

## Post-transplant complications

# Thyroid dysfunction after bone marrow transplantation for primary immunodeficiency without the use of total body irradiation in conditioning

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### Summary:

**Thyroid dysfunction, a common long-term complication following bone marrow transplantation (BMT), is frequently associated with total body irradiation (TBI) given in the pre-BMT conditioning protocol. We report our preliminary observation of the prevalence of thyroid dysfunction in children transplanted for primary immunodeficiency (PID) who were given cytoreductive conditioning with busulphan and cyclophosphamide, but without TBI. We evaluated thyroid-stimulating hormone (TSH) and free thyroxine (fT4) in 83 survivors transplanted between 1987 and 2002. We found nine children (10.8%) with clinical and/or biochemical thyroid dysfunction at 4 months to 4.5 years post-BMT of which three had positive antithyroid microsomal antibodies. Two patients were classified as primary and seven as compensated hypothyroidism (hyperthyrotropinaemia). Four patients with clinical features of hypothyroidism received replacement thyroxine, while five of the seven patients with compensated hypothyroidism remain off thyroxine because we suspect this may be a transient phenomenon. Abnormalities of thyroid function including severe primary hypothyroidism may occur post-BMT in children receiving chemotherapy conditioning without TBI. Thyroid function should be assessed regularly in this group of patients.**

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Bone marrow transplantation (BMT) is currently the best option for curative treatment of primary immunodeficiency.<sup>1</sup> The overall success rate is ~60%<sup>2</sup> and the

survivors generally appear to have normal growth, development and immune system function.<sup>3,4</sup>

Thyroid function abnormalities, with an overall incidence of 25–40%, are the commonest endocrine complications after allogeneic<sup>5</sup> and autologous<sup>6</sup> BMT in childhood. Hypothyroidism, often compensated and transient, is most common and usually presents at 6–12 months post-BMT, while frank clinical hypothyroidism is rare.<sup>7</sup> Euthyroid sick syndrome<sup>8</sup> and transient thyrotoxicosis<sup>9</sup> may also occur within the first 6 months post-BMT and progress to hypothyroidism later. The mechanisms of hypothyroidism developing post-BMT remain unclear.<sup>10</sup> Although classically associated with total body irradiation (TBI) given in the pre-BMT conditioning, thyroid dysfunction has been reported after chemotherapy-only conditioning.<sup>11,12</sup> Other factors, including the underlying disorder necessitating the BMT, the process of transplantation itself (ie T cell depletion (TCD), graft-versus-host disease (GvHD), viral infection or reactivation, adoptive transfer from the donor) and immune reconstitution post-BMT could all increase susceptibility or expose the patient to thyroid damage.<sup>10</sup>

We report abnormalities of thyroid function in our series of children treated for different primary immunodeficiency (PID) and juvenile malignant osteopetrosis (OP) with BMT without TBI as part of the conditioning protocol.

### Patients and method

In 83 long-term survivors transplanted in our centre between 1987 and 2002 for different PID ( $n=81$ ; SCID = 49, CID = 9, WAS = 7, CGD = 11, XL-HIM = 5) (SCID: severe combined immunodeficiency; CID = combined immunodeficiencies; WAS = Wiskott–Aldrich Syndrome; XL-HIM: X-linked hyper-IgM Syndrome (CD40-ligand deficiency) and OP ( $n=2$ ), thyroid function was evaluated at regular follow-up ( $n=79$ ) or at presentation with clinical symptoms suggestive of thyroid dysfunction ( $n=4$ ). Since 2000, all long-term survivors >2 years post-BMT ( $n=43$ ) have had their thyroid function evaluation at annual follow-up, and those within the first 2 years post-BMT ( $n=36$ ) at 3 monthly intervals during the 1st year and 6 monthly during the 2nd year. All patients were diagnosed according to the current classification for primary immunodeficiencies,<sup>13</sup> and the BMT procedure and conditioning

