Kawasaki disease: Studies on etiology, treatment and long-term follow-up
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Chapter 1

GENERAL INTRODUCTION AND OUTLINE OF THE THESIS
1. GENERAL INTRODUCTION

Kawasaki disease (KD) is an acute, medium-vessel vasculitis that predominantly occurs in children less than 5 years of age. The main complication of this rare disease is the development of coronary artery aneurysm (CAA) as a consequence of coronary arteritis. KD was first described in 1967 in Japan by Dr. Tomisaku Kawasaki. Seven years later the first English publication by Dr. Kawasaki about KD appeared and two years later in 1976 the first Dutch case was reported. Nowadays, KD has been reported worldwide in all ethnic and racial groups, but still much is unclear about this pediatric disease.

Epidemiology

Children under the age of five years are mostly affected with a male predominance (male to female ratio = 1.5 to 1). The disease is markedly more prevalent in Japan and other Asian countries (69 – 240 per 100,000 children <5 years of age) than in Western countries (4-15 per 100,000 children <5 years of age). In Japan, the recurrence rate has been reported to be ~4% and the proportion of cases with a positive family history is ~2%.

Etiology

Despite more than 4 decades of research, the cause of KD is still unknown. The leading hypothesis is that KD reflects an abnormal inflammatory response to one or more unknown infectious triggers in genetically predisposed individuals. A genetic predisposition to susceptibility is suggested by the striking difference in incidence between different ethnic groups, which is maintained following migration to countries with a lower incidence. In addition, the incidence of KD is increased in siblings of KD patients and in children born to parents with a history of KD. The clinical and epidemiological features of KD support an infectious cause, including the presence of self-limiting symptoms that usually do not recur, the age distribution, laboratory features, seasonal variation, and the occurrence of epidemics. Its rarity in the first few months of life and in adults suggests an agent to which adults are immune and to which only the very young infants are being passively protected by maternal antibodies. However, efforts to identify an infectious agent in KD have not been successful to date.

Symptoms and diagnosis

There is no specific diagnostic test available for KD and the diagnosis is therefore based on the presence of clinical criteria. These diagnostic criteria include: 1. bilateral non-exudative conjunctival injection; 2. oral mucosal changes, such as erythema of the lips or strawberry tongue; 3. changes of the extremities, such as edema, erythema and desquamation; 4. polymorphous rash; and 5. cervical lymphadenopathy. Classic KD is defined as the presence of ≥5 days of fever and ≥4 the 5 classic criteria. According to the guidelines of the American Heart Association (AHA), incomplete KD cases
are defined as patients with ≥5 days of fever and less than 4 classic criteria, but who have involvement of the coronary arteries upon echocardiography or a set of suspect laboratory criteria. These laboratory criteria include C-reactive protein (CRP) ≥30 mg/L, and ≥3 of the following supplemental laboratory criteria: albumin <30 g/L, anemia for age, elevation of alanine aminotransferase, platelets after day 7 ≥450 x 10^9/L, white blood cell count ≥15 x 10^9/L, and urine ≥10 white blood cells/high-power field (in the absence of a positive culture).

**Treatment**

Standard treatment of the acute KD phase is well-established and consists of a single dose of high-dose intravenous immunoglobulin (IVIG) at 2g/kg, preferably given within 10 days after the onset of fever. IVIG preparations consist of human pooled plasma-derived immunoglobulin G (IgG) from healthy blood donors. The mechanism of action of IVIG in KD is still unknown, but treatment with IVIG shortens the duration of fever and reduces the incidence of CAAs from 25% to less than 10%. Oral aspirin is also given because of its anti-inflammatory (at higher doses) and anti-thrombotic properties (at lower doses), although there is limited evidence for its efficacy in reducing the CAA rate. The majority of patients treated with IVIG and aspirin respond promptly within 48 hours. However, a subgroup of patients fails to have a good clinical response to a single infusion of IVIG and has persistent or recrudescent fever. These IVIG non-responsive patients are at higher risk for the development of CAAs compared to those who respond. The optimal therapy for these patients remains controversial as controlled trial data are lacking. Additional IVIG treatments, high-dose intravenous pulse methylprednisolone, TNF-alpha blockade, cyclosporine A, methotrexate, and anti-CD20 treatments have been used for IVIG non-responsive patients. Large, multicenter clinical trials in different ethnic populations are warranted to evaluate the safety and efficacy of these treatments.

A concern about the use of IVIG is that the passively acquired antibodies can block replication of live-attenuated viral vaccines and hence the subsequent active immune response for generating an immunological memory against these viral agents. It is therefore recommended to defer vaccination with live-attenuated vaccines after administration of IVIG. However, there is no clear consensus about the appropriate time interval for active immunization after IVIG treatment for KD. The interval recommended in different national and international guidelines varies between 6 and 11 months. Studies about the interference of IVIG with active immunization responses are limited, especially in KD patients who are treated with high-doses of IVIG.

