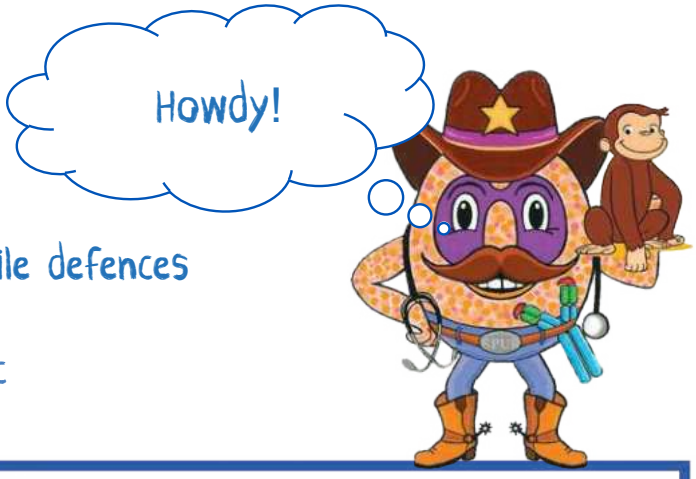
DR SPUR'S MYSTERY CASE



A case of fragile defences

Welcome to Dr Spur's Immunology Clinic
Referral letter:

Dr Lawn
Paediatrician

854 Wheat Street
Grasfontein
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Tel: 048 957 1234

Dear Dr Spur

I am treating a ten-month-old boy diagnosed with di George syndrome. He has a history of failure to thrive, which was mostly attributed to his cardiac anomalies (more specifically, a ventricular septal defect which has since been repaired). I am concerned about his infection history. Over the past four months he has experienced multiple episodes of upper respiratory tract infections characterised by nasal congestion, clear to mucopurulent rhinorrhoea, intermittent low-grade fever, cough (initially dry, progressing to a productive cough with occasional wheezing), feeding difficulties and refusal of feeds during episodes. He does not have any palatal anomalies.

Despite symptomatic treatment with nasal saline irrigation, antipyretics and antibiotics on at least two occasions, the symptoms would resolve slowly over 10–14 days, only to recur within another week or two. Between infections, he never seems to return to baseline, exhibiting a persistent nasal discharge and a 'wheezy chest'.

Two of these episodes progressed to lower respiratory tract infections, necessitating hospital admission.

Do you have any experience with DiGeorge syndrome and immunodeficiency?

Yours sincerely

Dr Lawn

Did you know?

DiGeorge syndrome (DGS) and 22q11.2 deletion syndrome (22q11.2DS) are closely related, but they are not entirely interchangeable. 22q11.2DS refers to the genetically confirmed chromosomal microdeletion, while DGS describes a clinical presentation with characteristic features such as facial anomalies, heart defects and immune deficiencies. Most DGS cases have a 22q11.2 deletion, but some may not.[1]

Dear Dr Lawn

Thank you for the referral.

Indeed, DGS (or 22q11.2DS) is associated with impaired T-cell development due to thymic hypoplasia. Most cases are caused by a heterozygous chromosomal microdeletion at 22q11.2 and this is the most prevalent microdeletion syndrome. Although DGS follows an autosomal dominant inheritance pattern, the majority of cases result from de novo 22q11.2 microdeletions.[2,3]

DGS classically comprises a constellation of signs and symptoms associated with defective development of the pharyngeal pouch during embryogenesis. The phenotype of DGS is quite heterogenous, even more so the immunological competence of affected patients, which ranges from normal to a severe combined immunodeficiency (SCID).[2]

Pathogenesis of cellular and humoral immunodeficiency in DGS

T-cells

As early as the eighth week of gestation, bone marrow-derived T-cell precursors migrate to the developing thymus, where normal T-cell maturation relies on a two-way interaction between these precursors and the thymic stroma. In this specialised micro-environment, positive and negative selection processes ensure the development of self-tolerant T-cells, with functional receptors able to recognise major histocompatibility complex (MHC) molecules on antigen-presenting cells. The disruption of this tightly regulated process results in impaired central tolerance, altered T-cell subset distribution, regulatory T-cell dysfunction, abnormal B-cell responses and cytokine dysregulation.[3,4]

B-cells

T-cells play a crucial role in coordinating the immune response, with T-cell help being essential for B-cell activation, class-switch recombination, somatic hypermutation and germinal centre formation in lymphoid tissues. Whereas B-cells may develop normally in the bone marrow, their ability to generate strong, long-lasting antibody responses is severely diminished without T-cell–mediated cytokine signalling and direct cell–cell interactions via costimulatory molecules.[3,4]

Consequently, despite normal B-cell numbers, inadequate T-cell help leads to failure to produce high-affinity class-switched antibodies (such as IgG and IgA), which results in a combined immunodeficiency.[3]

Disorders causing T-cell lymphopenia, or dysfunction, profoundly impair B-cell function.