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was performed according to the guidelines of the ESID/EBMT Working Party (European Society for immunodeficiency Disorders/European Group for Blood and Marrow Transplantation).<sup>2</sup>

Thyroid-stimulating hormone (TSH) and free thyroxine (fT4) were measured by the immunoassay system (Advia Centaur, Bayer). The reference range used was that provided by the assay kit manufacturers (TSH normal range 0.35–5.5 mIU/l; fT4 normal range 11.5–22.7 pmol/l). The intra-assay and interassay coefficient of variations (CVs) provided by the manufacturer for measurement of TSH (at a mean value of 5.6 mIU/l) were 2.4 and 3.4%, respectively. The intra-assay and interassay CVs provided by the manufacturer for measurement of fT4 (at a mean value of 14 pmol/l) were 2.3 and 1.9%, respectively. A normal thyroid profile was defined by a normal fT4 with a normal or low TSH, primary hypothyroidism by a low fT4 with a high TSH and compensated hypothyroidism (hypothyrotropinaemia) by a normal fT4 with an elevated TSH.

Antithyroid microsomal antibodies were measured by the particle agglutination method (Serodia) in patients with symptoms suggestive of thyroid dysfunction or with a laboratory abnormality of thyroid function.

## Results

We found clinical and/or laboratory thyroid dysfunction in nine (three female and six male) of 83 patients (10.8%). Patients with clinical symptoms of hypothyroidism presented at 9–18 months post-BMT, while laboratory thyroid dysfunction was discovered at 4 months to 4.5 years post-BMT (Table 1).

Indications for BMT in the nine patients with clinical and/or laboratory thyroid dysfunction post-BMT were WAS ( $n=2$ ), OP ( $n=1$ ) and SCID ( $n=6$ ; one of each due to mutations in *RAG2* (recombinase activating gene), *C $\gamma$ C* (common gamma chain), *Artemis* and *ADA* (adenosine deaminase), and two in *JAK3* (Janus associated kinase) genes).<sup>13</sup> All patients were clinically euthyroid before BMT and the three that were evaluated had normal thyroid function tests pre-BMT. The six SCID patients received haploidentical parental TCD bone marrow while the patients with WAS and OP received whole marrow from an unrelated donor ( $n=2$ ) and from a phenotypically matched parent ( $n=1$ ). All donors were clinically euthyroid, and six who were evaluated (donors for patients 2, 4–7 and 9) had normal thyroid function tests. Patients 3 and 4 had previously unsuccessful BMT procedures for which they received cytoreductive conditioning without TBI. The first eight patients received conditioning with busulphan and cyclophosphamide, patients 1, 2 and 3 received additional anti-T lymphocyte globulin (ATG) (rabbit ATG, IMTIX-SANGSTAT) and patient 9 did not receive conditioning. None of the patients received TBI (Table 1).

All patients engrafted and showed donor chimerism of T cells with donor or mixed chimerism of B cells (data not shown). Their T cell function assessed by *in vitro* response to mitogen phytohaemagglutinin (PHA) or by *in vivo* clearance of pre-existing viral infection was normal (data

not shown). Patients 5, 8 and 9 remain on intravenous immunoglobulin (IVIg) substitution at the moment; others (patients 1–4, 6, 7) have normal immunoglobulin production and are making specific antibody responses to protein vaccine antigens.

Acute GvHD<sup>14</sup> occurred in four (patients 1, 2 and 6 had grade II and patient 7 grade I) while two patients (1 and 2) had limited (transient) chronic GvHD.<sup>15</sup> Thyroid microsomal antibodies were detected in three patients (3, 4 and 6).

