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11

Down Syndrome and Periodontal Disease

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1. Introduction

Periodontal diseases are inflammatory diseases of the supporting structures of the teeth (Cochran, 2008; Kornman, 2008). They are initiated by periodontopathic bacteria and result in progressive destruction and loss of the periodontium (Cochran, 2008; Kornman, 2008). Progression of periodontal disease eventually leads to tooth loss (Chambrone, et al., 2010). Periodontal diseases are multifactorial with complex pathogenesis (Cochran, 2008; Kornman, 2008).

Plaque bacteria trigger a host inflammatory response in the gingival tissues (Kornman, 2008). Neutrophils migrate from within the gingival tissues towards the gingival crevice and build a barrier wall against the bacteria (Kornman, 2008). Within the gingival connective tissue, the gingival macrophages and fibroblasts produce inflammatory cytokines (e.g. interleukin-1 and tumor necrosis factor- alpha) that activate collagenases and other degrading enzymes (Kornman, 2008). These enzymes when released and activated destroy the gingival collagen. Lymphocytes are recruited to the gingival lesion to initiate an adaptive immune response and help with containing the infection (Kornman, 2008). With persistence of the microbial infection, the inflammatory changes in the gingival tissues expand apically and reach the alveolar bone (Cochran, 2008). Inflammatory mediators such as interleukin-1, interleukin-6, tumor necrosis factor alpha and prostaglandins induce osteoclasogenesis (Cochran, 2008). Increased inflammatory activity disrupts the normal balance of bone formation/resorption and results in alveolar bone loss (Cochran, 2008).

Periodontal disease is a serious and morbid oral condition among Down-syndrome (DS) affected individuals (Morgan, 2007). Gingivitis and periodontitis start early in life and their severity increases with age (Reuland-Bosma, et al., 1988). Periodontal disease advances rapidly in DS individuals and is characterized by severe gingival inflammation, loss of periodontal attachment and radiographic alveolar bone loss (Agholme, et al., 1999; Saxen, et al., 1977). Heavy amounts of plaque and calculus are often present (Morgan, 2007). Periodontal disease is an important cause of tooth loss among DS individuals (Reuland-Bosma, et al., 2001).

The exact reason (or reasons) for this increased susceptibility to periodontitis is (are) not known. Understanding the pathogenesis of periodontitis in DS individuals would greatly help with the management and control of the destructive process associated with the disease and help DS affected individuals retain their teeth hopefully throughout their lifetime.

Previously researchers have investigated factors usually associated with periodontitis such as subgingival plaque microbial composition, immune and inflammatory responses *individually* in DS affected individuals. The individual factors investigated were never collectively evaluated together to provide an overall understanding of the pathogenesis of periodontitis in

individuals with DS. The objective of this chapter is to review in a systematic fashion all the involved factors previously reported *together* to generate a hypothetical collective model of the pathogenesis of periodontal disease in individuals with DS. Such a model would enhance our understanding of periodontal disease development/progression in this vulnerable group, would help with disease management, would identify gaps in knowledge, and would provide enlightenment for future research endeavors.

In this review I have searched the available dental/medical literature for studies investigating the main factors suspected in the increased susceptibility to periodontitis in DS individuals. I have summarized the main findings from these studies and used this information to generate a hypothetical model of the pathogenesis of periodontitis in DS individuals.

2. Methods

The methodology applied in this review covers the literature search strategy, inclusion and exclusion criteria for choosing articles, screening of articles and quality assessment of the selected articles.

2.1 Search strategy

Electronic searching was performed using the following databases: MEDLINE (1948-2011) and PubMed. The search terms that were used related to the subject groups of interest: Down syndrome and mental retardation; the oral condition: gingivitis, periodontitis, periodontal disease, gingiva, periodontium, tooth loss; etiological factors: microbiological (dental plaque, subgingival plaque, periodontopathic bacteria), immune factors (neutrophils, lymphocytes, antibody production) and inflammatory factors (cytokines, prostaglandins, metalloproteinases) and the type of study: comparative study, randomized controlled trial, or review. The search was limited to English language literature. The electronic search was supplemented by checking bibliographies of review papers. One hundred forty five articles were initially identified.

2.2 Inclusion criteria

Studies were included if they met the following minimum criteria:

1. Human subjects with Down syndrome.
2. Clinical measures of periodontal status.
3. Microbiological, immune or inflammatory measures.
4. Comparison of DS subjects to a control/comparison group(s).
5. Written in English.

2.3 Exclusion criteria

Editorial letters, historical reviews and descriptive studies such as case reports were excluded. In addition, studies that did not specifically address the main focus of the search or duplicated other studies were also excluded.

2.4 Screening and selection of papers

At first the articles were screened by title and abstract. A review of abstracts based on the criteria above led to initial consideration of 32 articles. Then full text was retrieved either

electronically or in printed format. Further review of full texts resulted in inclusion of 20 articles.

2.5 Quality assessment

Systematic reviews need to assess the methodological *quality* of the included studies (Pai, et al., 2004). Quality within the context of this chapter refers to the minimization of bias. An objective of this assessment was to judge the strength of the scientific evidence with higher score given to studies free of bias. To minimize bias, the comparison group needs to be matched as close as possible to the DS group. In addition, the evaluated parameters should be assessed in the same manner between the groups. Studies with an adequately matched control group were scored higher than studies that used population data or previously collected data for comparison.

The instrument used for judging articles for this chapter was based freely on the use of STROBE methodology (von Elm, et al., 2007) evaluating the following parameters:

- Down syndrome diagnosis: clearly stated and explained.
- Inclusion of a comparison group: well matched (age, gender, race) or not.
- Periodontal parameters: how periodontitis was defined and measured. Adequate if clinical attachment level was reported. Inadequate when only periodontal probing depth or radiographic measurements are reported.
- Laboratory methodology to assess microbial, immune or inflammatory factors: was the methodology clearly explained. Was the methodology appropriate or not.
- Examiner calibration: adequate if reported, inadequate if not reported.
- Descriptive information: characteristics of study participants (number of subjects, gender, mean and range of age) were clearly presented.
- Confounders identified: confounders that may affect periodontal status such as age, gender, and plaque levels were clearly defined.
- Data analysis: adequate when multivariate analysis adjusting for confounders was presented. Inadequate if only bivariate analysis was presented.

