

# Multiple Organ Dysfunction Syndrome in Children With Sepsis: Role of Genetic Factors

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**Summary:** This review summarizes current knowledge on the impact of genetic markers on susceptibility, severity, and outcome of acute inflammatory disorders in children, with a special focus on systemic infections. A 14-year-old child with *Neisseria meningitidis* bacteremia, complicated by septic shock and multiple organ dysfunction, is discussed as an exemplary case, and linked to the application of genetic epidemiology and the study of common disorders in children. The current pertinent literature is comprehensively reviewed and limitations and future directions are discussed.

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**A**s presented in the first clinical case by Symons and Picca in this issue, the early clinical presentation of the 14-year-old patient with a flu-like prodrome, headache, nausea, emesis, and fatigue appears nonspecific, but combined with the rapid development of fever (warm core and cool periphery), shock, and hypoperfusion (mottled skin, hypotension), it raises the suspicion of systemic *Neisseria meningitidis* bacteremia and septic shock, especially in a young adolescent. The clinical course of the patient is characterized by refractory hypotension and development of a petechial rash, consistent with Waterhouse-Friderichsen syndrome. At this point, several of the key clinical findings on presentation indicate not only the presence of the systemic inflammatory response syndrome (SIRS), but also of multiple organ dysfunction. According to the adult multiple organ failure score, circulatory, respiratory, and neurologic failure are evident

at the time of presentation, and in the subsequent 24 hours hematologic and renal failure ensue. According to the meningococcal septic shock score<sup>1</sup> and based on the available laboratory and clinical data, this patient has a risk for mortality of approximately 80%, a grim outlook. The initial volume resuscitation of 5 L in the first hours appears adequate, however, the subsequent, continuous administration of more crystalloid solutions is less favorable and may be associated with an increased risk for mortality.<sup>2,3</sup> In addition, acute kidney injury (AKI) is evident on the first morning after admission, based on a 50% increase in serum creatinine level, and although the benefit of an earlier nephrology consultation is debatable, the clinical condition of this patient makes a spontaneous recovery of kidney function rather unlikely and the subsequent need for renal replacement therapy appears all but inevitable.

This case illustrates an overwhelming systemic inflammatory response with resulting multiple organ dysfunction syndrome (MODS) including AKI in response to a systemic gram-negative bacterial infection. The role of the host immune response to inflammatory stimuli and its significance for the development and manifestation of MODS and AKI has been increasingly recognized. Bacterial infection, which

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represents an environmental influence, induces an immune response in the host that is modulated in part by genetic factors. The recognition and description of genetic factors that predispose to an overwhelming inflammatory response such as the one described in the aforementioned case could facilitate the development of risk markers for the susceptibility to and/or the severity of organ dysfunction including AKI. This summary attempts to outline the current knowledge on the role of genetic polymorphisms in MODS and AKI, to describe a selection of candidate gene polymorphisms, and to provide possible future implications.

### GENETIC POLYMORPHISM IN HEALTH AND DISEASE

Although most of the DNA sequences among humans are identical, as little as 0.1% of the human genome accounts for all interindividual variability or *gene polymorphism*.<sup>4</sup> Polymorphism may be found in the promoter or 5'-flanking region where it may influence transcriptional activity<sup>4</sup>; in the exons or coding sequences where it may be silent or affect the structure, binding, or trafficking of the gene product; in the introns or intervening sequences where it may impair messenger RNA processing; or in the 3'-untranslated region of a gene where it may affect RNA half-life or translation into protein.<sup>5</sup>

Three forms of human gene polymorphisms have been described<sup>4</sup>: single nucleotide polymorphism, typically consisting of a single nucleotide substitution; variable number of tandem repeats or minisatellite polymorphism, consisting of in-tandem insertion of multiple repeats of nucleotide sequences of less than 100 base pairs<sup>4</sup>; and microsatellite polymorphism, consisting of several repeats of a short motif of 1 to 5 nucleotides.

### THE CANDIDATE GENE APPROACH

In a candidate gene approach, candidate genes are selected if they are likely to modify host responses to environmental stimuli; for example, the inflammatory response to an infectious stimulus such as described in the earlier case by Symons and Picca. Such a

candidate gene can then be tested in an affected population. It is important to note, however, that associations cannot prove a causal relationship and that a candidate genetic polymorphism associated with a disease might be merely located in proximity to other pathogenic genetic factors, as in linkage disequilibrium. The more traditional approach of a linkage analysis, in which co-inheritance of a disease phenotype along with a specific region of the genome is identified, has been proven useful for the identification of monogenic conditions, such as polycystic kidney disease in which environmental factors play only a minimal role.

