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Original article

Immunological abnormalities in CHARGE syndrome

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Abstract

Immune deficiency can be part of CHARGE syndrome but often receives only limited attention. We present two patients with CHARGE syndrome confirmed CHD7 mutations who had severe T-cell deficiency, and review 15 CHARGE patients from the literature with immunological problems. Most of them had severe T-cell deficiency, although the spectrum also included mild T-cell deficiency and isolated humoral immune deficiency. We conclude that immunodeficiency can form an important symptom in CHARGE syndrome although the frequency and exact nature are still insufficiently known. We propose to evaluate immune functions in all CHARGE syndrome patients, to estimate the frequency and nature of the accompanying immunodeficiency, and to obtain better data regarding prognosis and management.

Keywords: CHARGE syndrome; CHD7; DiGeorge sequence; Microdeletion 22q11; Thymic hypoplasia; Thymic aplasia; Immunodeficiency; T-cell; Cell-mediated

1. Introduction

In 1979 CHARGE syndrome was defined as the association of ocular *c*olobomas, *h*eart malformations, *a*tresia of the choanae, *r*etarded growth and development, *g*enital abnormalities,

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and ear anomalies with hearing loss [11]. It took until 2004 for CHD7 to be reported as a causative gene [27]. The clinical presentation of CHARGE syndrome is known to be extremely variable [2,6,10,12,21], and screening for mutations in CHD7 has facilitated recognition of an even wider phenotypic range [13,26].

The phenotypic overlap between CHARGE syndrome and chromosome 22q11 microdeletion syndrome is well recognised. Patients with 22q11 microdeletions may have a very wide range of clinical features, but typically present with cardiac malformations, cleft palate or velopharyngeal insufficiency, facial dysmorphism which includes ear anomalies, and the DiGeorge sequence.

The DiGeorge sequence has been defined as a third and fourth pharyngeal pouch complex (absence or hypoplasia of the thymus and/or parathyroid glands) [14] and may include a variable T-cell deficiency and other immunological disturbances. Severe T cell deficiency occurs in less than 5% of patients with DiGeorge sequence [3]. Some have allowed a more extended clinical spectrum, including cardiac and facial anomalies [5]. The sequence can occur as part of several entities [10], of which the 22q11 microdeletion is the most well known [9]. The DiGeorge sequence has been found in patients with CHARGE syndrome, but this has acquired only limited attention until now.

Here we present two patients with CHARGE syndrome with confirmed CHD7 mutations who had severe T-cell immune deficiencies, and review the literature concerning immunological abnormalities in CHARGE syndrome to date.

2. Methods

2.1. Patients

Patient 1 was born at 37 weeks gestation to healthy unrelated parents after an unremarkable pregnancy weighing 2.53 kg. He was delivered by emergency caesarean section after signs of placental abruption. He was asystolic at birth and required resuscitation for 9 min before circulation could be established. However, subsequent cranial ultrasound and EEG suggested only mild hypoxic injury. Congenital anomalies were noted immediately and further investigation confirmed bilateral choanal atresia, a small atrial septal defect, a significant patent ductus arteriosus with congestive cardiac failure, dysplastic ears, and a small penis with hypoplastic scrotum. Ophthalmologic examination and renal ultrasound were normal. Surgery for the choanal atresia on day 5 of life was abandoned because of repeated episodes of desaturation. On day 7 he developed a large pulmonary haemorrhage requiring rescuscitation. Platelets and clotting studies were normal and subsequent CT chest and angiogram did not find any abnormal vessels, thus the underlying cause was not clear. The choanal atresia was corrected by stent insertion on day 16 and was noted to be mixed bony and membranous bilaterally. A microlaryngobronchoscopy showed intermittent compression of the left main bronchus by an enlarged pulsatile left atrium, but no other abnormality. He developed hypocalcaemia (calcium 1.49 mmol L^{-1} (nl 1.96–2.66), phosphate 2.66 mmol L^{-1} (nl 1.5–2.6), albumin 32 g L^{-1} (nl 26–36), PTH 0.7 pmol L^{-1} (nl 0.7–5.6), 25-hydroxyvitamin D 68 nmol L^{-1} (nl 15–100)) which persisted and required calcium and 1-alpha vitamin D supplementation. Hypothyroidism (free T4 12.2 pmol L^{-1}; nl 19–39 pmol L^{-1}, TSH 12.7 mU L^{-1}; nl <6 mU L^{-1}) treated with thyroxine, and lymphopenia (white cell count 7.55×10^9 L^{-1}, lymphocyte count 0.64×10^9 L^{-1}; nl 3.0–13.5×10^9 L^{-1}) requiring prophylactic Fluconazole and Septrin treatment were evident. Because of the very low lymphocyte count a full karyotype could not be obtained; FISH analysis

excluded a deletion of 22q11.2. The lymphopenia was present from the first day of life onwards. Lymphocyte subsets demonstrated absent T cells but normal numbers of B and NK cells and there was no proliferative response to phytohaemagglutinin. Serum immunoglobulins showed low IgG (3.11 g L^{-1}; nl 5–17 g L^{-1}) with slightly high IgA (0.1 g L^{-1}; nl 0.01–0.08 g L^{-1}) and IgM (0.37 g L^{-1}; nl 0.05–0.2 g L^{-1}). Thymic ultrasound revealed a severely hypoplastic thymus.