The first two patients, both male, presented with clinical features of hypothyroidism 18 and 12 months post-BMT for WAS (Table 1). Another two, a boy and a girl, had milder symptoms suggestive of hypothyroidism at 9 and 12 months post-BMT for OP and SCID, respectively. Two of these four (patients 1 and 4) were classified as primary hypothyroidism based on their laboratory tests, and were started on replacement thyroxine therapy. The other two were followed up at 3–6 monthly intervals and started on replacement thyroxine after 3 (patient 2) and 24 months (patient 3), as their clinical features and elevated TSH levels persisted in spite of normal fT4. A further five patients were only discovered on routine formal thyroid function testing as they had no clinical symptoms suggestive of hypothyroidism. Patient 6 is from the group of patients on annual follow-up ( $n=43$ ) and was discovered at 4.5 years post-BMT but his elevated TSH level returned to normal within the next 6 months. The other four (patients 5, 7–9) are from the group tested repeatedly during the first 2 years post-BMT ( $n=36$ ). Therefore, seven patients were classified as having compensated hypothyroidism (patients 2, 3, 5–9). Although two (patients 2 and 3) were treated with thyroxine, in the remaining five (patients 5–9) we suspect that this could be a transient phenomenon so they remain off treatment but under active clinical and biochemical review.

Of the four patients started on replacement thyroxine, one with primary (patient 1) and one with compensated hypothyroidism (patient 2) had cGvHD. Although both had transient autoimmune thrombocytopenia post-BMT, neither had anti-thyroid microsomal antibodies (Table 1). Both had adenovirus infection pre-BMT and Epstein–Barr virus (EBV) reactivation post-BMT, the latter causing clinical features of EBV-related lymphoproliferative disease (LPD) in patient 2. The other two patients who were started on thyroxine replacement (patients 3 with compensated and 4 with primary hypothyroidism) had no evidence of GvHD, but interestingly, both had antithyroid microsomal antibodies.

## Discussion

This is the first report of thyroid dysfunction occurring after BMT for different PID and OP. It is of note that none in our cohort of 83 children received TBI as part of their conditioning. Combined clinical and/or laboratory thyroid dysfunction was found in nine children (10.8%). Four children who had mild to moderate clinical symptoms presented within the 1st or 2nd year post-BMT, while those with only laboratory thyroid dysfunction presented as early

**Table 1** Patient characteristics

Patient sex/ age at BMT	Dg.	TFT pre-BMT	Donor/TFT (date BMT)	Conditioning	GVHD prophylaxis	GVHD time post-BMT	Infections pre/ post-BMT	HT symptoms	Time post last BMT TSH (0.3–4.7 mIU/l) fT4 (11–23 pmol/l)	ATM Ab's	Thyroxine duration effect
1 M/6 year	WAS	N	URD (C mm)/ N/A (11/97)	Bu16/Cy200 ATG 25 mg/kg	MTX, CsA	a-(II) <sup>a</sup> , skin/gut 8 months c-(L/T)	Adenovirus EBV reactivation	Dry skin Hair loss Cold intolerance Poor growth	1.5 year TSH 235; fT4 < 1	Neg	4 years Symptoms resolved
2 M/1.5 year	WAS	N	Father (ph m)/ N (11/98)	Bu16/Cy200 ATG 25 mg/kg	MTX, CsA	a-(II) <sup>b</sup> , gut 4 months c-(L/T)	Adenovirus EBV reactivation BLPD	Flaky skin Coarse hair Cold intolerance Lethargy Poor appetite	1–1.5 year TSH 6–9; fT4 N	Neg	3.8 years Symptoms resolved
3/M 1. 6 months 2. 8 months 3. 1.3 year	OP	N/A	1. Father (TCD)/ N (11/99) 2. UCSC (DP mm)/ N/A (1/00) 3. URD (DP mm)/ N/A (8/00)	1. Flu 150/Bu8/ Cy200 ATG 12.5 mg/kg 2. ATG 25 mg/kg 3. Bu16/Cy200 ATG 10 mg/kg	1. Nil 2. Nil 3. MTX, CsA Pred	Nil	Nil	Dry skin Constipation	9 months–2 year TSH 16–25; fT4 N	> 1/6400	1 year Symptoms resolved
4/F 1. 1 months 2. 1.5 year 3. 2 year	SCID RAG2	N	1. Father (TCD)/ N (8/98) 2. Father (TCD)/ N (12/99) 3. Mother (TCD)/ N (8/00)	1. Bu8/Cy200 2. Nil 3. Bu16/Cy200	1. Nil 2. Nil 3. CsA	Nil	Nil	Dry skin Itchiness Lethargy	1 year TSH 430; fT4 3	1/3200	2 years Symptoms resolved
5 F/ 4 months	SCID ADA	N/A	Father (TCD)/ N (1/02)	Bu16/Cy200	CsA	Nil	Nil	Nil	4–16 months TSH 7–13; fT4 N	Neg	No
6 M/1 year	SCID CGC	N/A	Father (TCD)/ N (5/97)	Bu8/Cy200	CsA	a-(II) <sup>c</sup> skin/gut/liver 7 months	PCP	Nil	4.5–5 years TSH 11-N; fT4 N	> 1/6400	No
7 F/2 months	SCID Artemis	N/A	Father (TCD)/ N (6/01)	Bu16/Cy200	CsA	a-(I), skin 1 month	Nil	Nil	15 months TSH 10; fT4 N	Neg	No
8 M/2 months	SCID JAK3	N/A	Mother (TCD)/ N (7/02)	Bu8/Cy200	CsA	Nil	Nil	Nil	8 months TSH 6; fT4 N	Neg	No
9 M/8 months	SCID JAK3	N/A	Father (TCD)/ N (10/01)	Nil	CsA	Nil	PCP, BCG Astrovirus	Nil	10–18 months TSH 5–7; fT4 N	Neg	No

