patients with severe aortic regurgitation.

3.7. Aortic Valve Replacement (AVR)

Heart failure due to the development of acute aortic regurgitation is currently the leading cause of death from infective endocarditis [45]. When patients respond dramatically to medical therapy, surgical therapy can be delayed until heart failure and infection are controlled and the patient is more stable [46]. The purpose of stabilizing congestive heart failure was to allow sterilization of the blood stream prior to operative intervention to reduce the incidence of valve dehiscence and new nidi of infection.

Aortic valve replacement (AVR) can be safely and effectively accomplished during the course of active infective endocarditis and that urgent valve replacement should be considered [47] in patients who develop heart failure due to valve destruction.

Anaesthetic management may be difficult due to hypotension despite hyperdynamic LV function and hypoxaemia due to severe pulmonary edema can complicate induction in patients with acute aortic regurgitation.

3.8. Transcatheter AVR

It is difficult to arrive at a standardized definition of appropriate candidates for TAVI (Transcatheter aortic valve implantation), *i.e.*, patients who are considered

too high-risk for conventional AVR and would derive more benefit from the transcatheter procedure.

The acute onset of severe aortic regurgitation (AR) is a medical emergency due to the inability of the left ventricle to quickly adapt to the abrupt increase in end-diastolic volume caused by the regurgitant flow and results in hypotension [48]. These patients are contraindicated for surgical treatment because of high surgical risk. Hence, the transcatheter AVR procedure, might represent a successful and life-saving intervention for treatment of patients with severe aortic regurgitation who present with acute refractory cardiogenic shock [49].

The first reports of minimally invasive transfemoral transcatheter AVR [50] and the first successful transapical TAVI without CPB (cardiopulmonary bypass) using the Cribier-Edwards Balloon Expandable Valve (Sapien TM valve) in humans were reported in 2006 [51] [52]. TAVI is recommended mainly for patients with calcific aortic stenosis with or without regurgitation in elderly patients (>65 years) and it is not offered to patients with isolated rheumatic aortic valve disease. This procedure needs more accurate assessment of aortic annular size to determine the size of transcatheter valve and it should be ≤ 29 mm since the largest valve size is 29 mm. Furthermore, transcatheter valves are unlikely to have durability comparable to the best surgical tissue valves and had a high incidence of paravalvular leak, which has been shown to have a negative impact on long-term outcomes. As a result of some encouraging outcomes from PARTNER trial, the SAPIENTM valve was approved for commercial use in inoperable patients with symptomatic aortic stenosis [53].

Few cases of infective endocarditis (IE) after TAVR (transcatheter aortic valve replacement) had been reported and its incidence ranges between 0% and 2.3% [54]. The space between the bioprosthesis and the native aortic valve cusp might be a suitable nidus for the accumulation of pathogens during transient bacteraemia [55].

3.9. Surgical AVR

Since the mortality with medical therapy alone is extremely high, early aortic-valve replacement has been undertaken at several institutions, with a substantial reduction in mortality [56]. Clinically, early surgery was considered to be a greater risk than delayed surgery because of tissue inflammation and the surgery was technically more difficult. Surgery should be rapid in case of hemodynamic deterioration, uncontrolled infection and large, mobile vegetations. Determination of proper timing of surgical intervention in patients with heart failure, controlled medically and those with neurological complications is difficult. Ideally, aortic-valve replacement can be performed after the completion of antibiotic therapy, but before the progressive destruction of valvular and myocardial tissue. In fact, the duration of antibiotic treatment before surgery does not appear to influence the perioperative mortality, nor the rate of recurrent infective endocarditis [57]. Aortic valve surgery may be timed with reference to whether

the premature mitral valve closure is mild or severe. Very early mitral-valve closures had severely volume-overloaded ventricles and are candidates for early valve replacement. Patients with grade II premature mitral valve closure require urgent AVR and grade II premature mitral valve closure and mitral regurgitation should undergo emergent AVR.

Systemic embolism is relatively a weak indication for early valve replacement, but an exception is fungal endocarditis, the operation appears to be indicated at the time of diagnosis to eradicate the infection [58] [59]. Griffin and associates have recommended prompt valve replacement even in patients with mild congestive heart failure in order to prevent sudden death due to coronary embolism [60]. The indications of surgical intervention for vegetations with high risk of embolism are shown in **Table 2**.

In presence of stroke, delay the surgery for 2 - 3 weeks [62] because of major neurological risk and the presence of coma is a contraindication to surgery.