The studies included in the review were scored as follows:

- Score 1: when all the parameters presented above were reported in the study.
- Score 2: when only DS diagnosis, inclusion of a comparison group, clinical periodontal measures and laboratory measures were reported.
- Score 3: other than score 1 and 2.

3. Results

A total of 20 articles were selected, 5 articles related to microbiological evaluations, 3 articles related to neutrophil function, 3 articles related to gingival cellular immunity, 4 articles related to antibody production and 5 articles related to degrading enzymes and inflammatory mediators. All selected articles met the minimum inclusion criteria previously described. Two articles were scored as 1, fifteen articles were scored as 2 and three articles were scored as 3.

Nineteen out of the twenty selected studies were designed as cross-sectional case-controlled studies. Thus in addition to the DS group, they included a matched comparison group of either medically healthy and periodontally healthy individuals or a comparison group with mental disability other than DS. One study was longitudinal (Zaldivar-Chiapa, et al., 2005).

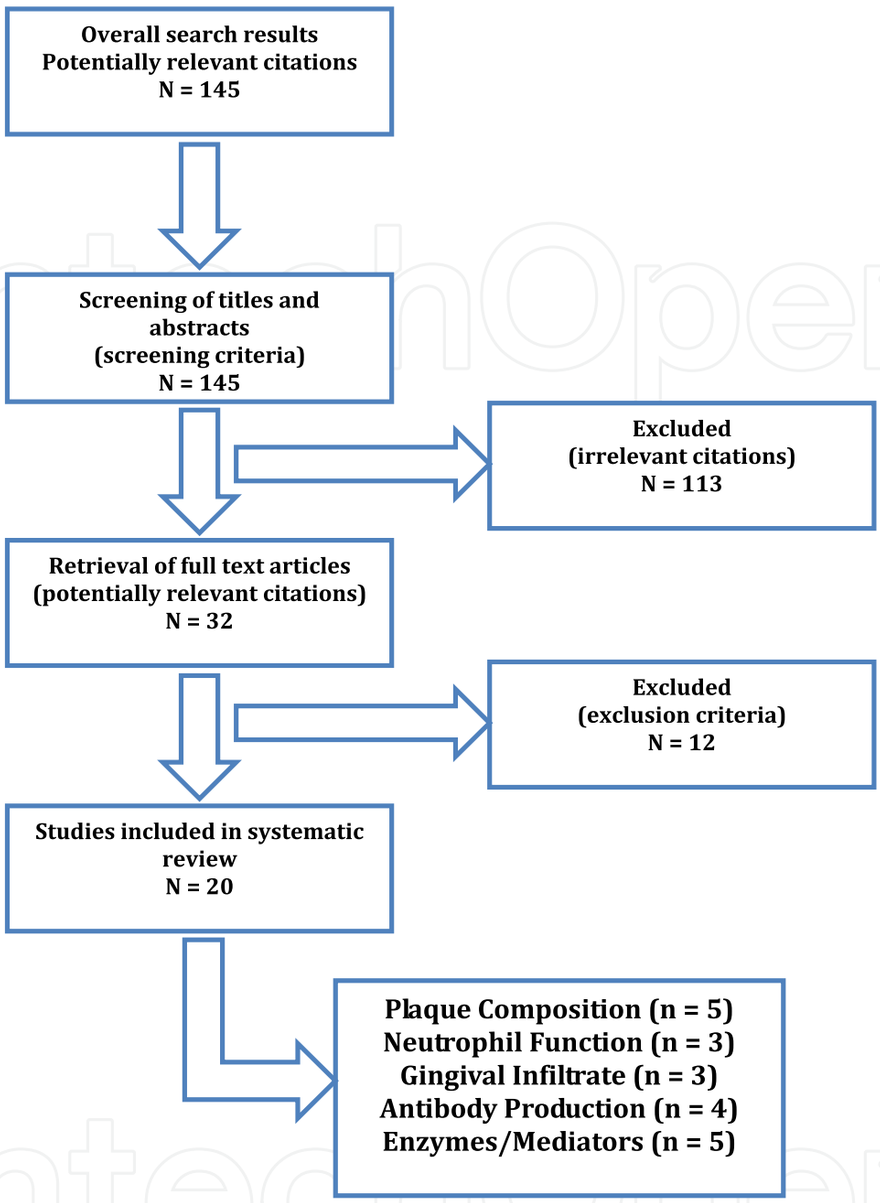


Fig. 1. Summary of search strategy.

Down subjects in most of the studies were either children or young adults. Few of the selected studies included DS adults (Amano, et al., 2001; Chaushu, et al., 2007; Komatsu, et al., 2001; Sakellari, et al., 2005; Sohoel, et al., 1995).

3.1 Summary of study methodologies

Microbiology studies employed a variety of techniques including culturing, polymerase chain reaction and checkerboard DND-DNA hybridization techniques to investigate the composition of subgingival plaque. All the studies attempted to compare the subgingival plaque composition of DS individuals to a matched comparison group. In addition some studies attempted to determine at what age important periodontopathic bacteria become

detectable in DS individuals. A few studies attempted to investigate the association between presence of periodontopathic bacteria and clinical periodontal parameters in DS individuals. Neutrophil function studies mainly focused on neutrophil chemotaxis. Neutrophil chemotaxis was measured by the Boyden chamber method. All selected studies compared neutrophil chemotaxis of DS individuals to a matched comparison group. One of the studies investigated the relation between neutrophil chemotaxis measures with clinical and radiographic periodontal measures.

Gingival cellular immunity studies examined the immune cellular composition, expression of HLA Class II antigens on the surfaces of immune cells and gamma/delta T-cell receptor-bearing lymphocytes in discarded gingival tissues from DS individuals. Indirect immunofluorescent techniques were used to examine the gingival tissues. All the selected studies compared the gingival tissue cellular findings in DS individuals to medically and periodontally healthy individuals.

The selected antibody production studies focused on specific antibodies against some important periodontopathic bacteria. The studies examined either serum antibody titers or salivary antibody levels. All selected studies used an enzyme-linked immunosorbent assay (ELISA). Four of the selected studies compared the antibody serum titer or saliva levels in DS individuals to matched controls. One study made the comparison to a normal adult reference serum pool.

