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Эффективность хирургического лечения амиодарон-индуцированного тиреоидита

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Цель. Амиодарон, относящийся к антиаритмическим препаратам III класса, является жизненно важным лекарством, однако он способен провоцировать развитие амиодарон-индуцированного тиреоидита (АИТ) – редкого, но сложного и угрожающего жизни побочного эффекта. АИТ может вызвать серьезную сердечную дисфункцию и привести к сердечной недостаточности. Заболевание обычно поддается медикаментозному лечению, но небольшая группа пациентов не отвечает на терапию, и у них функция сердечно-сосудистой системы продолжает ухудшаться. Больным из этой группы обычно выполняют тотальную тиреоидэктомию. Без хирургического удаления щитовидной железы состояние пациентов ухудшается; смертность среди непрооперированных пациентов достигает 30–50%. Целью данного исследования был поиск признаков, которые бы позволили более точно определить момент, когда пациента следует направлять на операцию, а также оценка эффективности этого метода лечения.

Методы. Нами был проведен ретроспективный анализ серии случаев АИТ у пациентов, которым была выполнена тотальная тиреоидэктомия с целью лечения АИТ в период с 1998 по 2015 г., что было необходимо для оценки эффективности такой терапии, а также показаний для нее.

Результаты. Мы наблюдали быстрое и значительное снижение уровня T_4 после операции. Симптомы заболевания, как правило, исчезали после операции. Однако каких-либо четких показателей того, как долго следует проводить медикаментозную терапию, в рамках данной когорты больных нами выявлено не было.

Заключение. Врачам следует рассматривать хирургическое вмешательство как действенный и эффективный способ лечения амиодарон-индуцированного тиреотоксикоза. Тем не менее остается неясным, когда следует направлять пациентов на это лечение. При лечении этих сложных пациентов следует применять индивидуальный подход.

Ключевые слова: *щитовидная железа, тиреоидит, тиреоидэктомия, эндокринная хирургия.*

Efficacy of the surgical management of amiodarone-induced thyroiditis

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Aim. Amiodarone, a class III anti-arrhythmic can be a life-saving medication however it can also cause amiodarone-induced thyroiditis (AmIT). Though rare, it is a complex and life-threatening side effect. AmIT can cause significant cardiac dysfunction and lead to cardiac failure. Though generally treated medically, a small sub-group do not respond and their cardiovascular function continues to deteriorate. This select group is referred for a semi-elective total thyroidectomy. Without surgical removal of their thyroid gland these patients will continue to deteriorate, with a 30–50% mortality rate for those not operated on. The aim of this study was to assess for any indicators as to when these patients should be referred for total thyroidectomies and the efficacy of this method of treatment.

Method. A case series of patients with amiodarone-induced thyroiditis treated with a total thyroidectomy from 1998–2015 was used to retrospectively assess the efficacy and indicators for surgery.

Results. T_4 values decreased quickly and significantly after surgery. Patients' symptoms mostly resolved after surgery. No clear indicators were found to be common throughout the cohort as to how long medical therapy should be pursued.

Conclusion. Clinicians should view surgery as an effective and efficient treatment avenue for amiodarone-induced thyrotoxicosis. However, it is not clear when this treatment should be instigated. A case-by-case approach should be adopted when treating these complicated patients.

Key words: *thyroid gland, thyroiditis, endocrine surgical procedures, thyroidectomy.*

Introduction

Amiodarone, a class III anti-arrhythmic, can be a life-saving medication in the treatment of tachy-arrhythmias. It has been shown to improve survival rates in patients with heart failure and can be very useful in cases where other antiarrhythmic drugs are ineffective or contraindicated, however it has multiple side effects [1]. Amiodarone is 37% iodine and is generally administered in doses 50–100 times the daily iodine requirement. This iodine load can trigger increased thyroid hormone synthesis and release. Yet amiodarone also decreases peripheral de-iodination of thyroxine (T_4) to triiodothyronine (T_3) by inhibiting liver type I iodothyronine 5'-deiodination of T_4 [2].

This interference in thyroid function can lead to amiodarone-induced thyrotoxicosis (AmIT), a complex and life-threatening side effect with an incidence of 3–5% in Australia [3]. It is difficult to manage due lack of response to medication, worsening of tachy-arrhythmias in patients with poor cardiac function and the possibility of needing to continue amiodarone to control an arrhythmia [3]. AmIT can cause significant cardiac dysfunction and lead to cardiac failure. Cardiologists have been advised to assess thyroid function and morphology prior to initiation of amiodarone [1]. The duration between amiodarone use and the presentation of AmIT is variable and can range from two to 47 months [4].

Thyrotoxicosis is diagnosed by clinical signs and symptoms and thyroid functions tests (TFTs). The signs and symptoms can include; relapse and/or worsening of an arrhythmia with cardiac insufficiency, nervousness, tremor, fatigue, muscle weakness and weight loss [5]. The onset is rapid and fulminant. TFTs usually show a low thyroid-stimulating hormone (TSH), a high T_4 and normal or slightly high T_3. There is little evidence of an autoimmune mechanism being involved, as serum anti-thyroglobulin, anti-microsomal, and anti-thyrotropin receptor antibodies are usually undetectable.

