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CLINICAL AND GENETIC DIVERSITY IN DIAMOND-BLACKFAN ANAEMIA: AN UPDATE FROM THE UNITED KINGDOM

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Background: Diamond-Blackfan anaemia (DBA) is an inherited bone marrow failure syndrome (IBMFS) caused by mono-allelic, loss-of-function mutations in ribosomal protein (RP) genes. DBA is rare and has a wide spectrum of clinical manifestations, hence the utility of patient registries.

Aims: We evaluated the clinical and genetic spectrum of DBA in a large cohort of patients in the UK, aiming to identify novel features of the disease.

Methods: We performed a retrospective analysis of data from 103 confirmed cases of DBA, including 4 multiplex families. All living patients had undergone at least one assessment at our specialized centre in the last 5 years. Data were collected from family interviews, patient records and referring clinicians.

Results: The 103 patients with DBA were born in a 48-year period (1967-2015), *i.e.*, an incidence of 3 per million live births. Demographic and clinical characteristics are shown in Table 1. NGS analysis of 80 RP genes plus *GATA-1* identified pathogenic mutations in 71% of cases and 7 putative novel mutations, currently undergoing validation. To date, mutation screening of *both* parents has been performed in 32 families with DBA. Twenty-five mutations are sporadic while 7 are autosomal dominant; in 3 of the latter, the parent is a silent 'carrier' without anaemia. In one case of an affected child, the causative mutation was undetected in the peripheral blood of both parents but was present in 7/22 embryos generated for *in vitro* fertilisation, suggesting germline mosaicism. 80.5% of cases in our cohort presented within the first year of life. For the first time we report a high rate of perinatal problems in DBA. Prematurity +/- intrauterine growth restriction (IUGR) occurred in 31/87 (35.6%) of evaluable patients. Specific abnormalities included: hydrops fetalis (3/87), prematurity (22/87) and IUGR (16/87). In addition to congenital anomalies classically associated with DBA, we identified abnormalities of the spine and axial skeleton in 9.2% of patients. These did not correlate with a particular genotype. Our cohort exhibited multiple comorbidities, including some not previously reported to be associated with DBA: herniae (10.7%), neuropsychiatric (17.4%) and gastrointestinal (GI) disorders (25.7%). These complications were not associated with particular treatment regimens. In terms of the natural history of DBA, a lower proportion of our patients (22%) than previously reported in the literature (40%) were able to maintain a normal Hb on long-term steroids. Three patients failed a metoclopramide trial. In total there were 4 incidents of malignancy (MDS, B-ALL, BCC and cervical intraepithelial neoplasia) in 4 different patients. The lower incidence in our cohort compared with that reported by the North American DBA registry may be explained by differences in the median ages of the 2 cohorts (12y *versus* 18y, respectively) and the shorter follow-up of our patients.

Summary/Conclusions: This retrospective analysis of the UK's DBA cohort confirmed several findings from other registries but also revealed novel features, including a high prevalence of i) premature birth and neonatal complications ii) abnormalities of the axial skeleton and iii) neuropsychiatric disorders. Prospective longitudinal studies are warranted to better characterise these co-morbidities and to confirm whether they are intrinsic to DBA or arise as complications of treatment. Above all, the observed clinical heterogeneity in our cohort highlights the need for novel therapies that target the multisystem manifestations of DBA, not just the anaemia.

Table 1.

Demographic and clinical characteristics of 103 patients with DBA in the United Kingdom.
Incomplete information was available for some individuals therefore the number of patients for whom data were available (N=) is included for each parameter.

Parameter	N (%) or median [range]	Parameter	N (%) or median [range]
Female/male	55/48	Congenital anomalies N=98	
		None	19 (19.4)
Ethnicity		Single anomaly	24 (24.5)
Caucasian	83	Multiple anomalies	55 (56.1)
African	3	➢ Cardiac	35 (35.7)
Asian	10	➢ Upper limb	33 (33.7)
Middle Eastern	3	➢ Axial skeleton including spine (confirmed on imaging)	9 (9.2)
Mixed	2	❖ Spina bifida	1
Caribbean	1	❖ Cervical spine fusion	3
Other	1	❖ Abnormal spinal curvature	3
		❖ Cervical ribs	1
Age at inclusion in study (yrs) N=103	11.9 [1.2-49.4]	➢ Craniofacial	27 (27.6)
		➢ Genitourinary	5 (5.1)
Birth weight (kg) N=68	2.9 [1.25-5.2]		
Age at diagnosis N=97	2.4 months [22/40 in utero - 20 years]	Co-morbidities N=103	
		Endocrine dysfunction	
Haemoglobin at diagnosis (g/L) N=81	43.8 [17-94]	➢ Osteopenia/Osteoporosis + Vitamin D deficiency	15
		➢ Adrenal insufficiency	3
RP gene mutation/deletion by NGS+/-Multiplex Ligation-dependent Probe Amplification N=100		➢ Thyroid dysfunction	2
		➢ Growth Hormone dysfunction	2
RPS19	19	➢ Hypogonadism	2
RPS26	14	➢ ≥2 of above	4
RPL5	14	➢ Total	28 (27.0)
RPL11	12	Grommets/hearing aids	20 (19.4)
RPS24	3	Strabismus	7 (6.8)
RPL35A	3	Umbilical or inguinal hernia	11(10.7)
Other RP genes (RPS7, RPS10, RPS17, RPL15, RPS29)	6	Neuropsychiatric disorders	
		➢ Seizures	2
Awaiting validation - novel mutations in known RP genes (n=4) or novel RP genes (n=3)	7	➢ Delayed motor development	4
		➢ Global developmental delay	2
None detected	22	➢ Mood disorder	3
		➢ Learning difficulties	7
Short stature <0.4th centile N=89	27 (30.3)	➢ Total	18 (17.4)
		GI disorders	
Treatment status at time of study N=103		➢ Severe dairy intolerance	5
Transfusion-dependent; steroid failure	39 (37.9)	➢ Oesophagitis	9
Transfusion-dependent; steroid intolerant	7 (6.8)	➢ Colitis	1
Transfusion- dependent; steroid not yet trialled	3 (2.9)	➢ Chronic diarrhoea/constipation	10
Steroid- responsive	23 (22.3)	➢ ≥ 2 of above	4
Anaemia not requiring treatment	3 (2.9)	➢ Total	29 (25.7)
Remission post-steroids	6 (5.8)		
Spontaneous remission	4 (3.9)		
BMT	16(15.5)		
Deceased	2(1.9)		