TFT = thyroid function tests; HT = hypothyroidism; URD = unrelated donor; USCT = unrelated stem cell transplant; C/DP mm = HLA C or DP locus mismatch; Ph m = HLA phenotypic match; TCD = T cell depletion; Bu = busulfan; Cy = cyclophosphamide; ATG = anti-T lymphocyte globulin; Flu = fludarabine; CsA = cyclosporin A; MTX = methotrexate; Pred = prednisolone; a-GvHD = acute graft-versus-host disease (grade); c-GvHD = chronic graft-versus-host disease; L/T = limited, transient; BLPD = B lymphoproliferative disease; ATM Ab = antithyroid microsomal antibody; PCP = pneumocystis pneumonia; N/A = not available.

<sup>a</sup>Skin biopsy — no evidence of a-GVHD. Responded to methylprednisolone.

<sup>b</sup>Lower gut biopsy — apoptotic crypt cells suggestive of a-GVHD; features of EBV driven BLPD.

<sup>c</sup>Skin biopsy — no evidence of a-GVHD. Responded to methylprednisolone; when stopped, rash reappeared but responded to further methylprednisolone.

as 4 months or as late as 4.5 years post-BMT. There appear to be at least two groups of patients: the majority with raised TSH levels and normal thyroxine concentrations (seven patients, 78%) that can potentially return to normal and a smaller group with unequivocal primary hypothyroidism (two patients, 22%).