### GENETIC POLYMORPHISM IN ACUTE INFLAMMATORY DISORDERS

#### The Proinflammatory Axis

An overwhelming acute host defense response to infectious or noninfectious triggers such as burns or trauma may induce a SIRS.<sup>6</sup> This response results in the systemic release of biologically active mediators, which can lead to organ dysfunction and failure.<sup>7</sup> The association of proinflammatory cytokines with adverse clinical outcomes in acute inflammatory states has been well documented.<sup>8-12</sup>

Proinflammatory cytokines such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin-1 $\beta$  (IL-1 $\beta$ ) exert systemic effects by causing stimulation of platelet-activating factor, prostanoid, and nitric oxide synthesis by vascular endothelial cells, which in turn leads to vasodilatation, capillary leak, intravascular coagulation, systemic hypotension, and organ dysfunction as illustrated in the case. Chemokines such as IL-8 facilitate recruitment of neutrophils to target tissues where the latter may release reactive oxygen species and proteolytic enzymes leading to tissue damage. In addition, TNF- $\alpha$  and IL-6 also induce protein catabolism.<sup>13</sup>

#### The Anti-Inflammatory Axis

In response to the SIRS, a subsequent compensatory anti-inflammatory response can be observed. Immunomodulatory cytokines and mediators, including IL-10, IL-1 receptor antagonist, and soluble TNF receptors, are key contributors to the

**Table 1. Positive Association Studies Between Polymorphisms of Selected Cytokine/Chemokine Genes and Acute Infectious/Inflammatory Disorders in Children**

Gene	Polymorphic Allele	Acute Illness	Reference
<b>Cytokines</b>			
TNF- $\alpha$	-308 A allele (TNF $\alpha$ 2)	Higher disease severity and mortality in meningococcal infection	28
TNF- $\alpha$	-308 A allele (TNF $\alpha$ 2)	Susceptibility to cerebral malaria	29
TNF- $\alpha$	-308 A allele (TNF $\alpha$ 2)	Neonatal acute renal failure	32
TNF- $\alpha$	-308 A allele (TNF $\alpha$ 2)	Prolonged mechanical ventilation and supplement oxygen requirement in preterm neonates	33
TNF- $\alpha$	-238 A allele	Increased preterm birth and early childhood mortality, and increased malaria morbidity	108
IL-1 $\beta$	-511 allele 2/2	Febrile seizure in children	40
IL-1 $\beta$	-511 allele 1/2	Survival in meningococcal disease	96
IL-1 receptor antagonist	+2018 C allele	Susceptibility to and mortality from meningococcal disease in children	97
IL-6	-174 C allele	Neonatal acute renal failure	32
IL-6	-174 C allele	Increased incidence of late blood stream infection in ventilated VLBW infants	51
IL-10	-1082 GA genotype	Meningococcal disease	53
IL-10	-1082 A allele	Increased incidence of late blood stream infection in ventilated VLBW infants	51
<b>Chemokines</b>			
IL-8	-251 A allele	RSV bronchiolitis	63
RANTES	-28 CC, -403 GA, and intron 1.1 TT genotypes	Increased susceptibility to severe RSV bronchiolitis	66

Abbreviations: VLBW, very low birth weight; RSV, respiratory syncytial virus.

compensatory anti-inflammatory response.<sup>14</sup> It can therefore be postulated that the extent of the host inflammatory response is determined in part by a balance between proinflammatory and anti-inflammatory mechanisms, and that modulation of these mechanisms could be used as a therapeutic strategy.<sup>15,16</sup>

### POLYMORPHISM OF CANDIDATE INFLAMMATORY RESPONSE GENES

The following section highlights selected candidate gene polymorphisms that previously have been associated with adverse outcomes in acute infectious and inflammatory states, with a special emphasis on the pediatric population (Table 1).

