

IS ACROMEGALY A HYPERCOAGULABLE CONDITION? CASE REPORTS AND REVIEW OF THE LITERATURE

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Abstract

Introduction: Cardiovascular complications are a major cause of morbidity and mortality in patients with uncontrolled acromegaly. However, there are no published reports of an increased risk of venous thromboembolism (VTE) in such patients. We report three patients with uncontrolled acromegaly who presented with VTE.

Clinical Cases: A 52-year-old male with uncontrolled acromegaly despite transsphenoidal (TSP) surgery and medical therapy presented in 2012 with acute chest pain and shortness of breath that was later confirmed as secondary to pulmonary embolism. A 44-year-old male immigrant, previously treated for acromegaly with radiation therapy alone, in 1992, in his native country, was referred to our centre in 2006 for acromegaly which remained uncontrolled despite medical therapy until 2009 when he achieved remission through TSP surgery. He had several episodes of VTE between 2008 and 2010. A 69-year-old male with uncontrolled acromegaly for 28 years despite two surgical resections and radiation therapy in 1986 and 1992, as well as continuous medical therapy, presented with VTE of the right axillary vein and bilateral pulmonary emboli in 2011. A thrombophilia screen in case 1 showed mild protein S deficiency, case 2 was homozygous for factor V Leiden (FVL) mutation and case 3 was heterozygous for FVL. Extensive investigations revealed no evidence of malignancy and echocardiography showed preserved ejection fraction in all three patients.

Conclusion: Patients with uncontrolled acromegaly may be at increased risk of VTE. However, larger studies are required to further assess this association and determine the underlying cause.

Key words: Acromegaly, pituitary tumours, thromboembolism

Introduction

Uncontrolled acromegaly is associated with an increased risk of cardiovascular (CV) abnormalities such as hypertension, left ventricular hypertrophy (LVH), endothelial dysfunction and cardiomyopathy.^[1] In fact, CV complications constitute the leading cause of morbidity and mortality in patients with acromegaly.^[2] Recent reports have suggested that changes in the coagulation and fibrinolytic system may also play a role in the pathogenesis of CV disease in acromegaly.^[3-5] To date, there are no published reports of an increased risk of venous thromboembolism (VTE) in acromegaly. We report three

cases of patients with uncontrolled acromegaly who presented with extensive VTE.

Case Reports

Case 1

A 52-year-old Caucasian male presented with typical phenotypic features of acromegaly in December 2009. Baseline serum IGF-1 and growth hormone (GH) levels were 1220 mcg/l (*n* 87–238) and 54.1 mcg/l (*n* <1 mcg/l), respectively; nadir GH after an oral glucose tolerance test was 29.3 mcg/l. Magnetic resonance imaging (MRI) of the sella revealed a 1.4 cm pituitary adenoma extending into the right cavernous sinus. He underwent transsphenoidal (TSP) tumour resection in June 2011, which led to a significant reduction in serum IGF-1, albeit without

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normalisation, at 15–20 % above the upper limit of normal (ULN). Follow-up MRI revealed a small residual tumour and the patient was offered repeat surgery or radiation therapy, which he declined. Due to the absence of medical coverage for somatostatin analogue therapy, cabergoline or pegvisomant, pharmacologic therapy with bromocriptine (10 mg daily) was initiated. He was unable to tolerate a larger dose due to nausea and dizziness. There was a slight reduction in his serum IGF-1, but it has remained uncontrolled, with serum IGF-1 consistently between 10 and 13% above ULN. To date, he declines further medical intervention. In September 2012, he presented with acute chest pain and shortness of breath and was subsequently diagnosed with a right upper lobe pulmonary embolism on computed tomography (CT) pulmonary angiography. No other risk factors for thromboembolism such as immobility, recent travel, malignancy or family history of VTE were identified. Anticoagulation with low molecular weight heparin was initiated until adequate warfarin therapy was established; he currently remains on a daily dose of 10 mg. A colonoscopy was performed in October 2012 which revealed three benign hyperplastic polyps and an echocardiogram showed mild diastolic left ventricular dysfunction but preserved systolic function. Thrombophilia screen [Table 1] revealed the following results: Fibrinogen 3.81 g/L ($n = 2.15\text{--}4.79$), negative D-Dimer (negative < 200 ng/mL), protein C 1.03 U/mL ($n = 0.74\text{--}1.64$), protein S 0.66 U/mL ($n = 0.7\text{--}1.47$) and negative Factor V Leiden (FVL) and prothrombin gene mutations.