The MMR vaccine is a live-attenuated vaccine that is included in the Dutch immunization program. All children born since 1987 receive this vaccine at the age of 14 months and as a booster at 9 years of age.
IgG or Fc-gamma receptors (FcγRs)

Since standard IVIG therapy is effective in the majority of the patients with KD, the IgG or Fc-gamma receptors (FcγRs) are of particular interest in KD research. The IgG receptors bind the Fc-domain of IgG and are expressed on different blood cells. Based on their affinity for monomeric IgG, three types of FcγRs can be discriminated in humans. FcγR type I is a high-affinity receptor, whereas type II and III are low-affinity receptors (Figure 1).

The current paradigm in FcγR biology states that the balance between the activating and inhibitory FcγRs determines cell activation and therefore immune reactivity in the host. In humans there are various activating isoforms of the receptor (FcγRI, FcγRIIa, FcγRIIIa and FcγRIIIb) and there is a single inhibitory isoform (FcγRIIb). The inhibitory and activating isoforms are being differentially expressed on various leukocyte subsets. Loss of expression of the inhibitory FcγRIIb, overrepresentation of the activating FcγRs or altered FcγR function may result in unbalanced immunity and auto-inflammation.

The genes encoding for the low-affinity FcγRs (FCGR2A, FCGR2B, FCGR2C, FCGR3A and FCGR3B) are located within one gene cluster on Chromosome 1q23. Variation in FcγR expression and function largely depends on single nucleotide polymorphisms (SNPs) and Copy Number Variation (CNV) within the FCGR2/3 gene cluster. CNV is defined as a DNA segment of 1kb or larger that is present at a variable copy number in comparison with a reference genome. From a functional perspective, gene copy number differences may contribute to variation in gene expression at the transcript and/or protein level. CNV has been related to

Figure 1. Schematic representation of the human FcγRs.
various autoimmune diseases. Within the *FCGR2-3* gene cluster, CNV has been identified in *FCGR2C, FCGR3A* and *FCGR3B*. A gene-dosage effect has been observed for these genes; one gene results in less surface expression of the FcγR than 2, 3 or 4 genes according to the gene copy number that may vary.

In our Genome-Wide association study (GWAS) on KD susceptibility, a SNP within *FCGR2A* (rs1801274, *FCGR2A*-131H>R) was identified as one of the most strongly associated genes. This SNP encodes for a Histidine to Arginine change at amino acid position 131, resulting in a substantial difference in the ability to ligate human IgG2. The identified SNP in *FCGR2A* is located just outside of the region of the *FCGR2/3* gene cluster that shows a high level of CNV, which had no SNP coverage in the GWAS (or any other GWAS performed). Thus, the results preclude any definitive testing for an association with one of the other *FCGR2/3* genes.

**Cardiovascular complications**

The main complication of KD is the development of CAAs in up to 25% of untreated patients and 5–10% of treated patients. CAA are most frequently identified in the proximal left descending coronary artery (LAD) and proximal right coronary artery (RCA), followed by the left mean coronary artery (LMCA), left circumflex coronary artery (LCX) and distal RCA. Age <1 year, male gender, delay of treatment, incomplete disease presentation, IVIG non-responsiveness and low serum albumin have been reported to be associated with the development of CAAs.

**Definition of CAA**

In 1984 the Japanese Ministry of Health and Welfare established criteria for the identification of CAA. According to these criteria, a coronary artery is defined as abnormal if the internal diameter is greater than 3 mm in children younger than 5 years of age or >4 mm in those older than 5 years of age, if the internal diameter of a segment measures at 1.5 times the size of an adjacent segment, or if the lumen is clearly irregular. More recent studies have reported that categorization for CAA by z-scores, with adjustment for body surface area (BSA), is more accurate than categorization by the dichotomous Japanese definition. A coronary artery z-score ≥2.5 (i.e., a coronary dimension is ≥2.5 SDs above the mean for BSA) is defined as abnormal. CAA can be defined as small (<5 mm or z-score 2.5-5), medium (5-8 mm or z-score 5-10) or giant (>8 mm or z-score >10).

**Other cardiovascular complications**

CAA are the most serious consequences of KD, but the disease may also result in other acute cardiovascular sequelae, including myocarditis, valvulitis, and vascular involvement of other vessels such as the axillary and renal arteries. Left ventricular dysfunction due to myocarditis has been documented in up to 50% of acute KD patients. This finding has
been supported by autopsy and biopsy studies showing that almost all patients with KD had some signs of myocarditis or pericarditis\textsuperscript{36-37}.