### TNF- $\alpha$ and TNF- $\beta$

Polymorphism within the 5'-flanking region of the *TNF- $\alpha$*  gene at positions -238 (G to A) and -308 (G to A) has been described. The -308 A allele is associated with increased TNF- $\alpha$  promoter activity<sup>17-19</sup> and production.<sup>20-23</sup> In adults, *TNF- $\alpha$*  gene polymorphism has been associated with adverse clinical outcomes in various acute inflammatory states including sepsis.<sup>24-30</sup> In particular the *TNF- $\alpha$*  -308 A allele has been associated with higher monocyte-derived TNF- $\alpha$  production levels, higher disease severity scores, and increased mortality rates in patients with dialysis requiring AKI.<sup>31</sup> In children, the *TNF- $\alpha$*  -308 A allele has been associated with neonatal AKI,<sup>32</sup> and with prolonged mechanical

ventilation and supplemental oxygen requirement in preterm neonates.<sup>33</sup>

The gene coding for TNF- $\beta$  is located in proximity to the TNF- $\alpha$  gene. Single nucleotide polymorphism at position +1069 (G to A) in the first intron of the gene has been characterized.<sup>34</sup> The TNF- $\beta$ 2 or A allele, which is more common than the TNF- $\beta$ 1 or G allele, is associated with higher IL-1 $\beta$  and TNF- $\alpha$  production,<sup>35</sup> and with adverse clinical outcomes in sepsis.<sup>36,37</sup> However, this association might be due to linkage disequilibrium between the TNF- $\alpha$  and TNF- $\beta$  polymorphism.<sup>38</sup>

### The IL-1 Family

The IL-1 family consists of IL-1 $\alpha$ , IL-1 $\beta$ , IL-1 receptors type I and II, and IL-1 receptor antagonist. Polymorphism of the IL-1 $\beta$  gene at position -511 (C to T)<sup>39</sup> is associated with acute inflammatory disorders.<sup>39-41</sup> The allele 2 of a 5-allele minisatellite polymorphism of the IL-1 $\beta$  gene has been associated with increased IL-1 $\beta$  production,<sup>42-44</sup> which has been linked to an increased susceptibility to sepsis.<sup>45,46</sup>

### IL-6

IL-6 is a pleiotropic cytokine that can exert both pro- and anti-inflammatory effects.<sup>47</sup> A single nucleotide substitution at position -174 (G to C)<sup>48</sup> is associated with reduced gene promoter activity.<sup>48,49</sup> Clinical studies of this polymorphism have yielded conflicting results. Nevertheless, an association with sepsis<sup>50</sup> and AKI in low-birth-weight infants<sup>32</sup> has been described. The IL-6 -174C allele also has been associated with an increased incidence of late blood stream infection in African American ventilated very-low-birth-weight infants.<sup>51</sup>

### IL-10

In addition to other IL-10 gene polymorphisms described in the literature, the single nucleotide promoter gene polymorphism at position -1082 (G to A) causes alterations in gene transcription,<sup>52</sup> leading to 3 levels of IL-10 expression: high (GG), intermediate (GA), and low producer (AA) genotype.<sup>18,52</sup> This polymorphism has been linked to susceptibility for clinical severity of meningococcal disease,<sup>53</sup> severity of community-

acquired pneumonia,<sup>54</sup> as well as with disease severity and mortality in AKI.<sup>55</sup> In ventilated very-low-birth-weight infants, the IL-10 -1082 A allele has been associated with an increased incidence of late blood stream infection,<sup>51</sup> but this polymorphism did not have a major influence on mortality or the development of bronchopulmonary dysplasia.<sup>56</sup> Children with the IL-10 -592 CC genotype as well as carriers of the -592 A-allele also have been shown to have a higher risk of hospitalization for respiratory syncytial virus than heterozygous carriers.<sup>57</sup>

### Chemokine Genes

Chemokines comprise a large and ever-increasing group of small chemotactic cytokines that can recruit leukocytes to sites of inflammation.<sup>58,59</sup> Chemokines also are expressed in renal tissue and thus may be important mediators of neutrophil and monocyte influx into renal tissue in response to systemic inflammatory conditions such as the SIRS or after renal ischemia-reperfusion.<sup>60</sup> Moreover, a host of chemokine genes are expressed to a high degree in renal tissue in experimental models of sepsis.<sup>61</sup> Genetic polymorphisms have been described for several chemokine genes and have been linked to acute inflammatory disorders.<sup>62-65</sup> Three single nucleotide polymorphisms, -28 (C to G), -403 (G to A), and intron 1.1 (T to C) in the RANTES gene, have been correlated with transcriptional activity, and with susceptibility to severe respiratory syncytial virus bronchiolitis in children.<sup>66</sup>