Other forms of iodine-induced thyrotoxicosis are generally managed conservatively due to their self-limiting nature. The long half-life of amiodarone (~107days) means that patients are still exposed to therapeutic levels for a long time after cessation. Conservative management may not be suitable due to the associated cardiac dysfunction as AmIT can worsen pre-existing arrhythmias, cardiac failure, angina pectoris and cardiomyopathy [1] Current practice is to withdraw amiodarone when feasible, however due to the long half-life of amiodarone this may not change the current clinical situation. Additionally, due to the inhibition of peripheral de-iodination, there can be a paradoxical worsening of the patient's condition on cessation of therapy.

There is a male predisposition with a male: female ratio of ~3 : 1 and a tendency to occur in iodine-deficient areas. There are also three types of AmIT. Type I occurs in abnormal thyroid glands via a Jod-Basedow phenomenon, where the iodine-loading unmasks underlying thyroid autonomy. Type II is a destructive thyroiditis leading to the release of preformed hormones from an intrinsically normal thyroid gland and type three is a mixed type. The histopathology for all types' shows marked destruction of follicles, with inflammation and fibrosis [6].

The medical management is challenging, poorly understood and lacks a proven, consistent therapeutic armamentarium, though the literature reports 20% of cases remit spontaneously [1]. In Australia, type I AmIT is managed by the simultaneous administration of thionamides (which block hormone synthesis by interfering with the iodine organification and the coupling of iodothyrosines) and potassium perchlorate (which competitively blocks iodide from entering the thyroid gland).

Type II AmIT is commonly treated by steroids as it is an inflammatory destruction of the gland [7, 8]. Prednisone at 40–60 mg/day has been recommended and often results in improvement in one to two weeks.

The glucocorticoids need to be continued for two to three months and then tapered slowly to avoid relapse [7, 8]. Radioiodine therapy is not feasible due to the suppressed iodine uptake, delayed effect and potential for further hormone release [9]. Mixed forms are best treated with a combination of the aforementioned medications [10].

Treatment may take up to four months to become effective and no regimens have demonstrated reliable success. These patients have pre-existing cardiac dysfunction and do not tolerate hyperthyroidism well; they require timely

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resolution of their AmIT [11]. Chemical treatment also has significant side effects. Thionamides require high dose maintenance and potassium perchlorate causes nephrotoxicity, bone marrow suppression and requires a minimum of eight weeks of therapy. Corticosteroids inhibit 5-monodeiodinase activity and can worsen T_4 thyrotoxicosis [12].

Overall, the difficulties with medical management are:

- amiodarone may be the only effective agent and cannot be ceased;
- cessation of amiodarone can cause paradoxical rise in T_3, worsening thyrotoxicosis;
- it may take months for the patient to achieve a euthyroid state with medication;
- the medication may never induce a response;
- the medication has known side effects.

Plasmapheresis and haemodialysis, can provide acute relief but only transient effects, are extremely expensive and impractical in the long term.

The small selection of patients who do not respond to medical treatments have uncontrolled thyrotoxicosis, the potential to develop a thyrotoxic crisis, and generally end-stage cardiac failure. This select group is referred for a semi-elective total thyroidectomy [7]. There is minimal research about this subset of patients and no guidelines as to when surgery is indicated. Usually total thyroidectomy is a last resort but it may need to be considered earlier in the treatment algorithm as it allows for rapid control and continuation of amiodarone [3].

Without a thyroidectomy these patients will continue to deteriorate, and have a mortality rate of 30–50% [9]. This rate is reduced to 0–13% when a thyroidectomy is performed [13]. The paradox of AmIT is that it often occurs in patients who require amiodarone for life-threatening arrhythmias yet these patients are often the least able to tolerate a thyrotoxic state.

These patients can have significant improvement in their functional status post-thyroidectomy [3]. If rapidly successful, medical therapy is unquestionably the best; but if the disease is severely and uncontrollably toxic, especially when T_3 levels are markedly increased, the patient certainly can benefit from thyroidectomy. It has proved to be not only a life-saving measure devoid of complications but also the only way to continue amiodarone therapy [14].

Thus, the agreed upon indications for surgery are:

1. when amiodarone is essential despite thyrotoxicosis;
2. type I or mixed AmIT, since the thyroid disorder may be similar to Grave's disease and therefore may maintain the thyrotoxicosis to which amiodarone contributes;
3. patients awaiting heart transplant;
4. failure of anti-thyroid treatment.

The current difficulty lies in defining the criteria of failure of medical treatment in a standardised manner, to avoid emergency thyroidectomy [15].

Surgery has been shown to rapidly treat the thyrotoxicosis and patients recover within a few days rather than enduring months of treatment without a definitive outcome [6]. Further research is needed to develop guidelines for which patients should trial medications and for what duration. The aim of this case series is to analyse these patients for any indicators which would suggest when these patients should be referred for surgery. The case series also aims to demonstrate the efficacy of a total thyroidectomy as treatment for AmIT.