The selected studies investigating degrading enzymes and inflammatory mediators mainly focused on matrix metalloproteinases (MMP) activity in gingival fluid. One study examined cultured fibroblast MMP activity. Two studies examined prostaglandin E2 (PGE2) and one study examined interleukin-1 (IL-1) in gingival fluid. All selected studies compared their findings in DS individuals with non-DS controls. MMP activity was assessed with a variety of techniques including gel electrophoresis, Western blot analysis and ELISA. PGE2 was assessed with a radio-immuno-assay and IL-1 with ELISA.

3.2 Summary of study findings

A summary of all selected articles and their main findings is presented in the following tables:

3.2.1 Subgingival plaque composition studies

Author	Scr.	DS	CG	Measures	Findings
Barr-Agholme 1992	2	37	37	Levels of *Aggregatibacter (Actinobacillus) actinomycetemcomitans*, *Capnocytophaga* and *Porphyromonas gingivalis* were determined in subgingival plaque samples.	*A. actinomycetemcomitans* was detected in the subgingival plaque in 35% of the DS adolescents and in 5% of the controls. On site level, *A. actinomycetemcomitans* and *Capnocytophaga* were more frequent in the subgingival plaque samples of DS children than in those of controls.

Author	Scr.	DS	CG	Measures	Findings
Amano 2000	2	60 Yng.	60	Ten periodontal pathogens were surveyed in subgingival plaque samples using a polymerase chain reaction.	All of the pathogens were detected with greater frequency in the DS children. *Tannerella forsythia* (*Bacteroides forsythus*), *Treponema denticola, Prevotella nigrescens,* and *Campylobacter rectus* were significantly prevalent throughout all age brackets of the DS children. The occurrence of *Porphyromonas gingivalis* was also significant in the DS subjects over 5 years old.
Amano 2001	2	67 Adt.	41	Ten periodontal pathogens were surveyed in subgingival plaque samples using a polymerase chain reaction.	No significant differences were observed in the bacterial profiles between the two groups.
Sakellari 2005	1	70	121 NC 76 MR	Clinical parameters and microbiological analysis by "checkerboard" DNA-DNA hybridization.	Important periodontal pathogens including *Porphyromonas gingivalis*, *Tannerella forsythia* (*Bacteroides forsythus*) and *A. actinomycetemcomitans* colonize these subjects earlier and at higher levels.
Reuland-Bosma 2001	2	17	17	Prevalence and proportions of the putative periodontal pathogens *A. actinomycetemcomitans, Porphyromonas gingivalis, Prevotella intermedia, Tannerella forsythia (Bacteroides forsythus), Peptostreptococcus micros, Fusobacterium nucleatum* and *Campylobacter rectus* in the subgingival plaque were determined using anaerobic culture techniques.	No differences in the prevalence of distinct suspected periodontopathic bacteria and bacterial subgingival composition between the DS group and the comparison group could be established.

Scr = score, DS = number of DS group, CG = number of comparison group, Yng = young, Adt = adult, NC = normal controls, MR = mental retardation not Down.

Table 1. Summarizes the findings of the subgingival plaque composition studies.

3.2.2 Neutrophil function studies

Author	Scr.	DS	CG	Measures	Findings
Izumi 1989	2	14	14	Periodontal clinical measures, radiographic measures and neutrophil chemotaxis.	DS patients showed significantly lower chemotaxis than healthy volunteers. Bone loss in DS subjects was inversely proportional to the chemotactic index.
Yavuzyilm-az 1993	2	15	15	Clinical periodontal parameters, chemotaxis and random migration of neutrophils.	The random migration and chemotaxis of neutrophils from DS subjects were significantly decreased in comparison with the control group.
Zaldivar-Chiapa 2005 Longitudinal	2	14	9	Clinical parameters and neutrophil function.	Neutrophil chemotaxis, phagocytic activity, and production of super-oxide anion were significantly decreased in the DS patients.

Scr = score, DS = number of DS group, CG = number of comparison group.

Table 2. Summarizes the neutrophil function studies.

3.2.3 Gingival immune response studies

Author	Scr.	DS	CG	Measures	Findings
Sohoel 1992	3	16	12	Indirect immune-fluorescence used to study immune cellular composition of gingival tissues from DS individuals.	Denser inflammatory infiltrate in DS individuals. Counting showed different cell distribution and cell profiles between DS subjects and non-DS subjects.
Sohoel 1995	3	16	14	Expression of HLA Class II antigens on the surfaces of immune cells.	Increased frequency of HLA Class II (HLA-expression on inflammatory cells and on keratinocytes of the oral gingival epithelium) in chronic periodontitis of DS patients compared to sections from non-DS subjects.
Sohoel 1995	3	NR	NR	Assessment of Gamma/delta T-cell receptor-bearing lymphocytes in gingival tissues.	Gamma/delta T-cell receptor-bearing lymphocytes are decreased in inflamed gingival tissues of DS individuals.

Scr = score, DS = number of DS group, CG = number of comparison group, NR = not reported.

Table 3. Summarizes the gingival immune cellular response studies.

3.2.4 Antibody production studies

Author	Scr.	DS	CG	Measures	Findings
Santos 1996	2	16	10	Circulating antibody titers to *A. actinomycetemcomitans*.	Significant differences were noted between the control group and the DS subjects (p = 0.05), with the DS periodontitis group having the highest response, followed by the DS gingivitis group and normal controls, respectively. The DS groups were not significantly different.
Morinushi 1997	3	75	RSP	Antibody titers to *Porphyromonas gingivalis (Pg), Prevotella intermedia (Pi), Treponema denticola (Td), Fusobacterium nucleatum (Fn), Selenomonas sputigena (Sel), A. actinomycetemcomitans (Aa),* and *Streptococcus mitis (Mi).*	IgG antibody titers to *Pg, Aa, Sel*, and *Mi* increased significantly with increasing gingival inflammtion score. Furthermore, the IgG antibody titers to *Pg* were higher ($P < 0.05$) in the most extensive disease group compared to the DS no-disease group. The IgG antibody titers to *Pg* at early puberty were significantly higher when compared to preschool children.
Barr-Agholme 1998	2	20	19	Salivary levels of immunoglobulins sIgA, IgM, and IgG subclass distribution and albumin, quantified by enzyme-linked immunosorbent assay.	The immunoglobulin levels of sIgA, IgM, the sum of IgG subclasses, and the concentration of albumin did not differ significantly between the 2 groups. However, the proportion of IgG1 expressed as percentage of the sum of total IgG was significantly higher ($P < 0.01$) in the Down syndrome group compared to controls. On the contrary, the proportion of IgG2, IgG3, and IgG4 subclasses in saliva did not differ between the 2 groups.
Chaushu 2007	2	40	39	The levels of total IgA, and specific antibodies to three common oral pathogens (*Porphyromonas gingivalis, Actinobacillus (Aggregatibacter) actinomycetemcomitans* and *Streptococcus mutans*) were analyzed.	The median secretion rates of the specific antibodies in whole and parotid saliva were 70-77% and 34-60% (respectively) lower in young DS individuals as compared to young controls and farther 77-100% and 75-88% (respectively) lower in old DS compared to young DS.