Case 2

A 44-year-old South Asian male who had recently immigrated to Canada was referred to our clinic in 2006. He had been diagnosed with acromegaly in his native country in 1990 where, in 1992, he was treated with radiation therapy only. Biochemical evaluation revealed an elevated IGF-1 of 352 mcg/l ($n = 109\text{--}284$) and multiple pituitary insufficiencies for which replacement therapy, in the form of hydrocortisone, L-thyroxine and testosterone, were initiated. Pituitary MRI showed a 7 mm left-sided pituitary tumour. Medical therapy with Sandostatin LAR 30 mg was initiated immediately and pegvisomant (15 mg daily) was added 6 months later for persistent disease (IGF-1 = 338 mcg/l). This resulted in transient normalisation of IGF-1, but serum IGF-1 started rising again in early 2009 with evidence of persistent 7 mm adenomatous tissue on MRI of the sella. He underwent TSP tumour resection in November 2009, which resulted in normalisation of serum IGF-1. He has remained in remission since then. Between 2008 and 2010, the patient developed two episodes of right thigh superficial thrombophlebitis (August 2008 and January 2010), two episodes of left saphenous vein thrombosis (November 2008), left popliteal vein thrombosis (February 2010) and pulmonary embolism diagnosed by a ventilation-perfusion scan (February 2010). Risk factors such as family history of VTE, immobility, recent travel or history of malignancy were not identified and he was initiated on long-term

Table 1: Thrombophilia screen*

Tests	Case 1	Case 2	Case 3
Fibrinogen (2.15–4.79 g/L)	3.81	4.75	3.83
Antithrombin III (0.80–1.40 U/ml)	NA ^a	0.94	0.86
D-Dimer (negative<200 ng/mL)	Negative	Negative	NA
Anti cardiolipin IgG (negative: <10 U/ml)	4.6	5.3	1.60
Lupus anticoagulant ratio (0.8–1.2)	NA	1.4b	1.0
Homocysteine (7.1–17.3 μmol/L)	14	NA	16.5
Protein C (0.74–1.64 U/mL)	1.03	NA	1.60
Protein S (0.7–1.47 U/mL)	0.66 (INR c NA)	NA	1.98
Factor V Leiden mutation	Negative	Homozygous	Heterozygous
Prothrombin G20210A mutation	Negative	Negative	Negative

*None of the workup was done during the acute thrombosis episode. For patients on warfarin, Protein C and Protein S were measured 7 days after discontinuing warfarin; anticoagulation therapy was switched to SC LMW heparin. Serum antithrombin III and fibrinogen levels were checked simultaneously. ^aNot available. ^bRatio: > 2.0 LA is strongly present. 1.6–2.0 LA is moderately present. 1.3–1.5 LA is weakly present.

^cInternational normalised ratio

anticoagulation therapy with warfarin. A colonoscopy was performed in June 2010 which showed no abnormality and an echocardiogram from October 2012 revealed mild LVH but was otherwise unremarkable. Thrombophilia workup showed the following: Fibrinogen 4.75 g/L, antithrombin III 0.94 U/mL ($n = 0.80-1.40$), anticardiolipin IgG 5.3 U/mL (negative = <10 U/ml), lupus anticoagulant ratio 1.4 ($n = 0.8-1.2$) and homozygous FVL mutation.

Case 3

A 69-year-old Caucasian male was originally diagnosed with acromegaly in 1985 while living in another province. He had undergone TSP surgery in 1986, followed immediately by fractionated radiotherapy (5000 cGY). Serum GH and IGF-1 levels remained elevated despite high-dose bromocriptine and Sandostatin (100 mcg TID) until he underwent further surgery followed by additional fractionated radiotherapy (2500 cGY) in 1993. He underwent drainage of an abscess in his left thigh in 2000 when he developed an episode of left calf deep vein thrombosis (DVT) that was treated with short-term anticoagulation therapy. He moved to Nova Scotia in 2005 and was referred to our centre. Initial assessment revealed multiple pituitary insufficiencies requiring hydrocortisone, L-thyroxine and testosterone replacement therapy. Pituitary MRI showed an empty sella, with no evidence of pituitary tumour. However, due to a persistently elevated serum IGF-1, he was maintained on octreotide LAR 30 mg every 4 weeks initially and subsequently switched to lanreotide 120 mg every 4 weeks in November 2008. His serum IGF-1 remained elevated. In 2010, he developed atrial fibrillation and was initiated on dabigatran. Pegvisomant 15 mg daily was added in February 2011, which resulted in normalisation of IGF-1 (194 mcg/l; $n 69-200$). He presented to his local hospital in July 2011 with right upper limb swelling, pain and redness as well as intermittent fever, pleuritic chest pain and shortness of breath. Duplex ultrasound showed occlusive venous thrombus in his right axillary vein and CT pulmonary angiogram revealed bilateral pulmonary emboli. Anticoagulation was initiated with IV heparin followed by warfarin. Both Sandostatin and pegvisomant were discontinued on this admission. Subsequently, pegvisomant was restarted in September 2011 and titrated to 20 mg daily in December 2011, leading to normalisation of serum IGF-1 (he was unwilling to take Sandostatin