Clinical Significance

This case series has shown how effective surgery is in treating AmIT. This research provides physicians with evidence of how prolonged medical therapy may not be the best treatment for these patients and how quickly surgery cures their condition. This research also shows how different each of patients is and how each case must be addressed on an individual basis.

Methods

A retrospective analysis was performed. From January 1998 to November 2015, pathology records were screened for thyroid tissue and the records of patients who had a total thyroidectomy to treat AmIT at The Prince Charles Hospital (TPCH), Australia were obtained and reviewed. Ethics approval was obtained from the Human Research and Ethics Committee (HREC) at TPCH.

Pre-operatively

The patients' demographics, co-morbidities, history of previous thyroid pathology and function, amiodarone use indications, doses and duration prior to the diagnosis, were noted. The patient's thyrotoxic symptoms, medical therapy (including agents used, doses and duration), indication for thyroidectomy and cardiac status were documented. Cardiac and thyroid function markers were assessed at three specific time points; diagnosis, pre-operative and post-operative.

Specifically, the factors assessed at all three time periods included; thyroid function tests (T_4, T_3, TSH, anti-thyroglobulin auto-antibodies (Tg-Ag), antibodies to thyroid peroxidase (ATPO), anti-thyroid-stimulating hormone receptor auto-antibodies (TR-Ab), heart rate and rhythm, blood pressure, cardiac ejection fraction (EF; heart function by NYHA guidelines), echocardiography findings and patient symptoms.

Anaesthesia and Surgery

All surgeries were performed under general anaesthesia. Thyroidectomy was as total as possible in each case.

Post-operatively

Post-operatively, thyroid function tests and symptoms were monitored to assess for the resolution of AmIT.

Results

AmIT group

Eleven patients underwent a total thyroidectomy under general anaesthetic for amiodarone-induced thyroiditis (AmIT) from January 1998 to November 2015. The salient features of the data are summarised in the following tables. Table one illustrates the range of patient demographics and their amiodarone use.

Table two highlights the clinical state of the AmIT patients prior to their operations.

The type of AmIT was not documented definitively for any of the patients and medications were at the discretion of the treating physician. Table three documents the medical treatments trialled, the duration, and any side effects encountered.

Table four illustrates the post-operative state of the patient as well as the histopathological findings.

The following graphs provide a graphical representation of the treatment of each AmIT patient and their T_4 levels over time. The graphs highlight when medications were started, stopped and doses changed. The graphs include the time at which the patient underwent surgery and the resultant T_4 values.

Table 1. Demographics and amiodarone use

Patient	Age	Sex	Indication for amiodarone	Duration of amiodarone before surgery (months)	Duration of thyrotoxicosis before surgery (weeks)
1	70	M	VT	40.5	8
2	82	M	AFib	38	9
3	51	M	SVT/AFlutter	5	11
4	52	M	VF	9	1.5
5	68	M	AFib	20	13
6	51	F	VT	>29	2
7	59	M	AFib	15	7
8	52	M	VT	43	6
9	48	M	AFib	21	2.5
10	63	M	AFib	33	7.5
11	34	F	Aflutter	14	14

Note: VT — ventricular tachycardia, Afib: Atrial fibrillation; SVT — supraventricular tachycardia; Aflutter — Atrial flutter; VF — Ventricular fibrillation.

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Table 2. Pre-operative thyroid and cardiac function

Patient	Pre-op symptoms	Pre-op cardiac function	Pre-op T_4 (pmol/L)	Pre-op TSH (mU/L)
1	Chest pain, palpitations, syncope, diaphoresis	Pacemaker in situ. HR: 68, BP: 140/75 EF: 20%	39	0.2
2	Dizziness, palpitations, sensation of missed beats, tremor, diarrhoea, increased appetite and weight loss	Atrial fibrillation. HR: 120, BP: 130/80 EF: 58% (8 months prior)	65	0.08
3	Palpitations	Sinus rhythm. HR: 70, BP: 115/70 EF: 68% (9 years prior)	22	0.05
4	Diarrhoea (in the setting of infective colitis)	Sinus rhythm. HR: 55, BP: 150/80 EF: Not documented	29	0.1
5	Palpitations, tremor, weight loss and irritability	Sinus rhythm HR: 65, BP: 125/70 EF: 39%	34	0.05
6	Occasional palpitations	Pacemaker in situ. HR: 78, BP: 135/60 EF: 27–30%	71	0.1
7	Orthopnoea, PND, SOBOE, AF, decreased appetite, tiredness	Atrial fibrillation. HR: 90, BP: 110/70 EF: 25%	46	0.1
8	Lethargy, decreased exercise tolerance	Sinus rhythm. HR: 60, BP: 150/70 EF: 63%	73	0.2
9	Shortness of breath, tachycardia, hot flushes and rigors	Sinus rhythm. HR: 122, BP: 170/80 EF: 67%	120	0.05
10	Lethargy, weight loss, diarrhoea and vomiting. Fever over a month on background of infective endocarditis. Encephalopathic with MODS	Atrial fibrillation. HR: 70, BP: 130/51 EF: 50-60%	47	0.5
11	Increased peripheral oedema, increased fluid retention, nauseated, abdominal discomfort and lethargic	Pacemaker in situ. HR: 60, BP: 90/43 EF: 19%	76	0.05

Note: HR: heart rate, BP: Blood pressure, EF: ejection fraction, MODS: multiple organ dysfunction syndrome.