Cranial MRI showed narrow internal acoustic meati bilaterally, atresia of the right external auditory canal, a dysplastic left vestibule, bilateral dysplasia of the semicircular canals with normal cochleas, absence of the right auditory nerve and hypoplasia or absence of the left auditory nerve. The olfactory bulbs were not visible. In view of the severity of the immune defect, predicted to require bone marrow transplant, together with his other problems, and following discussions with the parents, it was agreed that further intensive care support would be inappropriate and with palliative care support the patient died at 22 days of age. The clinical diagnosis of CHARGE syndrome was subsequently confirmed by molecular genetic analysis [13], which revealed a nonsense mutation c.934C → T (p.Arg312X) in exon 2 of the CHD7 gene. The parents were not tested for the nonsense mutation.

Patient 2 was born to healthy, non-consanguineous parents. Antenatal scans revealed increased amniotic fluid, no stomach bubble, possible horseshoe kidneys and a two-vessel cord. He was born after spontaneous normal vaginal delivery at 37 weeks gestation weighing 2.13 kg with Apgar scores of 5 and 9 at 1 and 5 minutes respectively. Multiple congenital abnormalities were diagnosed in the first day of life and he was subsequently confirmed to have oesophageal atresia, tracheoesophageal fistula, atrial and ventricular septal defects, patent ductus arteriosus, horseshoe kidneys, micropenis, partial agenesis of corpus callosum on cranial ultrasound, and low set ears with hypoplastic pinnae and absent ear lobes. Ophthalmologic examination was normal. On transfer to our hospital on day 2 of life he was found to have hypocalcaemia (calcium 1.76 mmol L^{-1} (nl 1.96–2.66); phosphate 1.79 mmol L^{-1} (nl 1.5–2.6); albumin 36 g L^{-1} (nl 26–36); PTH 3.2 pmol L^{-1} (nl 0.7–5.6) on day 4; 1,25-dihydroxyvitamin D 30 pmol L^{-1} (nl 40–150) on day 4) which persisted. Hypothyroidism (free T4 12.5 pmol L^{-1}; nl 19–39 pmol L^{-1}; TSH 10.8 mU L^{-1}; nl <6 mU L^{-1}) and lymphopenia (white cell count 5.63×10^9 L^{-1}; lymphocyte count 0.57×10^9 L^{-1}; nl $3.0–13.5 \times 10^9$ L^{-1}) were evident and hypogonadotrophic hypogonadism was suspected. Lymphocyte subsets showed marked T-cell lymphopenia (5%) with normal B and NK cell numbers suggestive of primary immunodeficiency such as DiGeorge syndrome. He was treated with calcium gluconate infusions from day 3 of life, and subsequently thyroxine as well as prophylactic Fluconazole and broad spectrum antibiotics. A clinical diagnosis of CHARGE syndrome was suspected. Because of the very low lymphocyte count karyotyping failed. FISH analysis excluded deletion of 22q11.2.

He underwent repair of the tracheoesophageal fistula on day 2 of life at which time a 4 cm long gap oesophageal atresia was noted and repaired at a second operation on day 4. Attempted extubation on day 8 failed and thereafter he continued to make poor respiratory effort. On day 12 whilst being ventilated he had an acute circulatory collapse associated with a profound metabolic acidosis and fixed dilated pupils. Cranial ultrasound performed during the resuscitation showed bilateral grade III intraventricular haemorrhage. Abdominal ultrasound demonstrated an expanding liver possibly indicating an intrahepatic bleed. Platelet counts were normal, but a coagulation screen showed deranged clotting. After discussions with the parents the resuscitation was discontinued and the patient died. Molecular genetic analysis confirmed the clinical diagnosis of CHARGE syndrome revealing a nonsense mutation c.3655C → T

(p.Arg1219X) in exon 15 of CHD7. The healthy parents were not tested molecularly for the nonsense mutation.