Clinical presentation

The clinical presentation of patients with DGS includes conotruncal cardiac anomalies, endocrine dysfunction and characteristic craniofacial features which include low-set ears, palatal anomalies (cleft palate/velopharyngeal insufficiency), ocular hypertelorism, nasal abnormalities, micrognathia, short philtrum and hooded eyelids. Additional findings may include neurological, skeletal and developmental abnormalities.[3,2,5]

The immunological phenotype of DSG can range from no immunological impairment to severe life-threatening infectious complications. Patients with partial forms or hypothymia can be susceptible not only to infections typically associated with T-cell deficiency, that is, viral and fungal infections, but also to bacterial infections, particularly of the respiratory tract, due to impaired humoral immunity.[3]

In patients with complete DGS or athymia, SCID-like symptoms develop, leading to early-onset opportunistic infections and a high risk of mortality.[3]

Immune dysregulation in the form of autoimmunity and atopy has been reported.[2]

Laboratory tests and diagnosis

The nomenclature has evolved, and current best practice is to refer to 22q11.2 deletion and duplication syndromes, reserving

TABLE I: LABORATORY FINDINGS ASSOCIATED WITH DGS/22Q11.2DS

Category	Test	Findings	Comment
Genetic	FISH	22q11.2 microdeletion	
	Chromosomal micro-array (CMA)	22q11.2 deletion (typically ~3 Mb)	More sensitive than FISH; defines size and gene content
Immunological	TREC assay (newborn screen)	Low or undetectable	Can be normal if very mild hypothymia
	Full blood count	N or ↓ lymphocyte count	
	Immunophenotype	N or ↓ CD3+, ↓ CD4+, ↓ CD8+ T-cells	B-cell counts are normal
	Naive T-cells (CD45RA)	↓ Naive CD4+ and CD8+ T-cells	
	Immunoglobulin levels (IgG, IgA, IgM)	↓ IgA (common), ↓ IgG or IgM (variable)	
	B-cell panel (memory B-cells)	↓ Class-switched memory B-cells	
	Vaccine response	Poor or absent response to protein or polysaccharide	Protein vaccine response: Tetanus Polysaccharide vaccine response: Pneumococcus

N: normal; ↓: Decrease; TREC: T-cell receptor excision circles

the term DGS for cases who present with a specific clinical phenotype.[1]

The diagnosis of DGS is made on clinical assessment, radiological studies and laboratory features and is correlated with genetic findings using techniques such as fluorescence in situ hybridisation (FISH) or chromosomal micro-array. The deletion associated with 22q11.2DS is too small to be visible on conventional karyotype.[2]

According to the International Union of Immunological Societies (IUIS), 22q11.2DS is classified as a combined immunodeficiency with associated or syndromic features.[6]

Table I summarises the laboratory findings.

How to manage

Owing to the wide range of clinical features, a multidisciplinary approach is recommended. The effective management of immunodeficiency in DGS requires early recognition and prompt treatment of infections. Maintaining a high index of suspicion and pursuing accurate pathogen identification in this vulnerable population are essential to reducing long-term complications.[2]

Prophylactic antimicrobial use in at-risk periods could be considered. Patients with significant humoral defects may benefit from immunoglobulin replacement therapy to provide passive immunity. Notably, surveillance studies have shown that T-cell production improves over time, with the most significant changes observed after the first year of life in patients with milder forms of DiGeorge syndrome.[7]

Research has shown that inactivated vaccines are completely safe in patients with DGS. Prospective data concerning live vaccines are lacking; however, retrospective studies have shown that live viral vaccines can safely be considered in those patients with a CD4 T-cell count of > 400 cells/uL, a CD 8 T-cell count of more than 200 cells/uL, a normal naïve T-cell complement and when vaccine responses to protein antigens have been demonstrated.[2,3]

Severe cases with complete athymia should be managed similarly to patients with SCID. This includes isolation, intravenous immunoglobulin replacement therapy, anti-microbial prophylaxis and strict avoidance of live vaccines. All blood products should be leukocyte-depleted, irradiated and cytomegalovirus (CMV)-negative. Early thymic transplantation or hematopoietic stem cell transplantation can be life-saving.[2,3]

Patients with DGS require frequent follow-up and although ~90% of chromosome 22q11.2 deletions are believed to occur de novo, parents should be offered genetic testing and counselling to determine the risk of future offspring being affected.[5]

Dr Spur's take-home message:

Dr Spur's mystery solved:

Dr Spur's mystery case solved: DGS/22q11.2DS is classified as a combined immunodeficiency due to thymic hypoplasia.

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