Scr = score, DS = number of DS group, CG = number of comparison group, RSP = reference serum pool.

Table 4. Summarizes the antibody production studies.

3.2.5 Inflammatory mediator studies

Author	Scr.	DS	CG	Measures	Findings
Halinen 1996	2	9	9	Clinical periodontal measures and matrix metalloproteinase (MMP-8 and -9) activities in saliva and in gingival crevicular fluid.	The endogenously active collagenase and total collagenase activities were slightly higher in GCF of DS children compared to healthy controls. GCF collagenase of DS patients was human neutrophil collagenase (MMP-8 or collagenase-2), in DS patients, but not in controls. Salivary collagenase in DS was high when compared to controls but of the same MMP-8 type as in control saliva.
Barr-Agholme 1997	2	15	15	Levels of prostaglandin E2 (PGE2) and interleukin-1 beta (IL-1 beta) were determined in gingival crevicular fluid.	The mean level of PGE2 in GCF was significantly higher ($P < 0.05$) in the Down syndrome group than in the control group. In GCF samples collected from sites characterized as non-inflamed, the mean level of PGE2 was significantly higher ($P < 0.001$) in the Down syndrome group than in the controls. The mean level of PGE2 in samples from inflamed sites, on the other hand, did not differ between the two groups. The mean level of IL-1 beta was not significantly higher in the Down syndrome group than in the controls.
Komatsu 2001	2	9	9	Enzyme activity and the mRNA expression pattern of matrix metalloproteinases (MMPs) of cultured gingival fibroblasts (GF) and fresh gingival tissues.	The production of the active type of MMP-2 in GF from Down's syndrome patients (D-GF) was found to be significantly higher ($P < 0.05$) than that of the control GF (C-GF) at the protein level.
Tsilingaridis 2003	2	18	14	Levels of prostaglandin E2 (PGE2), leukotriene B4 (LTB4), and matrix metalloproteinase-9 (MMP-9) in gingival crevicular fluid.	The mean levels of PGE2, LTB4, and MMP-9 were significantly ($P<0.05$) higher in GCF from Down syndrome patients compared to controls.
Yamazaki-Kubota 2010	1	14	14	Matrix metalloproteinase (MMP-8 and MMP-2) activity in gingival crevicular fluid.	Levels of MMP-2 and MMP-8 in Down's syndrome patients were higher than those in healthy control subjects.

Scr = score, DS = number of DS group, CG = number of comparison group.

Table 5. Summarizes the inflammatory mediator studies.

4. Discussion

Periodontal disease is a common problem among DS individuals with an estimated prevalence between 58% and 96% for those under 35 years of age (Morgan, 2007). The disease starts early in life and progresses with age eventually leading to tooth loss (Reuland-Bosma, et al., 2001; Saxen, et al., 1977; Saxen & Aula, 1982). Periodontal disease in DS individuals adversely impacts on the quality of their life (Amaral Loureiro, et al., 2007). The increased prevalence and severity of periodontal disease in DS individuals inspired many researchers to investigate the various factors that might be involved.

Periodontal diseases are initiated by bacterial plaque build-up in the dentogingival region (Kornman, 2008). It is well documented that DS individuals have difficulty with maintaining adequate oral hygiene levels and thus tend to harbor high levels of bacterial plaque on their teeth (Cohen, et al., 1961; Khocht, et al., 2010; Sakellari, et al., 2005). In addition, DS individuals following oral hygiene instructions have reduced ability to master adequate plaque control (Sakellari, et al., 2001). It was often surmised that mental disability associated with DS is an important factor in their reduced ability to maintain adequate oral hygiene and consequently increases their susceptibility to periodontitis (Desai, 1997; Morgan, 2007). Our group (Khocht, et al., 2010) recently showed in a multivariate model including traditional risk factors for periodontitis combined with mental disability that loss of periodontal attachment in DS individuals was not associated with mental disability. Thus other factors associated with DS might be involved.

It is well documented that DS is associated with immune deficiencies and host response impairment (Kusters, et al., 2009; Reuland-Bosma, et al., 1988). Infections, in particular respiratory infections are an important cause of death in DS individuals (Thase, 1982). The most likely reason for this increased susceptibility to infection and reduced immunity in DS individuals is an increased dosage of a protein product or products encoded by chromosome 21. Several proteins important in immune function are encoded on chromosome 21. Examples include superoxide dismutase (SOD), carbonyl reductase (NADPH) (Lemieux, et al., 1993) and integrin beta-2 (CD18). Increased SOD and NADPH production is associated with increased oxidative stress and tissue injury in DS individuals (Akinci, et al., 2010; Strydom, et al., 2009). Aberrant expression of CD18 integrin on immune cell surfaces in DS individuals may be associated with altered lymphocyte function (Kusters, et al., 2009; Taylor, 1987). The IL10RB component of the IL-10 receptor (involved with resolution of inflammation) is encoded by chromosome 21 and its function may be altered in DS individuals (Glocker, et al., 2009). In addition, it seems that interleukin-1 (IL-1) is upregulated indirectly by some chromosome 21 based genes (Mrak & Griffin, 2004). IL-1 is an important immune/inflammatory mediator. Its increased production in DS individuals was associated with brain tissue damage (Mrak & Griffin, 2004).

Since periodontitis is initiated by bacterial infections, indeed it is conceivable that altered immunity in DS individuals may be the primary reason for their increased susceptibility to periodontal infections. Perhaps reduced immunity in DS individuals would make it easier for virulent periodontopathic microbial species to colonize their subgingival plaque. If true, such elevated microbial presence, unchallenged and unchecked, would induce an intense inflammatory reaction within the gingival tissues. Increased gingival inflammation within the gingival tissues would lead to elevated production of degrading enzymes and alter bone remodeling. The end result of these inflammatory induced changes would be the loss and destruction of the periodontium and eventually tooth loss. Several studies (microbiological, immune and inflammatory) attempted to investigate these hypotheses.