There is a number of postulated mechanisms that could lead to abnormalities of thyroid function post-BMT.<sup>6,10,16</sup> First, thyroid hormone values above a quoted laboratory normal range will be seen in a small percentage of healthy subjects.<sup>17</sup> Euthyroid sickness with an associated increase in TSH levels is also a well-recognised phenomenon as patients recover from severe illness,<sup>18</sup> and we suspect that this is the underlying mechanism in at least one of the patients in our series. Third, during the BMT procedure itself virally induced inflammatory thyroiditis (eg CMV reactivation) or the adoptive transfer of antithyroid antibodies (or T cells) from the donor,<sup>10</sup> even when using the CD34+ selection procedure,<sup>19</sup> can cause thyroid dysfunction. None of the donors tested for six of our patients had antithyroid antibodies or thyroid disease, and there is no evidence in our series to implicate cytomegalovirus (CMV) infection although two patients had EBV reactivation. Fourth, autoimmune thyroiditis, although uncommon in young children, is the commonest cause of primary hypothyroidism in the general population.<sup>20</sup> However, the underlying diagnosis of PID is a well-recognised predisposing factor for the development of autoimmune disease even in very young children.<sup>21</sup> Patients with WAS, in particular, are prone to developing a wide spectrum of autoimmune disorders but there was no autoimmune thyroid disease reported in the two large patient series recently published.<sup>22,23</sup> In addition to the altered immune function due to the underlying immunodeficiency,<sup>21–23</sup> a haplotype that is associated with autoimmune illness (HLA DQ2 and/or DQ8) may predispose to thyroid dysfunction post-BMT.<sup>24</sup> In contrast to this, autoimmune thyroid damage and hypothyroidism have been reported in infants with combined PID such as IPEX (immunodeficiency, polyendocrinopathy, enteropathy, X-linked)<sup>25</sup> and Omenn syndrome.<sup>26</sup> None of our patients had clinical or laboratory features to suggest autoimmune thyroid disease before BMT. Therefore, although a theoretical possibility, primary autoimmune thyroid disease is not a likely underlying cause of hypothyroidism in our patients. Fifth, hypothyroidism post-BMT is usually associated with TBI given pre-BMT, and conditioning with chemotherapy without TBI is often considered as less likely to predispose to hypothyroidism post-BMT.<sup>16</sup> However, reports of thyroid dysfunction occurring after chemotherapy-only based conditioning<sup>7,8,11,12</sup> demonstrate that irradiation of the thyroid gland is not the only factor responsible. Inflammatory thyroiditis secondary to GVHD-induced damage is a potential cause of subtle thyroid dysfunction post-BMT. GVHD may stimulate and suppress the immune system, the latter due to either direct immunosuppressive effects or as a consequence of treatment, which may also affect endocrine function.<sup>10</sup> Two of our four patients who received thyroxine replacement had limited chronic GVHD post-BMT for WAS requiring immunosuppressive treatment, and both had EBV reactivation

(Table 1). Both received high dose busulphan (16 mg/kg), cyclophosphamide and ATG in conditioning, with cyclosporine A and methotrexate as GvHD prophylaxis and both received unmanipulated bone marrow. Neither had antithyroid microsomal antibodies, but both had autoimmune thrombocytopenia post-BMT. The third patient with limited transient chronic GvHD had the standard conditioning for parental TCD BMT for SCID. He had antithyroid microsomal antibodies and only transiently elevated TSH with normal fT4 at 4.5 years post-BMT. Two other patients who received thyroxine replacement had undergone previous unsuccessful BMT procedures for OP and SCID, with conditioning regimens including busulphan 8 mg/kg (and one of them had ATG). For the subsequent BMT procedure, both received high dose busulphan (16 mg/kg) and cyclophosphamide conditioning with cyclosporine A (one received methotrexate as well) as GVHD prophylaxis. One received unmanipulated and one parental TCD bone marrow, neither developed GvHD but both had antithyroid microsomal antibodies. Immune-mediated destruction of the thyroid is therefore another proposed factor.<sup>6,10,14</sup> Indeed, various autoantibodies including the antithyroid autoantibodies have been reported post allogeneic or autologous BMT,<sup>6</sup> but their occurrence is thought to be independent of acute or chronic GVHD and their clinical significance is unknown.<sup>27</sup> The current hypothesis is that autoantibodies are the expression of an abnormal (skewed) T and B reconstitution with altered immune response.<sup>6,10,14,27</sup> The observed development of autoimmune thyroid disease in patients treated with immunosuppressive monoclonal antibodies, that is, CAMPATH-1H for multiple sclerosis<sup>28</sup> and ATG for aplastic anaemia,<sup>29</sup> supports this hypothesis.