Valve repair is potentially applicable to the atrio-ventricular valves (mitral and tricuspid) and all the necrotic and infected tissue need to be excised and the defects are to be repaired.

For valve replacement in aortic valve endocarditis, homografts are especially useful since they have greater resistance to infection compared to prosthetic valves, but had high early calcification rates. Translocation of the aortic valve (Ross procedure-diseased aortic valve) is replaced with the patient's own pulmonary valve (pulmonary autograft) can be an alternative in prosthetic valve endocarditis and mechanical valves are preferred in younger individuals, anti-coagulants should be discontinued if CNS events occur during therapy.

3.10. Endovascular Therapy

Although progressive heart failure and systemic embolism are well-established indications for valve replacement in patients with bacterial endocarditis, there is uncertainty regarding the operative priority in patients with both intracranial aneurysm and acute heart failure. If valve replacement is selected first, cardiopulmonary bypass with systemic heparinization could cause lethal neurologic deficits [63]. A bioprosthetic valve, which does not require anticoagulation therapy, may be preferable to a mechanical valve in such conditions.

Septic emboli from vegetation can cause intracranial infected aneurysm and one-third resolve completely by the 4 - 6 weeks of antibiotic therapy. If there is a ruptured mycotic aneurysm, it must be resected, clipped or embolised before

Table 2. The high risk vegetations with embolic potentials as an indication for surgical interventions [61].

Size > 15 mm
Extreme mobility
Continuous increase in size despite adequate treatment
Persistence after 2 weeks of adequate antibiotic therapy

cardiac surgery. Urgent cerebral angiography and an endovascular approach to intracranial infected aneurysm, especially for solitary and peripheral lesions, is an acceptable option for some patients with active endocarditis and severely damaged valves.

Minimally invasive endovascular approach is used to embolize the aneurysm. For bacterial aneurysms, detachable balloon technique had been proven to be a simple procedure [64]. Coil embolization has steadily replaced neurosurgical therapy in ISAT (International Subarachnoid Aneurysm Trial) [65] and Guglielmi introduced the detachable platinum coil in 1989. Another new technique is injection of N-butyl-cyanoacrylate glue into the affected aneurysm.

The decision to use a coil or cyanoacrylate as an occlusive device depends on the location of the aneurysm. Cyanoacrylate is the logical choice if the aneurysm can be reached with a microcatheter since it permits simultaneous sealing of the aneurysm. The detachable coils may have the risk of perforating the inflamed and friable aneurysmal wall [66].

The endovascular techniques are preferred since they avoid craniotomy and the surgical handling of the swollen brain and also in patients who use anticoagulant drugs due to heart valve replacement [67].

3.11. Outcome

If heart failure is present, the mortality rate of native valve infective endocarditis is 55% - 85% in case of medical treatment only and 10% - 35% in operated patients. Heart failure also increases the perioperative mortality rate from 5% - 10% in patients without heart failure to 15% - 35% in patients with heart failure. Perivalvular infection such as abscesses and intracardiac fistulas occur in 10% - 40% of aortic valve endocarditis [68] and conduction disturbances are very specific for perivalvular infection [69]. Delaying surgery increases the risk of perivalvular infection and also increases the perioperative mortality [70].

The risk of death in individuals with aortic insufficiency, dilated ventricles and normal ejection fraction with asymptomatic is about 0.2%/year. Risk increases if the ejection fraction decreases or if the individual develops symptoms [71]. Left ventricular dysfunction determines to an extent the outlook for severity of aortic regurgitation and cardiovascular insufficiency is the largest single cause of postoperative mortality [72].

In the absence of operative intervention, the development of aortic regurgitation due to infective endocarditis is associated with a mortality of approximately 50% because of progressive hemodynamic deterioration. Early mortality of 27% for valve replacement occurs during the active stage of infection versus 12% in the healed stage [73]. In case of transcatheter aortic valve implantation (TAVI) procedure for “inoperable” patients, the 30-day mortality is typically < 10% and 1-year survival following TAVI has ranged from 65% to 80%. For endovascular therapy (clipping and coiling of infected intracranial aneurysm), the relative risk of poor outcome was 0.76% after 1-year of follow-up [74].