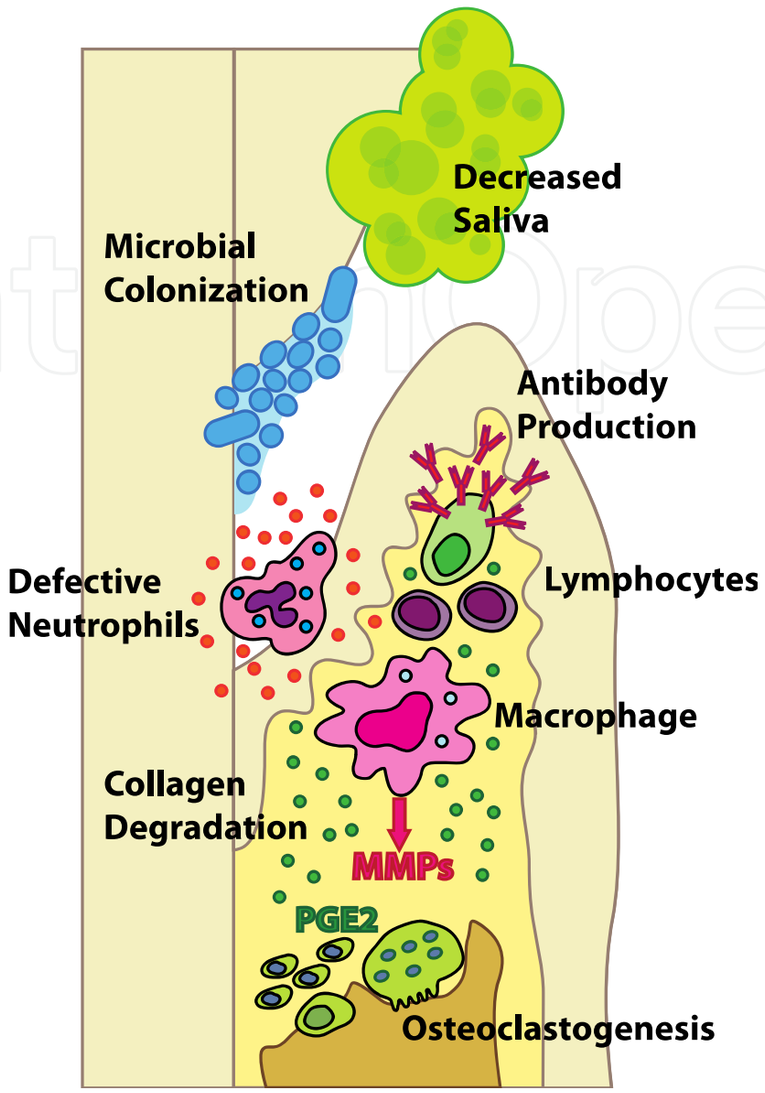


Fig. 2. The above schematic illustrates the main findings of the selected articles. Decreased salivary flow and associated decreased salivary antibody production. Neutrophils with defective chemotaxis incapable of reaching the target pathogens. Early colonization of the dentogingival region with periodntopathic bacteria. Gingival marginal tissues heavily infiltrated with immune cells such as macrophages and lymphocytes. Antigen presenting cells active in processing and presenting microbial antigens. Robust humoral antibody production. Macrophages and other gingival cells engaged in producing degrading enzymes (MMPs). Collagen degradation. Tissue injury and release of prostaglandins (PGE2). Increased osteoclastic activity and alveolar bone loss.

4.1 Microbiological studies

Barr-Agholme et al. (1992) reported increased presence of *Aggregatibacter* (*Actinobacillus*) *actinomycetemcomitans, Capnocytophaga and Porphyromonas gingivalis* in subgingival plaque of *adolescents* with DS. *A. Actinomycetemcomitans* was detected in 35% of patients with DS compared to 5% in the healthy, age and sex matched controls. The authors suggested that

this increased frequency of *A. actinomycetemcomitans* indicated an altered microbial composition in the subgingival plaque of DS patients as compared to healthy controls.

Amano et al. (2000) found various periodontal disease-causing bacteria present in *very young* DS patients. The authors reported that various periodontopathic bacteria could colonize the teeth in the very early childhood of DS patients. Pathogens in DS patient's subgingival plaque were detected with far greater frequency than in the age-matched controls. This may be the reason why these DS patients have such intense gingival inflammation. The authors concluded that periodontopathic pathogens establish a presence at a very early age, and that certain bacteria, like *P. gingivalis*, play a key role in the initiation of gingival inflammation.

Sakellari et al. (2005) evaluated seventy DS patients, 121 age-matched healthy individuals and 76 patients with cerebral palsy. Full-mouth recordings of clinical periodontal parameters were assessed and subgingival plaque samples were taken from the Ramfjord teeth and analysed for 14 species using "checkerboard" DNA-DNA hybridization. They reported that important periodontal pathogens colonize these subjects earlier and at higher levels compared with age-matched healthy individuals and patients with cerebral palsy.

Reuland-Bosma et al. (2001) compared subgingival microflora in DS adult patients to other mentally retarded individuals. Despite advanced periodontitis in DS patients, no differences in the prevalence of distinct suspected periodontopathic bacteria were established between the DS patients and the control group. The authors concluded that host factors are the most likely explanation for the advanced periodontal disease associated with DS patients.

Amano et al. (2001) took subgingival plaque specimens from 67 DS young adults and 41 age-matched systemically healthy individuals with mental disabilities (MD). The prevalence of *Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis, Bacteroides forsythus, Treponema denticola, Prevotella intermedia, Prevotella nigrescens, Capnocytophaga ochracea, Capnocytophaga sputigena, Campylobacter rectus, and Eikenella corrodens,* were investigated in subgingival plaque samples using a polymerase chain reaction method. The authors found no significant differences in the bacterial profiles between the groups.