Given these factors it is perhaps surprising that thyroid dysfunction is not more common post-BMT in children with different underlying PID, although our preliminary observation and largely cross-sectional study was not designed to detect transient abnormalities that may have occurred in some patients.

## Conclusion

Our results emphasise the importance of vigilance for thyroid disease post-BMT. Primary, symptomatic hypothyroidism can occur in children with PID after BMT, even in patients given cytoreductive conditioning without TBI. It may be of early or late onset and should be actively sought. However, transient abnormalities of thyroid function are more commonly observed and may be linked to recovery from severe illness in some patients.

We suggest that TSH and fT4 be measured pre-BMT, at 3 months post-BMT and at 6 monthly intervals during the first and second year post-BMT, and then annually or biannually at routine follow-up appointments. Children with biochemical hypothyroidism or persistent compensated hypothyroidism and associated symptoms should be treated with thyroxine supplementation to optimise well being and to prevent possible growth failure and delayed development.

## References

- 1 Buckley RH. Treatment options for genetically determined immunodeficiency. *Lancet* 2003; **361**: 541–542.
- 2 Antoine C, Muller S, Cant A *et al*. Long-term survival and transplantation of haemopoietic stem cells for immunodeficiencies: report of the European experience 1968–99. *Lancet* 2003; **361**: 553–560.
- 3 Gennery AR, Dickinson AM, Brigham K *et al*. CAMPATH-1M T cell depleted bone marrow transplantation for severe combined immunodeficiency: long term follow up of 19 children treated in the period 1987–1998 in a single centre. *Cytotherapy* 2001; **3**: 221–232.
- 4 Slatter MA, Bhattacharya A, Flood TJ *et al*. Polysaccharide antibody responses are impaired post bone marrow transplantation for severe combined immunodeficiency, but not other primary immunodeficiencies. *Bone Marrow Transplant* 2003; **32**: 225–229.
- 5 Katsanis E, Shapiro RS, Robison LL *et al*. Thyroid dysfunction following bone marrow transplantation: long-term follow-up of 80 pediatric patients. *Bone Marrow Transplant* 1990; **5**: 335–340.
- 6 Wedderburn LR, Jeffery R, White H *et al*. Autologous stem cell transplantation for paediatric-onset polyarteritis nodosa: changes in autoimmune phenotype in the context of reduced diversity of the T and B cell repertoires, and evidence for reversion from the CD45RO+ to RA+ phenotype. *Rheumatology* 2001; **40**: 1299–1307.
- 7 Al-Fiar FZ, Colwill R, Lipton JH *et al*. Abnormal thyroid stimulating hormone (TSH) levels in adults following allogeneic bone marrow transplants. *Bone Marrow Transplant* 1997; **19**: 1019–1022.
- 8 Toubert M-E, Socie G, Gluckman E *et al*. Short and long-term follow-up of thyroid dysfunction after allogeneic bone marrow transplantation without the use of preoperative total body irradiation. *Br J Haematol* 1997; **98**: 453–457.
- 9 Kami M, Tanaka Y, Chiba S *et al*. Thyroid function after bone marrow transplantation: possible association between immune-mediated thyrotoxicosis and hypothyroidism. *Transplantation* 2001; **71**: 406–411.
- 10 Sherer Y, Shoenfeld Y. Autoimmune diseases and autoimmunity post bone marrow transplantation. *Bone Marrow Transplant* 1998; **22**: 873–881.