Table 3. Medical treatment

Patient	Medications used	Duration of medication trial (weeks)	Side effects from medications
1	Carbimazole, prednisone	8	Nil
2	Beta-blockers, carbimazole and prednisone	9	Nil
3	Beta-blockers, carbimazole and prednisone	11	Nil
4	Carbimazole, prednisone	1.5	Neutropaenia
5	Beta-blockers, carbimazole and prednisone	13	Nil
6	Beta-blockers, carbimazole and prednisone	2	Felt exercise tolerance decreasing

Table 3. Medical treatment

Patient	Medications used	Duration of medication trial (weeks)	Side effects from medications
7	Beta-blockers, carbimazole and prednisone	7	Nil
8	Beta-blockers, carbimazole, prednisone and cholestyramine	6	Nil
9	Beta-blockers, carbimazole, prednisone, cholestyramine and lithium	2.5	Nil
10	Beta-blockers, carbimazole and prednisone	7.5	Nil
11	Beta-blockers, carbimazole and prednisone	14	Nil

Table 4. Post-operative state

Patient	Histopathology	Weight of gland (grams)	Post-op T_4 (pmol/L)	Post-op symptoms	Post-op cardiac function
1	Consistent with amiodarone-induced thyroiditis	14.15	9.1	No symptoms	Pacemaker in situ. HR: 69, BP: 110/60 EF: Not documented
2	Consistent with amiodarone-induced thyroiditis	37	8.1	Chest tightness and shortness of breath	Atrial fibrillation. HR: 103, BP: 130/75 EF: Not documented
3	Consistent with amiodarone-induced thyroiditis	26	11	Sore throat	Sinus rhythm. HR: 70, BP: 115/70 EF: Not documented
4	Consistent with amiodarone-induced thyroiditis	33.7	22	No symptoms	NSR. HR: 84, BP: 156/102 EF: Not documented
5	Consistent with amiodarone-induced thyroiditis	26	13	Ongoing tremor	Sinus rhythm. HR: 58, BP: 120/70 EF: Not documented
6	Consistent with amiodarone-induced thyroiditis	27.9	67	No symptoms	Pacemaker in situ. HR: 65, BP: 105/60 EF: 32%
7	Consistent with amiodarone-induced thyroiditis	33	6.1	Pain over surgical site	Atrial fibrillation. HR: 99, BP: 161/89 EF: Not documented
8	Consistent with amiodarone-induced thyroiditis	62	*	No symptoms	Sinus rhythm HR: 70, BP: 143/77 EF: Not documented
9	Consistent with amiodarone-induced thyroiditis	61	96	No symptoms	Sinus rhythm. HR: 108, BP: 150/80 EF: not documented
10	Unremarkable thyroid tissue	25	14	Ongoing encephalopathy	Atrial fibrillation HR: 76, BP: 170/60 EF: 50%
11	Diffuse enlargement with attacking follicles and infiltrating colloid (no diagnosis given)	29.6	16	No symptoms	Pacemaker in situ. HR: 60, BP: 90/43 EF: not documented

Note: HR — heart rate; BP — blood pressure; EF — ejection fraction.