The cited microbiological studies indicate early colonization of important periodontal pathogens in children and adolescents with DS. However, the microbial subgingival profile of *adult* DS individuals is not different from matched non-DS individuals. Perhaps reduced immunity in young DS individuals facilitates early colonization in comparison to young non-DS individuals with normal immunity. With age, and a combination of long-term exposure to pathogens and changes in immune response, non-DS individuals may also be susceptible to colonization by periodontal pathogens. However, despite lack of differences in microbial profiles between adult DS and non-DS individuals, adult DS individuals still show greater loss of periodontal attachment (Amano, et al., 2001; Reuland-Bosma, et al., 2001). This suggests that the host response to the same bacteria is different between DS and non-DS individuals. It seems that the immune-inflammatory response in DS is more intense resulting in greater tissue damage. The following studies will investigate this claim.

4.2 Immune dysfunction studies

As we said earlier, DS is associated with immune dysfunction (Kusters, et al., 2009). Various studies investigated different components of the immune system in relation to periodontitis in DS patients. These studies mainly focused on neutrophil function, the gingival immune cellular response and antibody production against periodontopathic bacteria.

4.2.1 Neutrophil function studies

Izumi et al. (1989) found a faulty neutrophil chemotaxis in DS patients. The authors reported that DS patients had significantly lower chemotaxis compared to healthy controls. Since the neutrophils are the main cells involved in the first line of host defense in a bacterial invasion, having a defective neutrophil chemotaxis can lead to the progression of periodontitis. Significant correlations were identified between the amount of bone loss and the age and chemotactic index of the DS patients. The authors found that the rate of periodontal destruction was dependent on the degree of defective chemotaxis.

Yavuzyilmaz et al. (1993) evaluated clinical parameters, chemotaxis and random migration of neutrophils in 15 patients with DS and 15 healthy subjects. Signs of more severe gingival inflammation were present in the DS group. The random migration and chemotaxis of neutrophils were significantly decreased in comparison with the control group.

Zaldivar-Chiapa (2005) examined patients with DS to evaluate the effectiveness of surgical and non-surgical periodontal therapies and to assess their neutrophil immunological status. The population consisted of 14 DS patients, 14 to 30 years old. Surgical and non-surgical periodontal therapies were compared in a split-mouth design. Clinical periodontal parameters were recorded at baseline, post-treatment, 6 months, and 1 year. Neutrophil chemotaxis, phagocytic activity, and production of super-oxide anion were compared between DS patients and healthy controls. Both surgical and non-surgical therapies showed a significant improvement in all the clinical parameters compared to baseline. Neutrophil chemotaxis, phagocytic activity, and production of super-oxide anion were significantly decreased in the DS patients. The authors concluded that the neutrophil impairment does not seem to affect the clinical response to therapy.

All the presented studies showed deficient neutrophil chemotaxis in DS subjects. The reason for impaired neutrophil chemotaxis in DS individuals may be secondary to increased oxidative stress associated with trisomy of chromosome 21 (Akinci, et al., 2010). Oxidative stress may impair internal cell function and disrupt chemotaxis. One study positively correlated such reduced chemotaxis with measures of periodontitis (Izumi, et al., 1989). Another study gave hope that despite reduced neutrophil chemotaxis, periodontal therapy aiming at reducing plaque and correcting periodontal architecture is still helpful (Zaldivar-Chiapa, et al., 2005).

4.2.2 Gingival Immune cellular response

Sohoel et al. (1992) examined the composition of mononuclear cells in the gingival inflammatory infiltrate in DS patients with marginal periodontitis. The authors reported that DS patients had a higher number of cells in the cellular infiltrate of chronic marginal periodontitis (CMP) compared to normal patients. There were also an increased number of CD22+ cells (B lymphocytes), CD3+ cells, CD4+ cells, CD8+ cells, and CD11+ cells (macrophages). There was also a significantly higher CD4+/CD8+ ratio in DS patients when compared to the normal controls, which could indicate active tissue destruction. This study concluded that DS patients have a more pronounced and altered gingival cellular immune response when compare to controls.

Sohoel et al. (1995) investigated the expression of HLA class II antigens in chronic marginal periodontitis (CMP) in patients with DS. Variations in the expression of HLA class II antigens on antigen-presenting cells play an important role in immune regulation. The results of this study indicated an increased frequency of HLA class II antigens in the

gingival tissues of CMP DS patients when compared to controls. There were significantly higher numbers of CD1a+ cells and ratios of HLA-DR+/CD1a+ cells and HLA-DP+/CD1a+ cells in the DS group compared to the control group. The authors concluded that there is a highly activated immune response in DS patients.

The same investigators (Sohoel, et al., 1995) also investigated gamma/delta T lymphocytes in gingival tissues of DS individuals. The T-cell receptor (TCR) of gamma/delta T lymphocytes is different from the alpha/beta TCR. The gamma/delta TCR binds to antigens that are intact proteins and antigens that are not presented within class I or class II histocompatibility molecules. The gamma/delta T lymphocytes usually reside within epithelial tissues and encounter antigens on the surface of epithelial cells. The researchers reported that the percentage of gamma/delta T lymphocytes in the gingival tissues of DS subjects was less than 1%.

The presented studies showed an intense presence of a variety of immune cells within the gingival tissues of DS patients with periodontitis. Increased production of HLA class II antigens on the surfaces of antigen producing cells suggests that the cells are locally engaged in specific immune responses. The low presence of gamma/delta T lymphocytes may increase the vulnerability to microbial noxious agents.

4.2.3 Antibody/immunoglobulin production

These studies investigated specific antibodies against periodontopathic bacteria in serum and saliva.

Santos et al. (1996) determined the circulating antibody titers to *Aggregatibacter (Actinobacillus) actinomycetemcomitans (Aa)* in sera of DS and normal patients. Eleven DS patients with periodontitis (pocket depth > 4 mm), five DS patients with gingivitis (inflammation and pocket depth < or = 3 mm), and 10 non-DS healthy subjects had blood drawn and analyzed for antibody response to *Aa*. The authors noted significant differences between the control group and the DS groups ($p = 0.05$), with the DS periodontal group having the highest response, followed by the DS gingivitis and normal controls, respectively.

Morinushi et al. (1997) obtained sera from 75 DS subjects (aged 2 to 18 years) and their gingival health assessed using a modified gingival inflammation index (PMA Index). Antibody titers to *Porphyromonas gingivalis, Prevotella intermedia, Treponema denticola, Fusobacterium nucleatum, Selenomonas sputigena, Actinobacillus actinomycetemcomitans, and Streptococcus mitis* were determined using a micro-ELISA. The average antibody titers to *A. actinomycetemcomitans, S. mitis*, and *F. nucleatum* exceeded those of the normal adult reference serum pool. In addition, IgG antibody titers to *P. gingivalis , A actinomycetemcomitans, F. nucleatum, S. sputigena*, and *S. mitis* correlated significantly with the modified PMA scores.