**Long-term follow-up: imaging**

In approximately half of the patients the CAAs resolve within 2 years. The likelihood that an aneurysm will resolve appears to be determined mainly by its initial size, with smaller aneurysms having a greater likelihood of regression\textsuperscript{38}. In the other half of the patients with CAAs, the aneurysms persist long-term and may lead to thrombus formation by blood flow turbulence and endothelial pro-coagulatory activity on the one hand, and stenotic vascular lesions on the other hand, which both can cause myocardial ischemia, infarction and sudden death. Patients with persistent aneurysms require life-long clinical follow-up and management. Patients with giant CAA (>8mm or z-score >10) have the most severe long-term prognosis. The long-term prognosis of patients with small and transient CAA or of those patients, who were without any coronary involvement during the acute phase of the disease, remains controversial. Although there is currently a lack of evidence for an increased long-term risk in these patients, this issue must certainly be further investigated because the former KD cases grow older and become adults.

**Current AHA guidelines**

In 2004 an expert committee of the AHA published guidelines for the diagnosis, treatment and long-term follow-up of patients with a history of KD\textsuperscript{11}. For long-term follow-up recommendations, patients are stratified in 5 risk levels according to their relative risk of myocardial ischemia and infarction. The suggestions done by the AHA for routine and invasive imaging during follow-up of each risk level are shown in Table 1.

In short, serial echocardiography and ECG are recommended for patients without coronary involvement or with transient coronary artery dilatations normalizing within the first 8 weeks after the acute presentation of the disease (risk levels I-II). For patients with persistent CAAs serial nuclear stress-tests and conventional coronary angiography (CAG) are recommended in addition to routine echocardiography and ECG examinations (risk levels III-V). These suggestions are based on a consensus of guidelines because long-term studies and prospective trials are lacking.

The imaging modalities recommended in the AHA-2004 guidelines have some significant limitations. Echocardiography is the first choice for routine coronary artery surveillance and is used to screen KD patients for the presence of coronary artery pathology\textsuperscript{39}. An important disadvantage of echocardiography is that only the proximal part of the coronary arteries can be visualized adequately and CAAs could therefore be missed. In addition, echocardiography may be limited by operator dependency and becomes progressively more difficult if a child grows and body size increases\textsuperscript{40}. Nuclear perfusion scans are recom-
mended to address ventricular function in relation to vascularization and ischemia with modest specificity, while resulting in high radiation exposure\textsuperscript{41, 42}. CAG is the gold standard for coronary artery evaluation and is able to detect CAAs, coronary artery stenosis and thrombotic occlusion, but results in risks associated with its invasive nature and the exposure to contrast and radiation\textsuperscript{43}. A well-known problem of CAG is vascular damage at the puncture site resulting in thrombosis and occlusion of the femoral artery, which may limit the repeated use. The described limitations of CAG and perfusion scans hamper adherence to the AHA-2004 guidelines in (young) patients with persistent CAAs. Although studies in KD patients are limited to date, new imaging techniques like cardiac magnetic resonance imaging (CMRI) and computed tomography (CT) angiography scanning are valuable alternatives for monitoring during the follow-up of patients with KD.

**Cardiac MRI**

Cardiac magnetic resonance imaging (CMRI) has emerged as a non-invasive and radiation-free imaging modality, which has the ability to evaluate the coronary artery anatomy, cardiac volumes and function and myocardial perfusion within one examination. CMRI offers a detailed image of the coronary anatomy and may delineate both proximal and the more peripheral CAAs that can be missed by routine echocardiography\textsuperscript{44, 45}. CMRI also facilitates pharmacological stress-testing in the same imaging investigation to assess reversible ischemia of the ventricular muscle wall as well as to visualize myocardial scar by the delayed contrast enhancement\textsuperscript{46, 47}.

### Table 1. AHA-2004 guidelines\textsuperscript{41}

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Coronary artery involvement</th>
<th>Routine follow-up and diagnostic testing</th>
<th>Invasive testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No coronary involvement</td>
<td>Echocardiography + ECG every 5 years</td>
<td>-</td>
</tr>
<tr>
<td>II</td>
<td>Transient CAA (disappear &lt;8 weeks)</td>
<td>Echocardiography + ECG every 3-5 years</td>
<td>-</td>
</tr>
<tr>
<td>III</td>
<td>Small to medium, isolated CAA (3–6 mm, z-score 3-7)</td>
<td>Annual echocardiogram + ECG; myocardial perfusion scan (stress-test) every 2 years if &gt;10 years of age</td>
<td>Angiography if non-invasive test suggests ischemia.</td>
</tr>
<tr>
<td>IV</td>
<td>Large, isolated CAA (&gt;6mm) or multiple aneurysms in 1 vessel</td>
<td>Biannual echocardiogram + ECG; biannual myocardial perfusion scan (stress-test)</td>
<td>CAG at 6-12 months; repeated CAG if non-invasive test or other findings suggest ischemia.</td>
</tr>
<tr>
<td>V</td>
<td>Obstruction of coronary artery</td>
<td>Biannual echocardiogram + ECG; annual myocardial perfusion scan (stress-test)</td>
<td>CAG to address therapeutic options.</td>
</tr>
</tbody>
</table>