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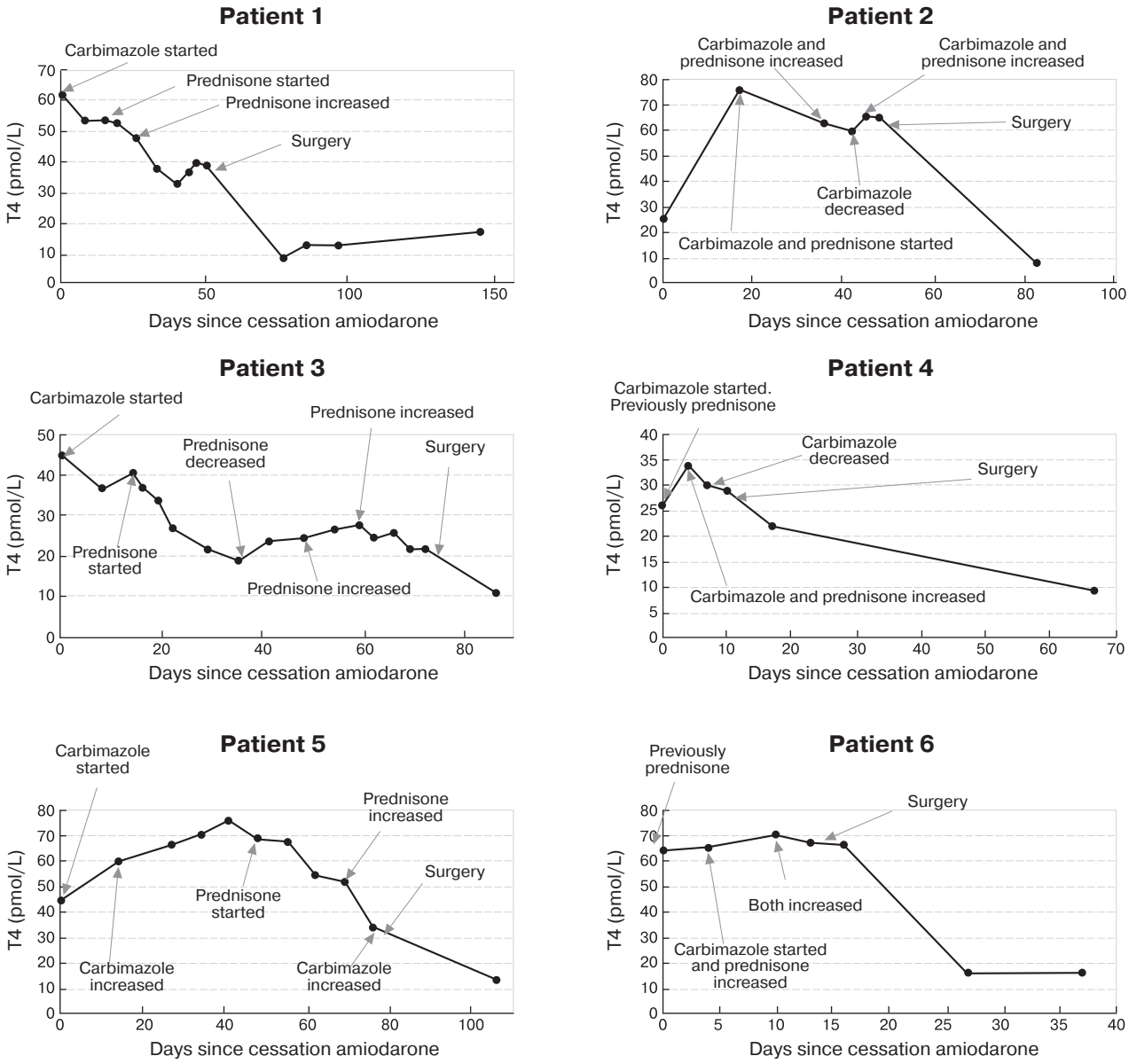
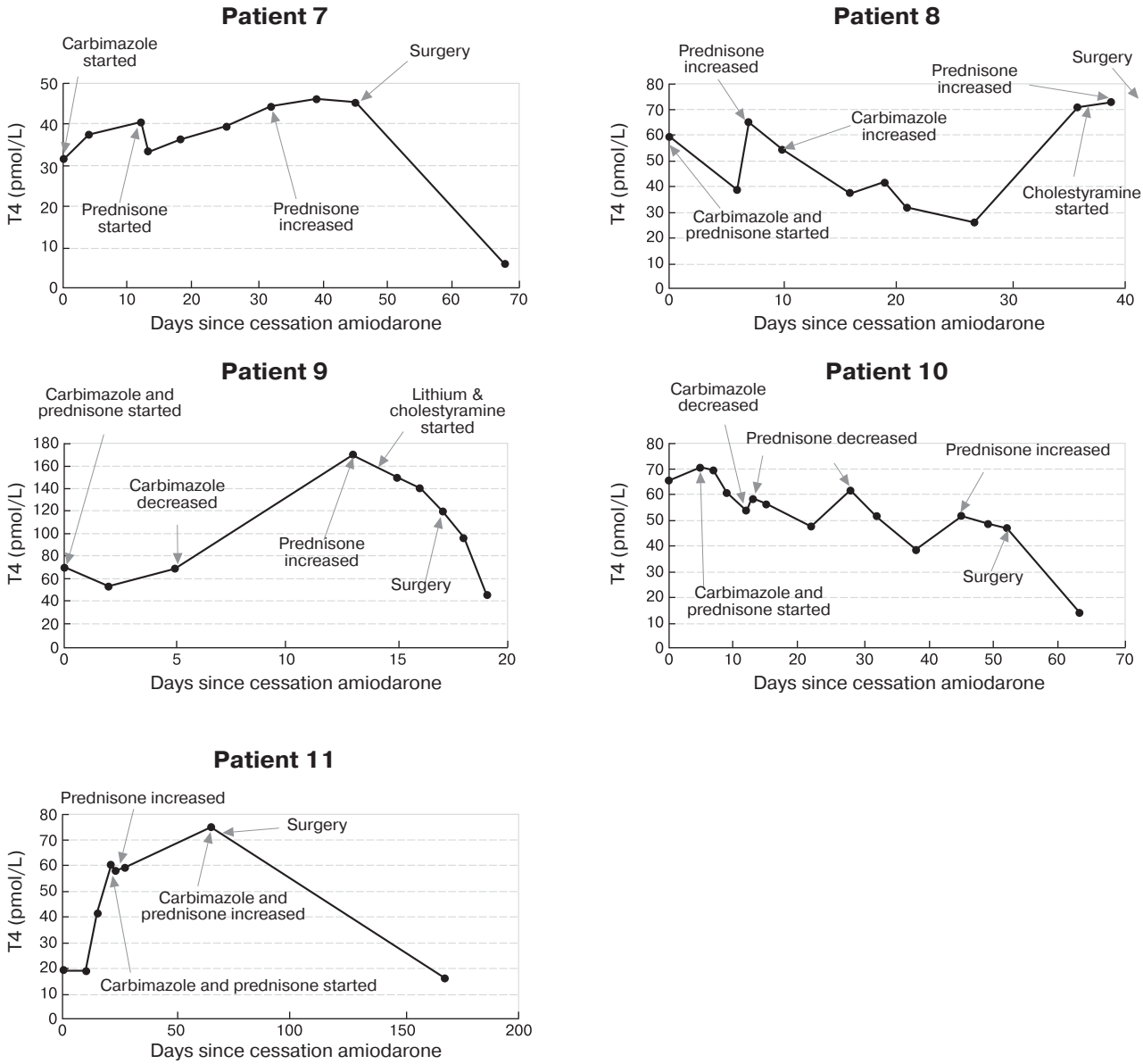