### Oxidative Stress-Related Genes

Neutrophil and endothelial cell-derived, cell membrane-bound reduced nicotinamide-adenine dinucleotide phosphate oxidases are involved in superoxide production and may play a role in the development of organ dysfunction caused by SIRS.<sup>67</sup> Neutrophil and monocyte-derived myeloperoxidase, involved in the synthesis of hypochlorous acid, may play a role in ischemia-reperfusion injury.<sup>68</sup> Antioxidant enzymes such as glutathione peroxidases<sup>69</sup> on the other hand inactivate hydrogen peroxide, lipid peroxides,<sup>70</sup> and peroxynitrite.<sup>71</sup> Superoxide dismutases are additional antioxidant enzymes

that inactivate superoxide anion.<sup>72,73</sup> The balance between pro-oxidative and anti-oxidative mechanisms plays an important and increasingly recognized role in the pathophysiology of AKI.<sup>67,74-77</sup>

The nicotinamide-adenine dinucleotide phosphate oxidase *p22phox* subunit +242 (C to T),<sup>78-80</sup> and the *catalase* -262 (C to T)<sup>81,82</sup> genetic polymorphisms have been characterized and in adults linked to organ injury,<sup>72</sup> and to adverse clinical outcomes in AKI.<sup>83</sup>

### GENE POLYMORPHISM-OUTCOME LINK IN MENINGOCOCCAL DISEASE

The featured case scenario describes a catastrophic course of a meningococcal infection, characterized by an overwhelming inflammatory response, profound and refractory hypotension and coagulopathy, followed by multiple organ dysfunction and failure. What is the evidence that would link this scenario to polymorphism of candidate genes? In fact, a host of clinical association studies exist that help address this question (Fig. 1).

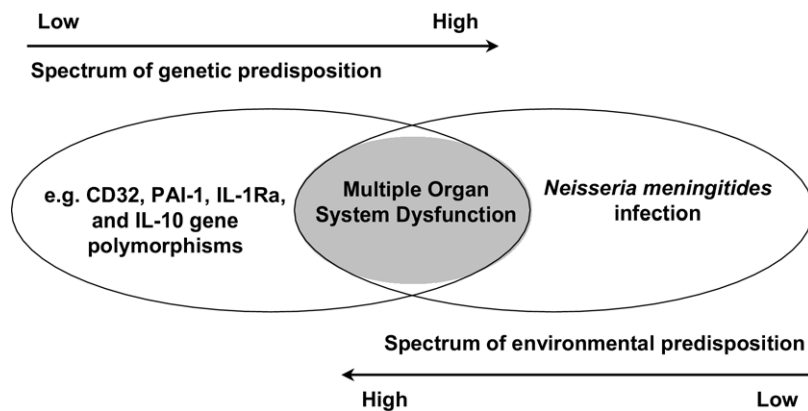
### Neutrophil Phagocytosis and Opsonization-Related Genes

Polymorphism H/R131 of the *Fc gamma RIIa* receptor or *CD32*, a receptor subtype for the Fc domain of IgG expressed on the cell surface of neutrophils, has been shown to decrease neutrophil phagocytotic activity of opsonized bacteria. Three case-control studies showed an association of the Fc gamma receptor subtype

RIIa-R/R131 with disease severity.<sup>84-86</sup> In addition, the genotypes *RIIIa-F/F158* and *RIIIb-NA2/2* were overrepresented in populations affected by the disease, suggesting an increased susceptibility.<sup>53</sup> On the other hand, one published report showed no association of this polymorphism with disease susceptibility or severity.<sup>87</sup> Two other genetic polymorphisms encoding proteins involved in opsonization, a splice site mutation in exon 10 (c.1487-2 A to G) in the *properdin* gene, and 3 promoter polymorphisms (-221Y/X, -550H/L, and +4P/Q) of *mannose binding lectin-2* were observed in a Danish family with a high incidence of meningococcal meningitis. The candidate gene variants cosegregated with biochemically confirmed deficiency in the gene products, and were associated with the development of meningitis in affected family members.<sup>88</sup> In addition, a functional (-496 C to T) single nucleotide polymorphism within the factor H gene was associated with increased factor H plasma levels, a known inhibitor of complement activation. The C allele was linked to an increased susceptibility for meningococcal infection.<sup>89</sup>

### Inhibition of Fibrinolysis Genes

A common functional insertion/deletion (4G/5G) polymorphism of the gene encoding plasminogen activator inhibitor-1 was identified as a candidate for the development of coagulopathy and organ dysfunction in meningococcal disease. The 4G/4G genotype was found to be associated with an increased plasma plasmino-



**Figure 1.** Multiple organ system dysfunction risk stratification in meningococcal infection. A model for genetic and environmental interaction. PAI-1, plasminogen activator inhibitor-1; IL-1Ra, IL-1 receptor antagonist.