2.2. Literature review

The public internet database Pubmed was searched using three MeSH terms (CHARGE syndrome; CHARGE association; immunology). Titles and abstracts (when available) were reviewed to determine whether the article could be relevant. All possibly relevant papers were studied in detail. Bibliographies of all papers were hand searched to identify additional possibly relevant articles. It became clear during this process that patients with CHARGE syndrome were sometimes only recorded as patients with 'DiGeorge syndrome', therefore we searched Pubmed using this key word too. Patients with CHARGE syndrome caused by a cytogenetically visible chromosome abnormality or in whom subsequently a 22q11 microdeletion was detected, were excluded.

3. Results

Eleven reports were found, documenting 15 patients with features of CHARGE syndrome and immune deficits. The findings are summarized in Table 1. A microdeletion 22q11.2 was excluded in all but one patient who preceded the availability of testing [28]. One patient described in the literature as having CHARGE syndrome [1] showed only limited features fitting the clinical diagnosis of CHARGE syndrome, and FISH for a microdeletion 22q11.2 was not performed. We remained sufficiently uncertain about the diagnosis to exclude the patient from our analysis. In contrast, a patient reported as having velo-cardio-facial syndrome [19,20] with unilateral choanal atresia, unilateral ear abnormalities, severe developmental delay and normal FISH 22q11.2 was included in our review as the diagnosis of CHARGE syndrome seems much more likely. In reviewing the literature we found no descriptions of patients with autoimmune disorders.

4. Discussion

CHARGE syndrome is a pleiotropic entity, and there are many reviews describing the various aspects of the syndrome [26]. However, the accompanying immune deficiency has not received much attention. The patients reported here are the first molecularly proven CHARGE patients with immune deficits.

The function of the CHD7 protein is still largely unknown. It has been shown to be a nuclear protein, physically associated with chromatin, and which can act as an activator of transcription [24]. Using in situ hybridization, Sanlaville et al. [23] analyzed the expression pattern of the CHD7 gene during early human development and found CHD7 is widely expressed in undifferentiated neuroepithelium and in mesenchyme of neural crest origin. Towards the end of the first trimester it is expressed in dorsal root ganglia, cranial nerves and ganglia, and auditory, pituitary, and nasal tissues as well as in the neural retina. No data are available on the expression in the third and fourth pharyngeal pouch or thymus.

The findings in the present two patients confirm the literature data that the most common manifestation of immunodeficiency in CHARGE syndrome is a mild to severe T-cell deficiency, although the spectrum also includes isolated humoral immune deficiency, as is also seen in del22q11 (Table 1). Thymic aplasia or hypoplasia is usually associated with compromised

Table 1
Clinical and immunological findings in patients with CHARGE syndrome in whom sufficient immunologic data were reported in the literature

Author	C	H	A	R Growth	Cognition	G	E Shape an.	Hearing an.	Other	Thymus	T-cells[a]	PHA	B-cells	Immune globulin
Wood, 2 [28]	−	ASD	U			+	+		Facial paralysis (u), glaucoma (u), hypoplastic parathyroid glands	H	Very low	Poor		
De Lonlay-Debeney, 4 [7]	U	BAV	−	+		+	+	+	Duplicated thumb, micrognathia, retro-oesophageal left subclavian artery	A	Very low			
De Lonlay-Debeney, 5 [7]	B	VSD, AAh	−				+		Hydrocephalus	N	(Low)			
Boudny [4]	B	AAr	B					+	Partial facial nerve palsy (U), erythroderma	A	(Low)	Poor	N	Low IgG, IgA, IgM
Theodoropoulos, 1 [25]	B	PDA	+	+	+		+	+			N	N	N	Low IgG2
Theodoropoulos, 2 [25]	B	TA	+	+			+				Low	Poor	N	Low IgG1
Theodoropoulos, 3 [25]	B	PS, PFA, PDA	+			−	+	+	Facial asymmetry		Low	N	N	N
Markert, 8 [16]	+	ASD, AAr	+			+			Absent corpus callosum		Very low	Poor	N	N
Markert, DIG002 [15−18,22]	U	PDA				+	+	+	CLP (B), hypoplastic kidneys, hydroureter (B), VUR (B)	A	Very low	Poor		Low IgA
Markert, DIG005 [17,18,22]	B	DCA, PS, PDA, left SVC			+	+		+	Laryngomalacia, abnormal peristalsis hypopharynx, micrognathia	A	Very low	Poor	N	
Markert, DIG010 [18,22]	B	PDA	+			+		+	Hydronephrosis, VUR		Very low	Poor		
Markert, DIG011 [18,22]	B	CAV, abnormal bilateral SVC			+			+	CLP (U), inguinal hernias, partial agenesis callosal body, single kidney, hydronephrosis		Very low	Poor		
Markert, DIG103 [19]	B	PDA, AAr, vascular ring	+			+		+	Swallowing dysfunction, hiatal hernia, Dandy Walker, mega cisterna magna		Very low			
Markert, DIG107 [19,20]		ASD	+	+				+	Facial nerve palsy, vocal cord paralysis, swallowing dysfunction, intermittent rash	A	Very low	Poor		High IgE
Markert, DIG106 [19,20]	−	VSD, PDA, AAh CoA, AS	U	+	+		+		CP, ischemic brain injury, rash	A	Very low	Poor		