therapy). In October 2012, warfarin was discontinued and dabigatran 150 mg BID was restarted due to difficulty achieving a consistently therapeutic INR on warfarin. He underwent left total knee replacement in December 2012 and 8 weeks later, while still on dabigatran, he presented with extensive DVT extending from the right external iliac to the popliteal vein. He was initially treated with low molecular weight heparin for recurrent thrombosis and bridged to warfarin therapy. He had no other risk factors for VTE such as malignancy or family history of VTE. His echocardiogram showed mild aortic root and ascending aorta dilatation and concentric LVH with diastolic dysfunction but normal right ventricular size and normal biventricular systolic functions. Colonoscopy revealed three hyperplastic polyps but was otherwise unremarkable. Thrombophilia testing showed: Fibrinogen of 3.83 g/L, antithrombin III 0.86 U/ml, anticardiolipin 1.6 U/mL, protein C 1.6 U/mL and protein S 1.98 U/mL, negative prothrombin gene mutation but heterozygous for FVL mutation.

Discussion

VTE can be associated with significant adverse outcomes if not promptly recognised, whereas timely initiation of anticoagulation therapy significantly reduces early morbidity and mortality.^[6] Several studies have shown that patients with acromegaly have abnormalities in the coagulation and fibrinolytic systems that could potentially predispose to increased risk of VTE.^[3-5,7,8] Plasma fibrinogen, an important clotting protein produced in the liver, has been reported to be significantly elevated in individuals with active acromegaly compared with healthy controls and plasma fibrinogen levels have a positive correlation with serum IGF-1.^[3] Remission of acromegaly with surgery or medical therapy is associated with a reduction in plasma fibrinogen levels.^[3] Another study^[4] assessed coagulation markers in 22 patients with active acromegaly and reported elevated levels of fibrinogen, tissue plasminogen activator (t-PA) and PA inhibitor-1 (PAI-1) while protein S activity and tissue factor plasminogen inhibitor were decreased in these patients compared with healthy controls, potentially creating a pro-thrombotic environment. Elevated PAI-I is both an independent risk factor for VTE and the major determinant of elevated plasma clot lysis time, increasing VTE risk even after adjusting for other coagulation and

fibrinolytic markers.^[7] However, with the exception of fibrinogen and protein S, the association between most other coagulation and fibrinolysis markers described above and VTE is inconsistent and, consequently, they are not measured in routine thrombophilia screening.^[8] In our patients, the thrombophilia screen was positive for homozygous and heterozygous FVL mutation in cases 2 and 3. This mutation is known to be associated with an increased risk of VTE in both heterozygous and homozygous individuals.^[9] We were unable to find any association between acromegaly and FVL in a comprehensive MEDLINE search of the English language literature, using the keywords: “Acromegaly,” “thrombosis,” “coagulation” and “FVL.” The two episodes of DVT post-surgery in case 3 represent an additional risk factor for VTE whilst the slightly low protein S level in case 1 and weakly positive lupus anticoagulant ratio in case 2 are not diagnostic of thrombophilia and are likely clinically unimportant.