Figure 1. T_4 values from diagnosis to post-operation, with documented medical treatment for each AmIT patient.



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Discussion

Background on The Prince Charles Hospital

This research was performed at The Prince Charles Hospital (TPCH). TPCH is 630 bed, major, tertiary referral hospital, located 10 kilometres from Brisbane city (the capital of the state of Queensland). It is the premier cardiac service for the state of Queensland, as well as northern New South Wales. It provides specialised services in complex interventional cardiology, structural heart disease, and cardiac electrophysiology. It is the centre for specialised state-wide services including heart and lung transplantation; adult cystic fibrosis; adult congenital heart disease; advanced heart failure; percutaneous valve therapies and complex cardiac care.

This background provides the foundation to a better understanding of this group of patients. The patients identified at TPCH with AmIT came from a cohort of cardiac cripples; each one had significant cardiac co-morbidities. This is considerably different from other hospitals which do not treat such patients and thus the results must be interpreted with this knowledge in mind.

Demographics

A review of the AmIT cases demonstrated several features that have previously been documented in the literature. Firstly, as shown in table 6, AmIT is seen more frequently in male patients. This study showed a male: female ratio of 9 : 2 and this is comparable to the literature which quotes a distribution of 3 : 1 [3]. This is suspected to be due to the higher frequency of males suffering from cardiovascular disease and being treated with amiodarone. The reverse can be seen with non-AmIT cases, showing a female predominance, as is well known for other thyroid pathologies.

Secondly, that there is a variable duration of amiodarone use before onset of symptoms. This has been previously documented by Mariotti et al (1999), who stated the duration of time before onset ranged between 2–47 months and as shown in table 1, all of the values from this study fall within that range [4]. Thirdly the time between diagnosis and surgery is also highly variable. This is likely related to the lack of guidelines available to direct management of these patients. However, all patients were operated on within the half-life of amiodarone (~107days), thus despite all patients being able to cease amiodarone, there may have been a residual amount in each patient's system. This means that no comment can be made about self-resolution of AmIT after elimination of amiodarone in these patients.

AmIT diagnosis

The diagnosis of AmIT was made for each patient by their elevated T_4, depressed TSH values, negative antibody levels and history of amiodarone use. Two patients did have elevated anti-thyroid peroxidase antibodies (ATPO) but were diagnosed as having AmIT by the endocrinology teams involved and later confirmed on histological analysis.

The type of AmIT diagnosed was not documented in any of the eleven cases. As differentiating between types of AmIT is quite difficult, this is understandable. However, as the type of AmIT dictates the treatment recommended, the treatment regimens were completely physician-dependent. Due the period of data collection, many different physicians were responsible for diagnosing, treating and referring these patients. This variability may have contributed to the difference in management of the patients.

AmIT treatment

The medical treatment regimens for the AmIT patients typically initiated one of two ways; carbimazole alone before adding prednisone (n = 3) and carbimazole with prednisone combined (n = 6, but two patients were currently on prednisone when the diagnosis was made). This would suggest that three patients were initially thought to have AmIT type I. Only one patient provided a previous history of thyroid dysfunction, while two patients were previously documented to have a goitre. Based on this history, these three patients were all started on carbimazole alone first.

The duration of the trial of carbimazole alone lasted an average of 22 days (range of 12–48 days). Prednisone was then added to the treatment regime due to the lack of response to carbimazole. It is likely that the patients were

re-evaluated to have a diagnosis of 'mixed-type' AmIT.