3.12. Follow-Up

The rate of recurrence of infective endocarditis at 5-year follow-up is around 1.5% per patient-year. The term reinfection is primarily used when a different microorganism produces a new episode of infective endocarditis in high risk patients such as previous valve disease or IV drug use. Relapse refers to a repeat episode of infective endocarditis, caused by the same microorganism as in previous episode due to incomplete treatment, suboptimal choice of initial antibiotics and persistent foci of infection. The occurrence of sudden death is mainly related to infection, as a result of ventricular septal erosion, producing complete heart block during medical therapy and also may occur due to coronary embolism after aortic valve replacement in infective endocarditis [75].

On follow-up for 2 months, the vegetation size was stable, but the aortic regurgitation decreases with an improvement in LV function on continuation of antifailure measures in this patient.

3.13. IE Prophylaxis

NICE (National Institute of Clinical Excellence) guidance [76] suggests that preoperative antibiotic prophylaxis is no longer routinely recommended due to allergic reactions of antibiotic therapy, but still advised in high risk patients such as acquired valvular heart disease, previous valve replacement and congenital structural heart diseases, excluding the repaired atrial or ventricular septal defects or patent ductus arteriosus.

3.14. Case Analysis

Since the patient had a bicuspid aortic valve as shown in **Figure 8** and a history of rheumatic fever during childhood, rheumatic inflammation occurred on the aortic valve and harboured the infective vegetation through the vascular access during the treatment of febrile episodes.

Patients with infective endocarditis are at risk of developing acute aortic regurgitation and the ECG can appear normal as in **Figure 1** and the chest X-ray usually shows pulmonary edema with normal heart size. A dilated left ventricular cavity with a normal left atrium as in **Figure 12** indicates that the volume overload on the left ventricle resulting a compensatory mechanism to maintain an adequate forward stroke volume by accommodating a large regurgitant fraction without an increase in end-diastolic pressure. The heart rate appeared normal (87 bpm) as the result of this compensation.

Even though the aortic regurgitation is acute as in **Figure 10** which showed a steep deceleration slope with a narrow width of regurgitant jet due to endocarditic lesion of aortic valve (endocarditic regurgitation). It is compensated in this patient and showed a lesser degree of decompensation as moderate LV dysfunction with an ejection fraction of 42% as in **Figure 13**, necessitating elective aortic valve replacement along with removal of vegetations with a mechanical prosthetic valve. Anticoagulation with warfarin to maintain the INR (international normalised ratio) between 2 to 3 is indicated after the clearance of active stage

of endocarditis with antibiotic therapy and surgery.

4. Conclusion

Complicated left-sided native valve infective endocarditis remains a serious disease with significant mortality and morbidity. The aortic valve is most commonly affected site in infective endocarditis patients without congenital heart disease [77]. Vascular-access-related infections are major source of bacteremia in this population [78]. Antimicrobial therapy can offer a curative treatment in only 50% of cases of infective endocarditis. Patients with large vegetations, intracardiac abscess (9% - 14%) or persisting infection (9% - 11%) almost always need surgery and most patients require valve replacement.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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Improved Visualization of the Anterior Thalamic Radiation in Bipolar Disorder by Diffusion Tensor Tractography

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Abstract

Diffusion tensor imaging (DTI) is a method for noninvasively measuring and imaging the diffusion of water molecules using MRI. Diffusion tensor tractography (DTT) can be used to presume macroscopic nerve fascicle distribution by determining, based on information obtained by DTI, whether the diffusion anisotropy vectors of adjacent voxels are continuous or not. We prepared a DTT map of the cerebral white matter nerve fascicles and investigated its usefulness for differentiation between Alzheimer's disease and bipolar disorder (BD), a major depressive disorder, based on the nerve fiber depiction, in addition to the fractional anisotropy and apparent diffusion coefficient values. We encountered two cases of BD in which the DTT image of the anterior thalamic radiation (ATR) improved following effective treatment with lamotrigine. Lamotrigine increases the synaptic strength due to its effect of promoting the traffic of the α -3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor on the neuronal membrane. Downregulation of postsynaptic AMPA receptor expression can reportedly be observed during depressive episodes in BD. We consider that visualization of improvement of the ATR in response to treatment with lamotrigine (related to its pharmacological effect on the AMPA receptor) is valuable, as it suggests reversibility of the damage of the nerve fibers in this disease condition.

Keywords

Diffusion Tensor Tractography, Bipolar Disorder, Diffusion Tensor Imaging, Magnetic Resonance Imaging, Anterior Thalamic Radiation

1. Introduction

BD is characterized by a long depressive phase, and particularly in cases with bipolar type 2 disorder in remission, the depressive state exceeds 50% and treatment of the extended depressive state remains an issue [1] [2]. With advances in the field of diagnostic imaging, numerous studies have utilized diffusion tensor imaging (DTI) to discuss the white matter integrity in BD, as well shown reduced FA values of the nerve fiber bundles in the anterior thalamic radiation (ATR), based on analysis of DTI [3] [4].