gen activator inhibitor-1 level and clinical severity at the time of hospital admission as well as with mortality,<sup>90</sup> the development of septic shock,<sup>91,92</sup> and vascular complications owing to disseminated intravascular coagulation and mortality<sup>93,94</sup> in several independent multicenter European case-control studies in pediatric populations. One other candidate gene polymorphism affecting fibrinolysis is the Thr325Ile dimorphism of the thrombin-activatable fibrinolysis inhibitor gene, which showed an association with increased susceptibility to and mortality from meningococcal disease.<sup>95</sup>

### Cytokine Genes in Meningococcal Disease

Among the *IL-1* gene family, studies of variants in the *IL-1 $\beta$*  gene at position -511<sup>96</sup> as well as the *IL-1 receptor antagonist* +2018 C to T variant<sup>97</sup> were associated with mortality in meningococcal disease. One single-center study linked the D variant of an insertion deletion polymorphism of intron 6 of the angiotensin-converting enzyme gene to prolonged intensive care unit stay and intensive care unit mortality. However, potential concerns about the link between angiotensin-converting enzyme activity and modulation of acute inflammatory responses and referral bias of this study of critically ill pediatric patients was well acknowledged by the investigators.<sup>98</sup> In one study testing multiple inflammatory cytokine gene polymorphisms, the *IL-6* -174 GG and *IL-10* -1082 AA genotypes were associated with increased disease severity and mortality but only the *IL-1* receptor antagonist variable number of tandem repeat polymorphisms was linked to increased susceptibility to meningococcal infection.<sup>99</sup>

### LIMITATIONS OF THE SINGLE CANDIDATE GENE APPROACH

The candidate gene approach typically includes testing for a statistical association of a candidate genetic marker with a specific clinical manifestation in a case-control setting. The risk of generating a false-positive result in such a setting is high, especially if the study design includes a small sample size, a lack of physiologic plausi-

bility, patient selection or recruitment from a single geographic region leading to lack of diversity.<sup>100</sup> If a genetic marker is tested as a predictor of mortality, the frequency of the most pertinent genetic risk markers may be altered by survival bias in a cross-sectional case-control design and prospective cohort studies should be preferred in that setting.<sup>101</sup> Linkage disequilibrium of the tested candidate gene polymorphism with another perhaps unidentified but causal polymorphism also could lead to false conclusions.<sup>102</sup> Finally, it is important to stress that extreme contradictory estimates in relatively small genetic association studies are not uncommon, in particular, early during the accumulation of the scientific evidence.<sup>103</sup>

Clinical studies of genetic polymorphism should therefore follow strict quality criteria and should include a plausible hypothesis with an a priori definition of the beneficial or harmful phenotypes to be observed, the functional significance of the gene polymorphism documented by altered expression of the gene product in in-vitro or in animal models, and a large enough study sample.<sup>104</sup> Good quality genetic association studies also should be designed prospectively, include an appropriate control group, and allow for correction of potential confounders. The genotype-phenotype association should be strong and specific to a predefined clinical effect, and ideally show a biological gradient or gene-dose effect. Finally, the results of genetic association studies also should be reproducible in additional distinct populations.

### FUTURE DIRECTIONS

Increasing success in the discovery of genetic risk markers and susceptibility factors may aid in the development of novel risk-stratification models that include genetic markers. Genetic susceptibility/risk markers are characterized by their stability over time and independence of gene product expression, in contrast to physiologic assessments and protein biomarkers, which could be expressed in situ and not be amenable to measurement in biological fluids such as serum or urine. Such novel risk-stratification tools may be superior to the current tools that include clinical and basic laboratory

results. However, the application of such models will be of limited clinical value without concrete therapeutic options that, if instituted early in the course of sepsis or other conditions predisposing to AKI or MODS, have the potential to alter the course of the disease.<sup>105,106</sup> Future genetic risk-stratification tools could estimate the predisposition of individuals to common complications of diagnostic or therapeutic procedures and, more speculatively, assist in the molecular design of therapeutic drugs, so-called *custom drugs*, specifically designed to optimize individualized patient care.<sup>107</sup> One example of such an approach could be gene therapy techniques that block injurious responses with, for example, anti-sense oligonucleotides.

Expanding the knowledge of polymorphism of immune-response genes may aid in the identification of individuals susceptible to acute inflammatory or infectious disorders such as the development of sepsis and MODS after trauma, burns, or systemic infections. The identification of potential genetic risk markers not only may facilitate the identification of at-risk individuals, but also allow for a more guided therapeutic approach to attenuate key pathophysiologic mechanisms and pathways that lead to organ dysfunction and adverse clinical outcomes in these conditions.

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