Malignancy is one of the major risk factors for VTE, but the associated risk is dependent on the type and staging of the tumour as well as therapeutic modalities.^[10] Occasionally, VTE can be the preceding manifestation of an occult malignancy.^[11] Several recent studies have shown that patients with acromegaly are at increased risk of developing colon, thyroid and urogenital malignancies.^[12-14] Consequently, in patients with acromegaly, colonoscopy is recommended for screening of colon cancer.^[15,16] Furthermore, acromegaly might be a component of other disorders such as multiple endocrine neoplasia type 1, McCune-Albright syndrome or other

genetic syndromes in which additional tumours in other organs may coexist and therefore potentially increase the risk of VTE.^[17] Patients with pituitary tumours who have received conventional radiation therapy also have a higher risk of developing secondary brain tumours.^[18] Although the presence of occult malignancy is exceedingly difficult to exclude, we were unable to find any evidence of malignancy despite thorough clinical examination, diagnostic colonoscopy and extensive imaging studies including ultrasound and CT scan of the chest, abdomen and pelvis.

Congestive heart failure (CHF), found in some patients with long-standing uncontrolled acromegaly, has also been reported to increase the risk of VTE.^[19] Blood stasis, chronic inflammatory-mediated endothelial dysfunction and reduced mobility are speculated to be among the potential underlying mechanisms.^[19,20] In one retrospective case-control study, the risk of VTE was significantly elevated in CHF patients with ejection fraction (EF) of <20% compared with those having EF >45%.^[19] The slight increase in VTE risk in the setting of preserved EF is thought to be due to the potential presence of diastolic dysfunction or right ventricular failure.^[19] Echocardiogram results in all of our cases showed normal EF with no findings of right-sided heart failure or any other significant abnormalities to account for VTE [Table 2].

Two of our patients had previous radiation treatment and developed recurrence of VTE shortly after the addition of pegvisomant. It is unclear if localised sellar irradiation is associated with an increased risk of VTE. Medical therapy

Table 2: VTE and risk factors

Risk Factors	Case 1	Case 2	Case 3
Number of VT episodes	1	5	4
Time since first unprovoked episode	21 months	71 months	23 months
VTE risk factors	No	Homozygous FVL	Heterozygous FVL, past history of DVT
Known malignancy	Negative	Negative	Negative
Colonoscopy	3 hyperplastic polyps	Normal	3 hyperplastic polyps
Echocardiogram	Mild diastolic dysfunction only	EF 57%. Normal RV function. Elevated diastolic filling pressure	Severe concentric LVH but normal biventricular function

VTE: Venous thromboembolism, EF: Ejection fraction, DVT: Deep vein thrombosis, FVL: Factor V Leiden, LVH: Left ventricular hypertrophy

with somatostatin analogues and pegvisomant has not been reported to cause VTE. Previously a small study in 5 healthy individuals who were given a 3-day treatment of pegvisomant showed decreased levels of VW antigen, but no changes in fibrinogen, factor VIII, PAI-I, t-PA or other coagulation markers were observed.^[21] Furthermore, data from the ACROSTUDY, a surveillance study of almost 1300 patients on pegvisomant for a mean of 2.3 years, did not report an increased risk of VTE.^[22]

FVL mutation is detected in about 25% of patients with VTE and is considered the most common thrombophilic disorder.^[9] The overall prevalence has been reported to be approximately 5% in Caucasian Americans, 3–15% in Europeans and it is considered rare among Asians.^[23,24] Whether this mutation is commoner in patients with acromegaly is not known. It is noteworthy that all three patients had longstanding uncontrolled acromegaly. Whether uncontrolled acromegaly simply enhances the risk of VTE in patients with pre-existing thrombophilic disorders, acts as an independent risk factor or is associated with an increased risk of other thrombophilic disorders, remains unclear. Presence of FVL mutation could potentially confound the association between acromegaly and increased VTE risk. Further studies are required to systematically assess this finding to appropriately counsel patients with acromegaly.

Conclusion

To the best of our knowledge, these cases constitute the first reported clinical association between active acromegaly and venous thrombosis. Possible explanations may include the presence of hereditary thrombophilia, an effect of GH or IGF-1 on the coagulation and fibrinolytic system, cardiac abnormalities or yet undiagnosed malignancy. Further studies should be conducted to assess this association.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