The ATR is a nerve fiber bundle connecting the dorsomedial nucleus of the thalamus to the prefrontal cortex; it is an important part of the so-called executive function circuit (cortico-striato-pallido-thalamic circuit) which connects the thalamus to the prefrontal cortex [5].

From our clinical experience, poor ATR visualization is an oft-recognized characteristic of BD on DTT.

In a previous paper, we reported that while the ATR can be visualized well in cases of MDD, it is poorly visualized in cases of AD [6]. In this report, we provide an account of the improvement of the subjective symptoms along with that of MRI visualization of the ATR following appropriate medical treatment in patients with BD with poor MRI visualization of the ATR prior to treatment.

2. Data Acquisition

The anterior thalamic radiation (ATR), cingulate fasciculus (CF), uncinate fasciculus (UF), superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus (ILF), inferior fronto-occipital fasciculus (IFOF), and Fornix (FX) were selected as the nerve fascicles to be traced. We performed DTT in about 2300 patients during the 6-year period from 2012 to 2018. In this study, the DTI data were transferred to the Philips Extended MR Work Space (Release 2.6.3.2) and analyzed using the Philips Fiber Trak (Release 2.6.3.2; Koninklijke Philips Electronics NV, Amsterdam, The Netherlands), a software useful for fiber tracking. The default settings were as follows: step width for nerve fiber tracking: 10 mm; conditions for termination of the fiber tracking: an FA value of <0.15 and a flip angle of >27 degrees. Using the multiple region-of-interest (ROI) approach and based on a tractographic atlas, Include-ROIs (to select fibers perforating the set region) were set up manually [7]. Exclude-ROIs (to exclude fibers perforating the set region) were also set for precluding other immixed nerve fibers.

Although there is involvement of the corticospinal tract and corticopontine tract in the ATR, it is feasible to achieve pure visualization of the ATR excluding fibers of the corticospinal tract and corticopontine tract by setting up an Exclude-ROI encompassing the nerve tracts of the midbrain (Figure 1). We defined the FA value as the average FA value for the entire ATR. The white matter structure peripheral to the ATR was visually assessed. In addition, visual evaluation of the ATR was defined as good when the nerve fiber fascicles of the ATR reached the boundary between the gray matter and white matter, and as poor

when not even a single nerve fascicle of the ATR reached that boundary line.

3. Case Presentations

3.1. Case 1: A 57-Year-Old Female Patient

The patient developed symptoms of depression first when she was in her 40's. She was hospitalized for treatment with symptoms of major depression and suicidal ideation at the age 48 years. She was hospitalized a total of three times. In year X she presented with mania and a return of the depressive state. She began to be treated for BD, but stopped taking her prescribed medication, which led to repeated manic episodes. In X + 4 years, during a major depressive episode, her oral prescription was changed from lithium to lamotrigine, as the patient complained that the lithium was causing edema. In X + 5 years, a repeat MRI showed improved visualization of the ATR. She continued to remain in a stable state, with no manic symptoms. In X + 6 years, her mental condition was still stable under continued monotherapy with 200 mg of lamotrigine.

3.1.1. The Results of Psychological Assessments

The Patient Health Questionnaire-9 (PHQ9) [8] score was 27 points (full score) at the initial examination, while at the assessment conducted 5 years later, it had improved to 5 points. Assessment of cognition by the Mini-Mental State Examination (MMSE) revealed a normal cognitive state, with a score of 30 points.

3.1.2. The Results of MRI Examinations

Visualization of the ATR was poor on the left side in the X year, while it was good in X + 6 years (Table 1) (Figure 2).

3.2. Case 2: A 63-Year-Old Male Patient

The patient had undergone a coronary stent placement after sustaining myocardial infarction at the age of 52 years. He was identified as having BD in the same year during a hospital visit, and was advised to seek psychiatric consultation, although he did not follow the advice.

Table 1. Changes of the FA and ADC values of the ATR in the two cases examined.