- 11 Michel G, Socie G, Gebhard F *et al*. Late effects of allogeneic bone marrow transplantation for children with acute myeloblastic leukemia in first complete remission: the impact of conditioning regimen without total-body irradiation — a report from the Societe Francaise de greffe de moelle. *J Clin Oncol* 1997; **15**: 2238–2246.
- 12 Afify Z, Shaw PJ, Clavano-Harding A, Cowell CT. Growth and endocrine function in children with acute myeloid leukaemia after bone marrow transplantation using busulfan/cyclophosphamide. *Bone Marrow Transplant* 2000; **25**: 1087–1092.
- 13 Chapel H, Geha R, Rosen F, (IUIS PID classification committee). Primary immunodeficiency disease: an update. *Clin Exp Immunol* 2003; **132**: 9–15.
- 14 Przepiora D, Weisdorf D, Martin P *et al*. Consensus conference on acute GvHD grading. *Bone Marrow Transplant* 1995; **15**: 825–828.
- 15 Gluckberg H, Storb R, Fefer A *et al*. Clinical manifestations of GvHD in human recipients of marrow from HLA matched sibling donors. *Transplant* 1974; **18**: 295–304.
- 16 Tauchmanova L, Selleri C, De Rosa G *et al*. High prevalence of endocrine dysfunction in long-term survivors after allogeneic bone marrow transplantation for hematologic diseases. *Cancer* 2002; **95**: 1076–1084.
- 17 Tunbridge WMG, Evered DC, Hall R *et al*. The spectrum of thyroid disease in a community: the Whickham survey. *Clin Endocrinol* 1977; **7**: 481–493.
- 18 De Groot LJ. Dangerous dogmas in medicine: the nonthyroidal illness syndrome. *J Clin Endocrinol Metabol* 1999; **84**: 151–164.
- 19 Karthaus M, Gabrysiak T, Brabant G *et al*. Immune thyroiditis after transplantation of allogeneic CD34+ selected peripheral blood cells. *Bone Marrow Transplant* 1997; **20**: 697–699.
- 20 Devendra D, Eisenbarth GS. Immunologic endocrine disorders. *J Allergy Clin Immunol* 2003; **111**: s624–s36.
- 21 Arkwright PD, Abinun M, Cant AJ. Autoimmunity in human primary immunodeficiency diseases. *Blood* 2002; **99**: 2694–2702.
- 22 Dupuis-Girrod S, Medioni J, Haddad E *et al*. Autoimmunity in Wiskott–Aldrich syndrome: risk factors, clinical features, and outcome in a single-centre cohort of 55 patients. *Pediatrics* 2003; **111**: e622–e627.
- 23 Schurman SH, Candotti F. Autoimmunity in Wiskott–Aldrich syndrome. *Curr Opin Rheumatol* 2003; **15**: 446–453.
- 24 Olivares JL, Ramos FJ, Olive T *et al*. Autoimmune thyroiditis after bone marrow transplantation in a boy with Wiskott–Aldrich syndrome. *J Pediatr Hematol/Oncol* 2002; **24**: 772–776.
- 25 Gambineri E, Torgerson TR, Ochs HD. Immune dysregulation, polyendocrinopathy, enteropathy, and x-linked inheritance (IPEX), a syndrome of systemic autoimmunity caused by mutations of FOXP3, a critical regulator of T-cell homeostasis. *Curr Opin Rheumatol* 2003; **15**: 430–435.
- 26 Kaino Y, Otoh Y, Tokuda K *et al*. Acquired hypothyroidism in a very young infant with Omenn's syndrome. *J Pediatr* 2000; **136**: 111–113.
- 27 Trendelenburg M, Gregor M, Passweg J *et al*. 'Altered immunity syndrome', a distinct entity in long-term bone marrow transplantation survivors? *Bone Marrow Transplant* 2001; **28**: 1175–1177.
- 28 Coles AJ, Wing M, Smith S *et al*. Pulsed monoclonal antibody treatment and autoimmune thyroid disease in multiple sclerosis. *Lancet* 1995; **354**: 1691–1695.
- 29 Todd A, Todd J. Graves' disease following successful treatment of severe aplastic anaemia with antilymphocyte globulin. *Clin Lab Haem* 1999; **21**: 69–70.