Abbreviations: CAG=conventional coronary angiography; ECG=electrocardiogram.
Long-term follow-up: psychosocial consequences

Prior studies have mainly focused on the etiology and the cardiac complications of KD, and studies evaluating the long-term psychosocial consequences on patients and their families are limited. We know from our clinical experience that families of children with KD experience a great deal of stress and anxiety in relation to the disease's acute and severe onset, the uncertainty about the diagnosis due to difficulties in diagnosing KD because of the lack of any specific diagnostic test (apart from the echocardiography results about the development of CAA), the potentially severe coronary artery involvement, and the requirements for long-term medical management. In addition, symptoms indicating central nervous system (CNS) involvement such as extreme irritability and aseptic meningitis may be present in a considerable number of patients. Other severe neurological complications like severe lethargy, facial nerve palsy, sensorineural hearing loss, hemiplegia and cerebral infarction have also been documented in the literature and experienced in the large Kawasaki cohort in the Netherlands that we have collected over the years. To provide comprehensive care for patients with KD, more insight in the psychosocial consequences of the disease on patients and their parents is also needed.

2. OUTLINE OF THIS THESIS

Part I - Epidemiology

In chapter 2 of this thesis, we describe the results of an epidemiological study of KD in The Netherlands. This study used the Dutch Pediatric Surveillance Unit (DPSU), a national system for surveillance of rare and new pediatric diseases, to examine the incidence, demographic characteristics, treatment regimen and cardiac outcome of KD in The Netherlands.

Part II - Treatment

The following two chapters of this thesis focus on treatment of acute and IVIG non-responsive patients with KD. In chapter 3, we review the current evidence for treatment of the acute KD phase, and we discuss the management options for IVIG non-responsive patients. In chapter 4, we report for the first time on the beneficial use of Anakinra, a human interleukin-1 receptor antagonist (IL-1 RA), in an IVIG non-responsive patient with severe coronary artery pathology.

Part III – IgG-related immunity

The two chapters of part III discuss IgG-related immunity in relation to KD. The aim of the study described in chapter 5 was to evaluate the IgG response to mumps, measles and rubella (MMR) vaccination in KD patients treated with IVIG in comparison with healthy controls. In addition, we focused on the influence of the interval from IVIG administration
to MMR vaccination on the effectiveness of the vaccine because there is currently no clear consensus about the appropriate time interval for active immunization after IVIG treatment. The genetic study described in chapter 6, focuses on fine-mapping of the FCGR2/3 gene cluster using a previously validated Multiplex Ligation-Dependent Probe Amplification (MLPA) assay developed in our laboratory. The FCGR2/3 gene cluster encodes for the low-affinity IgG receptors. The FCGR-specific MLPA assay had been developed by our research group in 2008 and was used to study the genetic variation of this complex gene cluster in KD. We hypothesized that CNV and SNPs in and around the FCGR2/3 gene cluster, regulating transcription and expression of the activating and inhibitory FcgRs, are associated with susceptibility to KD.

Part IV – Imaging during long-term follow-up

Part IV of this thesis focuses on the long-term cardiovascular consequences of KD. In chapter 7 and 8, we applied CMRI during the long-term follow-up of patients with KD. Chapter 7 describes a study about the feasibility of a comprehensive CMRI protocol to assess coronary artery pathology, reversible ischemia and myocardial infarction in patients with a history of KD. In addition, we assessed the performance of CMRI in comparison with echocardiography. In chapter 8 we investigated biventricular function by CMRI during the long-term follow-up of KD patients. CMRI is the reference standard for the assessment of biventricular function. In chapter 9 we compare carotid intima-media thickness (cIMT) as surrogate marker of cardiovascular disease between patients with history of KD and controls.

Part V – psychosocial consequences

In part V we present the data of a large study in almost 300 families about the long-term psychosocial impact of KD on patients and their parents. Chapter 10 describes the health-related quality of life (HRQOL) and psychosocial functioning of a large group of Dutch children and adolescents with a history of KD, in comparison with healthy controls. In chapter 11 we report the parental data of this study, including the HRQOL and parental perceptions of child vulnerability of parents of a child with history of KD. These reports contribute to the scarce literature about the psychosocial consequences of KD. Finally, in the summary and general discussion of this thesis (chapter 12) the major findings presented in this thesis are discussed with implications for clinical practice and directions for future research in KD, a disease that has remained enigmatic over the years.
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