Barr-Agholme et al. (1998) investigated the clinical periodontal conditions and salivary immunoglobulins in patients with DS. The results showed an altered distribution of IgG subclasses in saliva, with an increased amount of IgG1 in DS patients compared to controls. This is in agreement with other studies that show increased IgG1 in DS patients (Kusters, et al., 2009). On the contrary, the proportion of IgG2, IgG3, and IgG4 subclasses in saliva did not differ between the 2 groups. Also, in DS patients with bone loss, it was noted that they have an increased level of sIgA, compared to those DS patients without bone loss.

Chaushu et al. (2007) assessed age-related changes in the salivary-specific humoral immunity of DS subjects. Parotid and whole saliva were collected from a young group of DS, an older group of DS individuals and compared to two age-matched groups of healthy volunteers. The levels of total IgA, and specific antibodies to three common oral pathogens (*Porphyromonas gingivalis, Aggregatibacter (Actinobacillus) actinomycetemcomitans and Streptococcus mutans*) were analyzed. The median secretion rates of the specific antibodies in whole and parotid saliva were 70-77% and 34-60% (respectively) lower in young DS individuals as compared to young controls and farther 77-100% and 75-88% (respectively) lower in old DS compared to young DS.

The presented studies were somewhat controversial and indicated different antibody responses between saliva and serum in DS individuals. While in saliva the antibody response was low in DS individuals, in serum the antibody responses to several periodontopathic bacteria were elevated. The low antibody responses in saliva were associated with decreased salivary flow in DS individuals. The low salivary antibody activity may facilitate the colonization of periodontal pathogens in DS individuals. The elevated antibody titers in DS serum corroborate the gingival immune cellular activity described previously. It demonstrates that DS individuals despite known immune deficiencies are capable of mounting a humoral specific immune response. Such antibodies would find their way into the gingival tissues and fluid and help with containing the microbial damage. Increased antibody levels in gingival tissues may also accentuate the gingival inflammatory response through complement activation.

4.3 Inflammatory response studies

Inflammatory response studies focused on inflammatory mediators and degrading enzymes in gingival crevicular fluid.

4.3.1 Studies investigating inflammatory mediators

Barr-Agholme et al. (1997) investigated the levels of prostaglandin E2 (PGE2) and interleukin-1β (IL-1β) in gingival crevicular fluid (GCF). GCF was collected from both DS patients and healthy controls. They found the mean level of PGE2 in GCF was significantly higher in the DS patients as compared to the controls. This finding suggests an alteration in arachidonic acid metabolism in DS patients. The mean level of IL-1β in the GCF was not significantly higher in the DS patients as compared to the healthy controls. Perhaps the reason the IL-1β levels did not differ between the groups, despite the fact that the gingival inflammation was more severe in the DS group, may be because PGE2 has been reported to down-regulate the production of IL-1β (Kunkel, et al., 1987). This issue has not been revisited since and indeed is worthy of further investigation.

Tsilingaridis et al. (2003) determined the levels of PGE2, LTB4, and MMP-9 in GCF from 18 Down syndrome patients and from 14 controls matched with respect to age and degree of gingival inflammation. Clinical periodontal parameters were recorded including probing depth (PD) and bleeding on probing (BOP). The mean levels of PGE2, LTB4, and MMP-9 were significantly ($P<0.05$) higher in GCF from Down syndrome patients compared to controls. When comparing the two groups, the correlation coefficients for LTB4 to BOP and PD, respectively, as well as for MMP-9 to BOP significantly differed between Down syndrome and controls ($P<0.05$).

4.3.2 Studies investigating degrading enzymes

Halinen et al. (1996) characterized the periodontal status of 9 non-institutionalized DS children 9 to 17 years old relative to their age-matched systemically and periodontally healthy controls. Clinical periodontal parameters were recorded. They also assessed the collagenase and gelatinase activities in the gingival crevicular fluid (GCF) and saliva samples collected from DS patients and from the controls. The endogenously active collagenase and total collagenase activities were slightly higher in GCF of DS children compared to healthy controls. Western blot demonstrated that GCF collagenase of DS patients was human neutrophil collagenase (MMP-8 or collagenase-2). Salivary collagenase in DS was high when compared to controls but of the same MMP-8 type as in control saliva.

Komatsu et al. (2001) examined both the amount present and the enzyme activity of matrix metalloproteinases (MMP-2) in the gingival tissues of Down syndrome patients and controls. The authors reported that there was a significantly higher production of MMP-2 in the cultured gingival fibroblasts of the Down syndrome patients when compared with the controls. In addition, the mRNA expressions of membrane-type I metalloproteinases (MTI-MMP) and MMP-2 were markedly different when the cultured fibroblasts of the DS patients were compared to the controls. This would indicate that the increased amount of active MMP-2 produced in DS could be linked to the simultaneous expression of MTI-MMP, which could also be connected to the cause of periodontal disease that is seen in a majority of DS patients.

Yamazaki-Kubota et al. (2010) investigated levels of matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-8 (MMP-8) in gingival crevicular fluid (GCF) and detection of periodontopathic bacteria from subgingival plaque. Samples of GCF and plaque were isolated from central incisors. Levels of MMPs were evaluated by enzyme-linked immunosorbent assay, and periodontopathic bacteria were detected by polymerase chain reaction. Levels of MMP-2 and MMP-8 in DS patients were higher than those in healthy control subjects. In the DS group, increases in these MMPs were observed in GCF from patients with good oral hygiene and absence of bleeding on probing. The detection rate of periodontopathic bacteria in DS patients was higher than that in the control subjects. Surprisingly, MMP-2 levels in sites harbouring *Porphyromonas gingivalis* or *Aggregatibacter (Actinobacillus) actinomycetemcomitans* were lower than in those without these microorganisms.

The cited studies indicate increased matrix metalloproteinase activity in the gingival tissues of DS individuals. The presence of MMP-8 suggests that neutrophils in their frustration to reach their target pathogens release their enzymes extracellularly. Matrix metalloproteinases are involved in the breakdown of the extracellular matrix. Their increased activity in the gingival tissues of DS individuals explains the gingival tissue loss and associated clinical signs (increased probing depth and loss of attachment) described. In addition the increased levels of prostaglandin E2 in combination with increased activity of MMP-9 suggests increased osteoclastic activity and explains the increased alveolar bone loss described in DS individuals.