Case	Examination date	FA value		ADC value ($\times 10^{-3}$ mm ² /s)	
		Right	Left	Right	Left
1	X years	0.421	0.423	0.831	0.822
	X + 5 years	0.440	0.442	0.826	0.867
	X + 6 years	0.453	0.434	0.824	0.819
2	X years	0.460	0.481	0.872	0.829
	X + 9 months	0.434	0.439	0.918	0.894

Abbreviations: ADC, apparent diffusion coefficient; ATR, anterior thalamic radiation; FA, fractional anisotropy.

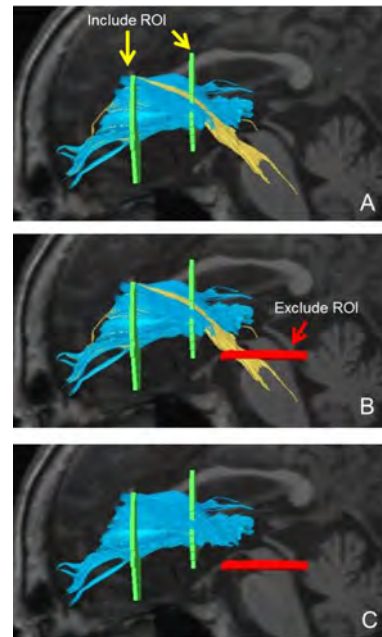


Figure 1. Sagittal T1-weighted image of the 58-year-old female patient with bipolar disorder overlaid with a diffusion tensor tractographic image of the left anterior thalamic radiation (ATR). A: The Include-region of interest (ROI) (yellow) is set on the coronal plane passing through the anterior commissure and the center of the genu of the corpus callosum. The ATR (light blue) passing through both is depicted together with the corticospinal tract and the cortical bridge (pink color). B: By setting the Exclude-ROI (red) on the cross-sectional plane passing the midbrain, the corticospinal tract and cortical bridges (pink color) traversing the same region were excluded. C: The ATR (light blue) is clearly visualized.

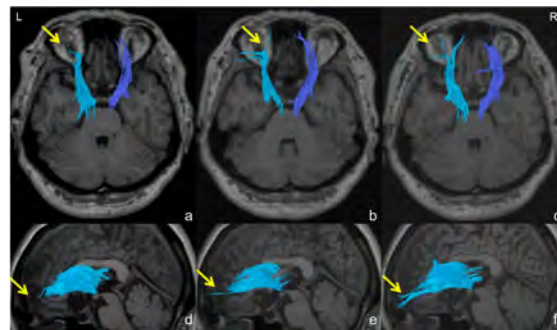


Figure 2. Diffusion tensor tractography of the anterior thalamus radiation (ATR) of Case 1 (right: blue, left: light blue). a, d: Year X (Initial consultation), b, e: X + 5 years, c, f: X + 6 years. Improved visualization of the ATR in X + 5 years (b, e) as compared to that in year X (a, d). Good visualization maintained in X + 6 years (c, f) (yellow arrows).

At the age of 62, he was in a state of major depression. He was started on treatment during the depressed phase of BD. In January, X year, he was given a prescription of lamotrigine 25 mg. When the dose of lamotrigine needed exceeded 100 mg, it was increased directly to 200 mg daily, and then 300 mg daily. Half a year after the treatment was started, the dose was at 300 mg. By X + 9 months later, the patient had recovered from a bedridden state to one where he

could perform his daily activities and shop for himself.

3.2.1. The Results of Psychological Assessments

The PHQ9 was 27 points (full score) at the initial examination, while at the assessment conducted after 2 months, it had improved to 23 points, and at the assessment conducted after 1 year, it had improved further to 7 points. Assessment of cognition by the MMSE revealed normal cognitive function, with a score of 30 points.

3.2.2. The Results of MRI Examinations

Visual assessment revealed improvements in both the left and right ATRs (**Table 1**) (**Figure 3**).

4. Discussions

4.1. Visual Confirmation of the Reversibility of ATR in Cases of BD

There is a research which reports that the average fractional anisotropy (FA) value of the ATR has decreased in BD [9].

However, as shown in the previous section, there was no consistency in the FA value and the apparent diffusion coefficient (ADC) value of the ATR (**Table 1**) in the two BD cases. The FA and ADC values assessed by DTI represent the average state of the nerve fiber bundles that can be tracked. Untracked areas are not included in the evaluation, with the result being that a greater portion of the injured areas of the fiber bundles is not assessed. However, the visual evaluation method based on DTT can be used to visualize the fibers radiating from the thalamus to the surface of the brain—in short, up to the point at which the density of the nerve fiber voxels becomes very low. Consequently, it was possible to capture minute changes in the nerve fibers, and the nerve fibers that could not be captured were considered to be injured. We were able to visually confirm reversibility of the ATR visualization following treatment.

