Endocrine Dysfunction in Diamond Blackfan Anaemia

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Background

Diamond Blackfan anaemia (DBA) is a rare disorder of red blood cell aplasia characterised by a normocytic, usually macrocytic anaemia and reticulocytopaenia. Short stature of multifactorial aetiology is often present. Some patients are glucocorticoid-responsive, while others remain transfusion dependent. Iron overload may be a sequelae of recurrent red cell transfusion, often necessitating chelation therapy.

Case History

Our patient was born at 39 weeks gestation weighing 2.53kg. There was assymetrical intrauterine growth retardation with a relatively large head at birth. It was during a clinic visit at 10 weeks of age that she was noted to be anaemic with a haemoglobin of 4.8g/dL, white cell count of $4.6X10^9$/L and platelets of $46X10^9$/L. Bone marrow aspirate demonstrated reduced erythropoiesis. A diagnosis of DBA was therefore made.

She was started on prednisolone aged 0.3 years at a dose of 32mg/metre^2/day, subsequently tapered and maintained at 0.76mg/metre^2/day. She initially responded well and did not require blood transfusions. For 12 weeks after starting prednisolone, her growth was static, but following this she grew parallel to the 3rd centile. This is in keeping with the prednisolone dosage, as amounts more than 4mg/metre^2/day tend to result in growth failure.

It is likely that her initial growth failure was due to a combination of intrauterine growth retardation compounded by prednisolone therapy. Prednisolone was stopped at the age of 1.6 years.

Other investigations for failure to thrive revealed no abnormalities with no evidence of malabsorption.

At age 3.1 years, growth hormone levels were measured. Following an arginine infusion, growth hormone levels ranged between 8.6 and 17 mU/L (normal >20). Baseline growth hormone level was 21 mU/L. IgF1 level was 22 mcg/L (normal range >50 for a child of this age).

These results were thought to reflect under-functioning of the pituitary gland as a result of chronic anaemia. In the absence of any haematological measures to improve her growth rate, growth hormone therapy was initiated in the form of Genotropin. She showed a reasonable response to this with increasing height velocity. She continued on growth hormone therapy until age 14.6 years. Her final height was 139 cm.

She was recommenced on prednisolone therapy aged 4.5 years due to persistent anaemia with little response. Prednisolone was therefore stopped, resulting in transfusion-dependent anaemia. Iron chelation therapy was commenced at the age of 7 years.

She has since presented to the adult endocrine services with oligomenorrhoea following the attainment of menarche at the age of 15. Her most recent parameters are outlined below. Ultrasound of the pelvis was normal.

	Result	Reference Range
LH	18.7 U/L	
FSH	8.1 U/L	
Oestradiol	163 pmol/L	
Growth hormone	1.0 ug/L	
IgF1	61 ug/L	96-417
Prolactin	239 mU/L	<630
TSH	1.18 mU/L	0.35-5.00
Free T4	14.2 pmol/L	9.0-21.0
Baseline cortisol	372 nmol/L	
30 minute cortisol following Synacthen	682 nmol/L	
HbA1c	32 mmol/mol	20-42
Parathyroid hormone	8.9 pmol/L	1.6-7.5
25-OH Vitamin D	48 nmol/L	>50
Adjusted calcium	2.23 mmol/L	2.20-2.60
Phosphate	0.97 mmol/L	0.80-1.50

Imaging

As she remains on iron chelation therapy with dexferrioxamine, her iron status continues to be monitored with magnetic resonance imaging (MRI).

Cardiac and liver MRI have demonstrated no evidence of myocardial iron overload.

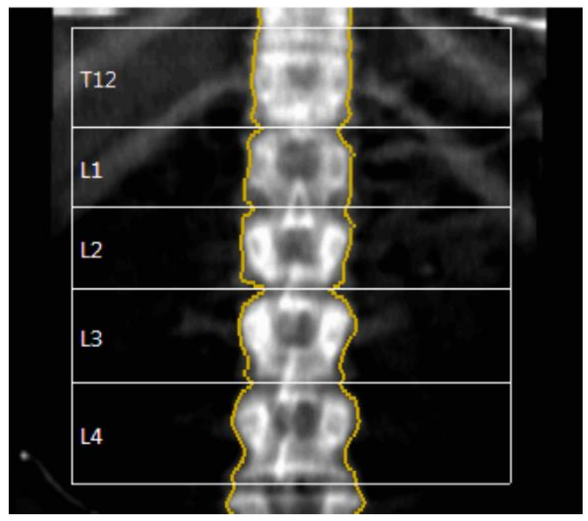

Image 1 – DEXA scan: AP spine bone density trend

In view of her prolonged periods on corticosteroid therapy, a DEXA scan was performed. This has showed a bone mineral density at the spine of 0.893g/cm^2, and at the total hip of 0.684g/cm^2. These results suggest osteopenia at the spine with borderline osteoporosis at the total hip. A repeat DEXA is planned for when she is 21 years of age.

Discussion

DBA characteristically presents within the first year of life with a normochromic and usually macrocytic anaemia[1]. It is a disorder due to a defect in the erythroid stem cells, and may be associated with congenital malformations, growth retardation[1], and a predisposition to malignancy[1,2].

Endocrine dysfunction is common in DBA. In a study of 57 patients, 53% of patients had one or more endocrinopathies including adrenal insufficiency (32%), hypogonadism (29%), hypothyroidism (14%), growth hormone dysfunction (7%), diabetes mellitus (2%) and diabetes insipidus (2%). Osteoporosis, osteopenia and parathyroid disease have also been described. These may be related to therapy, and have also been described in other haematological diseases associated with iron overload[2].

Initial treatment is often with prednisolone which is gradually weaned. Although approximately 80% of patients respond to corticosteroid therapy, only 40% have a sustained response without dose-limiting toxicity. Stem cell transplantation can be considered in specific patients[2].

Long term glucocorticoid therapy often results in iatrogenic Cushing's syndrome and adrenal suppression. Recurrent transfusions often result in iron overload requiring chelation therapy.

There are no specific DBA endocrine guidelines on screening. In view of the association with transfusion-related iron overload and endocrinopathies as outlined above, recommendations include:

- Regular assessments of growth and puberty.
- Growth hormone therapy should be considered as indicated.
- Delayed puberty should be investigated.
- Surveillance should continue into adulthood for secondary gonadal failure.
- Monitoring for the development of glucose intolerance.
- Assessment of adrenal and pituitary dysfunction in those on chronic glucocorticoid therapy or in the context of iron overload.
- Measurement of bone mineral density.

References

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2. Lahoti A, Harris YT, Speiser PW. Endocrine dysfunction in Diamond-Blackfan Anaemia: A Report from the DBA Registry. Pediatr Blood Cancer. 2016 Feb; 63(2):306-12.

BES2016 58--EP
Neuroendocrinology and pituitary
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DOI: 10.3252/pso.eu.BES2016.2016
Poster presented at: SfE BES 2016 7-9 November BRIGHTON