- Lombardi G, Galdiero M, Auriemma RS, *et al.* Acromegaly and the cardiovascular system. *Neuroendocrinology* 2006; 83:211-7.
- Orme SM, McNally RJ, Cartwright RA, *et al.* Mortality and cancer incidence in acromegaly: A retrospective cohort study. United Kingdom acromegaly study group. *J Clin Endocrinol Metab* 1998;83:2730-4.
- Landin-Wilhelmsen K, Tengborn L, Wilhelmsen L, *et al.* Elevated fibrinogen levels decrease following treatment of acromegaly. *Clin Endocrinol (Oxf)* 1997;46:69-74.
- Erem C, Nuhoglu I, Kocak M, *et al.* Blood coagulation and fibrinolysis in patients with acromegaly: Increased plasminogen activator inhibitor-1 (PAI-1), decreased tissue factor pathway inhibitor (TFPI), and an inverse correlation between growth hormone and TFPI. *Endocrine* 2008; 33:270-6.
- Wildbrett J, Hanefeld M, Fucker K, *et al.* Anomalies of lipoprotein pattern and fibrinolysis in acromegalic patients: Relation to growth hormone levels and insulin-like growth factor I. *Exp Clin Endocrinol Diabetes* 1997;105:331-5.
- Smith SB, Geske JB, Maguire JM, *et al.* Early anticoagulation is associated with reduced mortality for acute pulmonary embolism. *Chest* 2010;137:1382-90.
- Meltzer ME, Lisman T, de Groot PG, *et al.* Venous thrombosis risk associated with plasma hypofibrinolysis is explained by elevated plasma levels of TAFI and PAI-1. *Blood* 2010;116:113-21.
- Foy P, Moll S. Thrombophilia: 2009 update. *Curr Treat Options Cardiovasc Med* 2009;11:114-28.
- Rosendaal FR, Koster T, Vandenbroucke JP, *et al.* High risk of thrombosis in patients homozygous for factor V Leiden (activated protein C resistance) *Blood* 1995;85:1504-8.
- Young A, Chapman O, Connor C, *et al.* Thrombosis and cancer. *Nat Rev Clin Oncol* 2012;9:437-49.
- Murchison JT, Wylie L, Stockton DL. Excess risk of cancer in patients with primary venous thromboembolism: A national, population-based cohort study. *Br J Cancer* 2004; 91:92-5.
- Terzolo M, Reimondo G, Gasperi M, *et al.* Colonoscopic screening and follow-up in patients with acromegaly: A multicenter study in Italy. *J Clin Endocrinol Metab* 2005; 90:84-90.
- dos Santos MC, Nascimento GC, Nascimento AG, *et al.* Thyroid cancer in patients with acromegaly: A case-control study. *Pituitary* 2013;16:109-14.
- Kauppinen-Mäkelin R, Sane T, Välimäki MJ, *et al.* Increased cancer incidence in acromegaly a nationwide survey. *Clin Endocrinol (Oxf)* 2010;72:278-9.
- Melmed S, Colao A, Barkan A, *et al.* Guidelines for acromegaly management: An update. *J Clin Endocrinol Metab* 2009;94:1509-17.
- Katznelson L, Atkinson JL, Cook DM, *et al.* American association of clinical endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of acromegaly--2011 update. *Endocr Pract* 2011; 17 Suppl 4:1-44.
- Melmed S, Kleinberg D. Pituitary Masses and Tumors. In: Melmed S, Polonsky KS, Larsen PR, Kronenberg M. *Williams Textbook of Endocrinology*. 12th ed. Philadelphia,

- PA: Elsevier; 2011. p. 229-90.
18. Brada M, Ford D, Ashley S, *et al.* Risk of second brain tumour after conservative surgery and radiotherapy for pituitary adenoma. *BMJ* 1992;304:1343-6.
 19. Howell MD, Geraci JM, Knowlton AA. Congestive heart failure and outpatient risk of venous thromboembolism: A retrospective, case-control study. *J Clin Epidemiol* 2001; 54:810-6.
 20. Dean SM, Abraham W. Venous thromboembolic disease in congestive heart failure. *Congest Heart Fail* 2010;16:164-9.
 21. Muller AF, Leebeek FW, Janssen JA, *et al.* Acute effect of pegvisomant on cardiovascular risk markers in healthy men: Implications for the pathogenesis of atherosclerosis in GH deficiency. *J Clin Endocrinol Metab* 2001;86:5165-71.
 22. van der Lely AJ, Biller BM, *et al.* Long-term safety of pegvisomant in patients with acromegaly: Comprehensive review of 1288 subjects in ACROSTUDY. *J Clin Endocrinol Metab* 2012;97:1589-97.
 23. Kujovich JL. Factor V Leiden thrombophilia. *Genet Med* 2011;13:1-6.
 24. Rees DC, Cox M, Clegg JB. World distribution of factor V Leiden. *Lancet* 1995;346:1133-4.