5. A hypothesized model of the pathogenesis of periodontitis in Down syndrome

The presented articles viewed collectively suggest the following sequence of events in the pathogenesis of periodontitis in DS. Decreased salivary flow accompanied by reduced

salivary antibody production and defective neutrophil chemotaxis facilitates early microbial colonization in the dentogingival region and makes it easier for periodontal pathogens to gain a foothold. The heavy microbial presence initiates a strong gingival immune/inflammatory response characterized by the presence of high numbers of macrophages and lymphocytes in the gingival tissues. Antigen presenting cells are active in initiating adaptive immunity (as evidenced by the increased expression of HLA Class II antigens on inflammatory cells) and eventually the production of a strong humoral antibody response. The specific antibodies may help with containing the microbial infection. In addition, macrophages and other gingival resident cells (fibroblasts) seem to be engaged in high production of degrading enzymes. Frustrated neutrophils may release their degrading enzymes extracellularly into the gingival tissues. Tissue injury releases arachidonic acid metabolites (prostaglandins). The degrading enzymes and prostaglandins are involved with periodontal tissue destruction (figure 3).

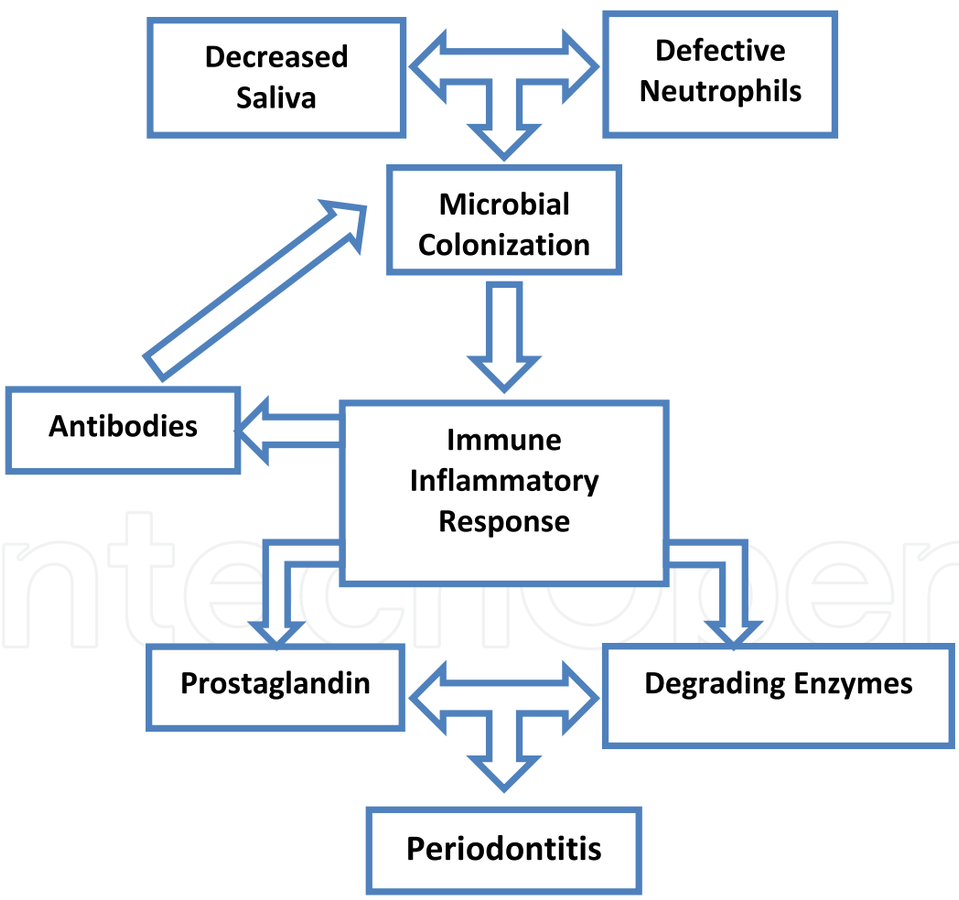


Fig. 3. Hypothesized model of periodontitis pathogenesis in Down syndrome.

6. Conclusions

In summary I have attempted to use the available periodontal literature on periodontitis in DS to construct a hypothesized model of the pathogenesis of the disease. Periodontitis in DS individuals is characterized by an intense and persistent immune/inflammatory response. Viewing this body of literature as a temporal sequence of events suggests that therapies aiming at reduction of microbial colonization could greatly benefit DS individuals by reducing the immune/inflammatory response and associated inflammatory mediators and degrading enzymes. The model also may suggest future therapies such as host response modulation. Strikingly absent from the model is information related to core immune/inflammatory abnormalities associated with DS such as increased oxidative stress, altered integrin expression (and associated altered lymphocyte function), altered IL-10 receptor expression (and possible impact on resolution of inflammation), and increased IL-1 production and their relation to periodontal disease. Further studies are needed to resolve these gaps in knowledge, and to access the implications for everyday periodontal care of this periodontally vulnerable population.

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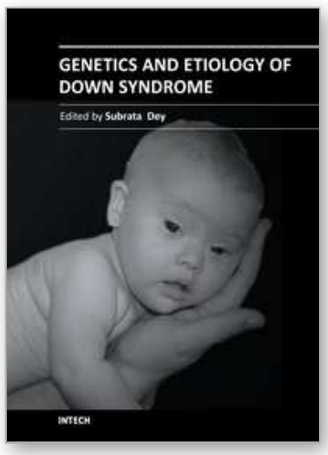
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This book provides a concise yet comprehensive source of current information on Down syndrome. Research workers, scientists, medical graduates and paediatricians will find it an excellent source for reference and review. This book has been divided into four sections, beginning with the Genetics and Etiology and ending with Prenatal Diagnosis and Screening. Inside, you will find state-of-the-art information on: 1. Genetics and Etiology 2. Down syndrome Model 3. Neurologic, Urologic, Dental & Allergic disorders 4. Prenatal Diagnosis and Screening Whilst aimed primarily at research workers on Down syndrome, we hope that the appeal of this book will extend beyond the narrow confines of academic interest and be of interest to a wider audience, especially parents and relatives of Down syndrome patients.

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