Except for two patients, all were treated with beta-blockers, however these medications were part of each patients' regular medications prior to the diagnosis of AmIT. This is to be expected as these patients had significant degrees of cardiac dysfunction.

Two patients had additional medications trialled; patient 8 was given cholestyramine and patient 9 was given cholestyramine and lithium. Cholestyramine is an ion exchange resin which has been shown to interfere with endogenous thyroid hormone absorption and block enterohepatic circulation [16]. Lithium has been shown to inhibit thyroid hormone release and reduce iodination of tyrosine residues but is infrequently used due to its toxicity profile [17]. Both agents were used late in the treatment of the patients and likely as a last attempt to control the thyrotoxicosis before referring to surgery.

This study spanned over 17years and the patients reviewed were cared for by different doctors. During this period, there was also many investigations and developments into the definition, pathophysiology and management of AmIT. Thus a controlled treatment regime for this group of patients was not likely. Overall, the same dose range for the medications was employed and these were similar to other studies in the literature [8].

Timing of Surgery

Figure 1 demonstrates the efficacy of the medications for each patient. The data points displayed and the information collected was innately determined by the regularity of blood samples taken and analysed. As can be seen from the graphs, the medications used tended to have either a temporary or small effect on the T_4 values.

The duration of the trial of medication was highly variable. This has previously been documented in the literature and a call for development of guidelines has been made. There was no evidence of a threshold T_4 level or duration of medical therapy that prompted a referral for surgery. The duration of medical treatment ranged from 1.5–14 weeks and the highest pre-operative T_4 values ranged from 34–170 pmol/L. From these results it would suggest that every patient is being treated on a case-by-case basis and the decision to refer to surgery is not one that can be simply based on T_4 values or duration of previous medical treatment.

Two patients were operated on within two weeks or less (patients 4 and 6). The indication given for the referral to surgery for both patients was 'non-responsive' to medication. The literature recommends longer trials of medication with haemodynamically stable patients. This is another example of physician variability.

When reviewing the patients individually, this method of management becomes more understandable. A comparison between the medical histories of two patients who are at the extremes of duration of thyrotoxicosis prior to surgery, demonstrates the significant difference that may be present between two patients.

For example, patient 9 had recently (2months prior) had a heart transplant and was suffering a long and unstable post-operation recovery when he developed AmIT. He underwent surgery within 2.5 weeks due to his inability to compensate for the increased stress on the cardiovascular condition. He was encephalopathic pre- and post-operation secondary to his multiple organ dysfunction syndrome. He had a regular heart rate of 125 bpm (beats per minute) at diagnosis and a blood pressure of 200/80 mmHg. These values continued both pre- and post-operation. His cardiac function, as measured by an echocardiogram two days prior to his surgery, showed a normal left ventricle size and function, a left ventricle ejection fraction (LVEF) of 65%, normal right ventricular size and function, bi-atrial dilatation and normal valves. He suffered no complications from the surgery but unfortunately passed away four days post-operation due to unrelated causes

In comparison, patient 11 whose background included multiple congenital cardiac defects which had been repaired, atrial flutter with a pacemaker and an automatic implantable cardioverter defibrillator (AICD), was operated on 14 weeks after diagnosis. She had significant cardiac dysfunction during this time, with a LVEF of 19%, left ventricular end diastolic diameter (LVEDD) of 6cm (normal is 3.9–5.3cm), a severely dilated and dysfunctional

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right ventricle with a right ventricular systolic pressure (RVSP) of 48 mmHg (normal range for <50years old 21.6–33 mmHg), as well as grade 2/4 mitral regurgitation and 3/4 tricuspid regurgitation [18].

However, despite her severe cardiac condition she was permitted to be thyrotoxic for 14 weeks before she was deemed suitable for an operation. She only had two medication changes, one was the day prior to the operation. However, during this time she remained hemodynamically stable with a paced heart rate of 60bpm and a blood pressure of 99/43 pre-operation and 134/54 post-operation. The symptoms she was experiencing were; increased peripheral oedema, increased fluid retention, nausea, abdominal discomfort and lethargy. She recovered well from the operation, suffering only mild hypocalcaemia but passed away from primary cardiac graft transplant failure after receiving a heart transplant two years later.

It may be suggested that patient 9 was also referred to surgery with more urgency due to his T_4 level. Patient 9 did have the highest T_4 level prior to surgery at 120 pmol/L. However, when reviewing the T_4 values of the other patients, there is no obvious correlation between time to surgery and T_4 values as the second highest T_4 value was patient 11, with a T_4 of 76, and she waited 14 weeks before having an operation. This comparison demonstrates that the most important feature in determining when a patient was referred to surgery, was not their background cardiac function or comorbidities, or their T_4 values but their current clinical condition.