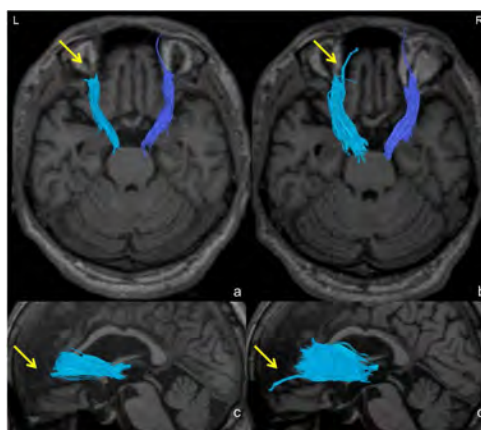


Figure 3. Diffusion tensor tractography of the anterior thalamus radiation (ATR) of Case 2 (right: blue, left: light blue). a: Year X (Initial consultation), b: 9 months later. Improved visualization of the ATR in X + 9 months (b) as compared to that in year X (a) (yellow arrows).

4.2. Pharmacological Effect of Lamotrigine (Association with the AMPA Receptor) and Improvement in Visualization of the Anterior Thalamic Radiation

In the two BD cases, where the anterior thalamic radiation (ATR) of DTT was improved, lamotrigine was effective. It has been suggested that neurological dysfunction of the glutamate system is involved in the pathophysiology of BD [10]. Ion channel-type glutamate receptors involved in excitatory neurotransmission are classified into three types: the N-methyl-d-aspartate (NMDA), AMPA, and kainic acid receptors [11]. Lamotrigine suppresses the Na channel in a voltage-dependent and frequency-dependent manner, stabilizing the neuronal membranes, with consequent suppression of glutamate release. It exhibits neuroprotective activity through suppression of glutamate release and induction of apoptosis in the medial prefrontal cortex; it has been shown to ameliorate pre-pulse inhibition deficit in an animal model of mania/schizophrenia [12]. Deficit of prepulse inhibition involves dysfunction of the control of sensory-motor information and is considered to be related to impairment of cognitive function due to abnormalities in attention [13]. In addition, the functional performance circuitry, the cortico-striato-pallido-thalamic circuit, is thought to be related to pre-pulse inhibition [14]. Together, these findings suggest improved function of the cortico-striato-pallido-thalamic circuit as a possible reason for the improved visualization of the ATR following treatment with lamotrigine. It has been reported that downregulation of postsynaptic AMPA receptor expression is observed during depressive episodes of BD; in contrast to lithium and valproic acid, lamotrigine increases synaptic strength due to its traffic-promoting activity of the AMPA receptor on the neuronal membrane, and may thereby improve depressive episodes [15]. Synaptic plasticity is related to learning and memory with long-term potentiation and increased efficiency of synaptic conduction due to increased firing of the pre-synaptic and post-synaptic cells which are thought to be involved. Increased expression of postsynaptic AMPA receptors is thought to be important for long-term potentiation [16].

The current observation of neural plasticity by DTT is considered to be a valuable demonstration of the neuroprotective effect of lamotrigine and of the importance of AMPA receptors. However, it is also important to note reports of the side effects of lamotrigine, including rash, dizziness, diplopia, and lymphadenopathy [17].

5. Conclusion

In this case series, using MRI based DTT, we have reported poor visualization of the ATR in BD which was not only improved in mental symptoms following appropriate medical treatment but also showed good visualization of the ATR in follow-up MRI examinations. This suggests that poor visualization of the ATR can be identified as an indication of impaired integrity of neuronal myelin of the brain in BD. ATR visualization by DTT, which makes nerve fiber plasticity pa-

thology visible, may also be a useful and convenient method that can be implemented quickly in the clinical setting in the near future.

Informed Consent

Informed consent for participation in the study was obtained from both patients.

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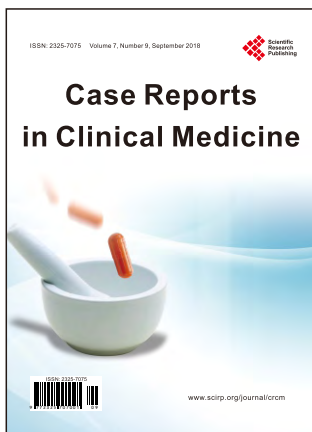
Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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