A, agenesis; B, bilateral; H, hypoplasia; N, normal; PHA, phytohemagglutinin response; U, unilateral; AA, aortic arch; AAh, hypoplastic aortic arch; AAr, right sided aortic arch; AS, aortic stenosis; ASD, atrial septum defect; BAV, bicuspid aortic valve; CAV, complete AV channel; DCA, dilated coronary sinus; CoA, coarctation of aorta; PA, pulmonary atresia; PDA, patent ductus arteriosus; PFA, patent foramen ovale; PS, pulmonic stenosis; SVC, superior vena cava; TA, truncus arteriosus; VSD, ventricular septum defect; CL, cleft lip; CP, cleft palate; VUR, vesicoureteral reflux; an., anomaly.

[a] Very low, number of either all T cells or naive T cells $<50\ mm^{-3}$; low, number of either all T cells or naive T cells $<700\ mm^{-3}$; (low), lymphopenia but exact number of T cells not known.

T-cell production [8] and is likely to underlie the immunodeficiency found in CHARGE syndrome. In a recent series of foetuses undergoing termination of pregnancy for prenatally diagnosed malformations, CHARGE syndrome was suspected at post-mortem and confirmed by CHD7 mutation testing in ten of them, of which seven had thymus hypoplasia or aplasia [23]. This high frequency of thymic dysgenesis contrasts with a recent report in postnatal patients [2], in whom the frequency of thymic hypoplasia was stated to be rare. This difference may be the result of patient selection bias but may also reflect difficulties in accurately assessing the thymus in living patients, unless they are undergoing open surgery.

Patients with low numbers of functionally normal T-cells may present with recurrent upper and lower respiratory infections or opportunistic and fungal infections. Antibiotic prophylaxis can be successful in them [25]. Patients with low or very low T-cells numbers together with poor or absent T-cell responsiveness to mitogens have a SCID-like phenotype, that often follows a lethal course. The two patients we report here and 12 of the 15 tabulated literature patients with sufficient information on their immunologic status had this phenotype. However, it seems likely there is a considerable publication bias providing a much higher chance for severely affected patients to be reported.

In the group of CHARGE patients with a SCID-like phenotype some have oligoclonal populations of T-cells that do not function normally [20]. The expansion of oligoclonal poorly functioning T-cells can lead to normal or only mildly depressed T-cell numbers, making the diagnosis of immunodeficiency difficult. These T-cells might generate autoimmune inflammatory responses similar to Omenn syndrome. The combination of oligoclonal T-cell phenotype and erythroderma should raise the possibility of this condition.

Isolated humoral immunodeficiency is rarely reported in patients with CHARGE syndrome. In a single patient with recurrent respiratory infections low IgG2 levels were noted [25]. This might be a more common finding if actively searched for, but several other factors are likely to contribute to recurrent airway infections in CHARGE patients too, such as choanal atresia, gastro-oesophageal reflux, bulbar and velopharyngeal incoordination, and congenital heart defects.

It is notable that both present patients had significant internal haemorrhages. However, it remains uncertain, whether this is just the consequence of medical treatment in severely ill neonates or whether this has a broader significance.

It is not clear whether the paucity of reports on immunodeficiencies in CHARGE syndrome indicates a low frequency, as patients with very severe immunodeficiencies might die before the diagnosis CHARGE syndrome is made and conversely mild (especially humoral) immune deficiencies may not be considered as the patients have several other malformations that might explain their increased infection rate. In addition, prior to the availability of CHD7 testing, patients with (likely) CHARGE syndrome and concomitant immune deficiency may have been reported as having DiGeorge syndrome instead of DiGeorge sequence [19,20].

We conclude that in newborns with severe immune deficiency, particularly T-cell abnormalities, CHARGE syndrome should be considered as a possible diagnosis. The exact frequency and nature of immunodeficiencies in CHARGE syndrome remains at present uncertain due to a possible publication bias. The finding that in one series, 30% of infants with a DiGeorge sequence that underwent thymus transplantation had CHARGE syndrome may indicate that frequency and severity can be considerably high [19]. We propose that all patients with CHARGE syndrome have their immune function evaluated, both to allow a better estimation of the immune function in CHARGE syndrome and to improve subsequent therapeutic and preventive management.

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