Another factor which must be taken into consideration is the number of therapies available to the patients. This is best exemplified by comparing patients 1 and 4. Patient 1 underwent surgery 8 weeks after diagnosis, whereas patient 4 had surgery within 1.5weeks. Patient 1 had poor cardiac function with an ejection fraction of 25% on the background of dilated cardiomyopathy, an AICD, mild coronary artery disease, an aortic valve replacement (mechanical), obesity, OSA (obstructive sleep apnoea), depression, gastro-oesophageal reflux disease (GORD), chronic kidney disease (CKD, stage IV), hypertension, hypogonadism, secondary hypothyroidism, iron deficiency, restless legs and had experienced a right cerebellar embolic stroke. Patient 4 had undergone a heart transplant the year prior to developing AmIT and had better cardiac function. However, he did have other comorbidities; type 2 diabetes mellitus, gout, CKD, obesity, previous abdominal hernia repair and gastrectomy. Both patients had similar heart rates, blood pressures and T_4 values. One main difference between these two patients is that patient 4 had been on prednisone since the heart transplant. This may have influenced management as a glucocorticoid could not be added but only increased in dosage for management of the symptoms and it also causes immunosuppression. This may have prompted earlier surgery in patient 4 in comparison to patient 1, who had worse cardiac function out of the two patients.

Thus, from analysing the patients' clinical status, comorbidities, cardiac function and T_4 levels with respect to time-to-surgery, it has been shown that poor clinical status and lack of potential treatments may be potential indicators for a shorter trial of medical management before surgical intervention. Yet as the timing of referral to surgery is a subjective decision made by individual physicians it is difficult to specifically identify an indicator.

Medication side effects

Patient 4 was the only patient to experience a side effect which could clearly be linked to the medication. To address this complication, the dose of carbimazole was decreased. Though this didn't result in rebounding T_4 values, the patient's response to the medication did appear to slow and they underwent surgery within four days. Patient six suffered a decrease in their exercise tolerance, however whether this was secondary to the medication is debatable as it may have been due to a decline in their cardiac function.

Except for patient eight; who was lost to follow up post-operatively, it can be seen that surgery had a larger and more definitive effect on the T_4 values than medication. T_4 values were recorded from time of diagnosis to one to two measurements post-operation. The ongoing follow up of T_4 values post-operation

was limited due to the initiation of thyroxine use for all patients. It is unlikely that monitoring of further T_4 values would have been of benefit towards this study.

It is difficult to determine the speed of the effect of surgery due to the period of time between the surgery and reassessing T_4 values post-operatively. Patients 3, 4, 6, 9 and 10 all had thyroid function tests taken within 2 weeks of surgery, whereas the remaining 6 patients had TFTs sampled much later after the surgery. Within these two weeks, patients 3, 6, 9 and 10 all at least halved their T_4 values. However, Patient 6 had a T_4 value recorded on day two post-operation which was very similar to their pre-op value and patient 9 only experienced a 20% decrease in T_4 value by day 1 post operation.

Patient 4 also had TFTs taken on day two post-operation, which showed a decrease in T_4 from 29 to 22pmol/L and no further blood tests until day 52 post-op, which resulted in a T_4 value of 9.2 pmol/L. As the other patients has blood tests at a much later time it is impossible to determine if their T_4 values had decreased at a similar rate, and then plateaued or if the decline was more gradual. Based on the results available, it would suggest that within two weeks, surgery was very effective in over 80% (n = 5/6) of cases. A structured prospective trial with an agreed upon sampling frequency would assist in determining the speed of the surgical effect.

Limitations of study

As previously mentioned, there were a few limiting features of this study. Firstly, the small sample size inhibits the performance of useful statistical analysis due to the lack of power in the study. This is a factor of studying rare diseases. A method to overcome this would be recruitment of more facilities to be involved in any prospective trials or to collate and analyse data from pre-existing research or facilities.

Another limitation in assessing the efficacy of surgery in treating AmIT, is the lack of structured regularity in thyroid function tests. As previously mentioned, a prospective study with regular and structured blood tests would assist in overcoming this limitation. Additionally, the inter-surgeon and inter-anaesthetist variability, is another variable which ideally would be controlled. However due to the rarity of the disease this is an unrealistic aim and the inter-surgeon and inter-anaesthetist variability must be calculated into the analysis.

This study is a retrospective analysis of chart notes and this lends itself towards bias. There is bias in the interpretation of the chart notes and in what information was documented for each patient. Though the charts were thoroughly reviewed to source all information, not all information was available for each patient; this was more evident in the older charts. Lack of information, results in an incomplete assessment of all the patients and prevents solid conclusions being documented.

Though only a single patient was loss to follow up, due to further medical review occurring at a distant private facility; this accounts for almost 9% of the patients in the AmIT group. Once again, a larger trial would assist in reducing this and improving the robustness of the study.

Conclusions

Surgery efficiently treated AmIT and allowed patients to become euthyroid via chemical replacement.

T_4 values, duration of medical trial and previous medical comorbidities/cardiac function, did not correlate to urgency in performing a thyroidectomy. The only noticeable feature was the severity of the symptoms experienced by the patient. Those with more severe symptoms were treated quicker than those who appeared to be compensating for their hyperthyroid status, despite significant comorbidities.

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