

# What's the relation between paranasal sinusitis (based on PNS-CT scan) and Kawasaki disease: A comparative study in children in Tehran, Iran

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## Research article

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## **Abstract**

## **Background**

Kawasaki Disease (KD) and rhino sinusitis are common in young Iranian population. Paranasal sinusitis can cause immunologic reactions and progress to KD. We compared the incidence of rhino sinusitis based on para nasal sinus- computed tomography scans (PNS-CT Scan), in KD cases with control group (head trauma)

## **Methods**

A prospective, case control study (2013-18) had done in Rasul Akram Hospital in Tehran, Iran. PNS- CT scan finding compared between 43 proven KD and 43 controls (head trauma). The PNS-CT scan changes compared between 2 groups respect to their ages, gender, site and type of sinusitis.

## **Results**

PNS-CT scan had been performed in 23 cases with proved KD and 43 non KD cases (control) with mean age of  $6.48 \pm 4.15$  years in KD cases without significant difference to controls ( $p = 0.14$ ). No significant difference had seen in gender between two groups. ( $p = 0.14$ ). The paranasal sinusitis had higher prevalence in KD cases in compare with controls: 41.86% (18 / 43) vs 20.9% (9 / 43) respectively ( $P = 0.036$ ). The mean age of children with sinusitis had not difference between groups ( $7.44 \pm 0.89$  vs.  $7.88 \pm 2.44$ ,  $p = 0.176$ ). Presence of sinusitis in cases and controls were not related to age, sex and site of sinusitis ( $p = 0.71$ ;  $0.80$ ;  $0.63$  respectively).

## **Conclusion**

The result of this investigation shows the high prevalence of paranasal sinusitis in KD which suggest the sinusitis as an important factor for developing the KD. Although, the presence of sinus pathology on a PNS- CT scan does not establish the causality between sinusitis and *KD*, but due to high prevalence of paranasal sinusitis in our pediatric population, we recommend PNS CT-scan for KD cases with prolonged URI (Upper Respiratory Tract Infection) symptoms more than 2 weeks. In KD cases with confirmed paranasal sinusitis, antibiotic treatment is recommended to prevent relapses and complications of the KD treatment.

## **Background**

Kawasaki disease (KD) is an acute febrile, systemic vasculitis syndrome of unknown etiology. Although the clinical features of KD are recognizable, but incomplete presentation of clinical symptoms may complicate and delay the diagnosis of KD (1, 2).

KD is the most common causes of acquired coronary disease among young children living in developed countries (1,2). The incidence of KD is increasing worldwide especially in some Asian countries(3–5). According to many references KD is diagnosed as an autoimmune disorder rather than an infectious disease. Wang et al, described the pathogenic role of infection for developing the KD (2) Bacterial antigens and super antigens (especially *S. aureus* and *S. pyogen*) might have a prominent role in progression to KD (3, 4). Early diagnosis and treatment of KD may decrease the coronary disease as along life sequel in affected children. According to the American Heart Association (AHA) criteria fever lasting more than 5 days is essential for KD diagnosis with two or three principal clinical features of KD without a known infection source.(6) The super antigen hypothesis; immune response, and genetic background on the response to infectious stimuli discussed by some authors (7–9). Nagata reported causes of KD in pediatrics (7) Nakamura et al studied etiological significance of infectious stimuli in KD(8). According to Menikou et al study, immune complexes has significant role in pediatric KD (9).Lloyd et al discussed infectious agent as etiologic factor in KD (10).

Sherman et al studied common infections in pediatric diseases (11);like others ,they found community acquired sinusitis as one of the most common infections for medical attention and visited by pediatrician(11,12). American Academy of Pediatrics recommended management of sinusitis and clinical practice guideline(12). In proven cases with sinusitis appropriate treatment is needed to decrease the risk of bacteremia and subsequent invasive infections ;orbital and preseptal cellulitis, meningitis, subdural empyema and brain abscess (12,13). Some authors reported chronic rhino sinusitis (CRS) as a common disease in children which is often undiagnosed due to subtle and nonspecific clinical symptoms. The diagnosis is usually made on clinical presentation and sometimes the help of specific radiographies or CT scans ( 11–13). Agius showed correlation between symptoms and PNS-CT scan in cases with CRS (15) indeed the super antigen hypothesis for the pathogenesis of chronic hypertrophic rhino sinusitis is considered by at least 2 authors ( 16,17 ).

Imaging studies is very important for diagnosis of CRS(16). Zeifir and Adibelli et al reported paranasal sinus development in children(18,19). Zeifer et al showed normal anatomy and inflammatory in paranasal sinus in Pediatric group( 18). PNS-CT scan is preferred for diagnosis of CRS in Children (19 ,20 ).According to Gualtieri et al, during childhood, CT scan provides higher resolution of bone and soft tissue and removes the overlapping structures in contrast to plain radiography (20).

KD is one of the common cause of hospital admission among Iranian children (21–25). In recent years rhino sinusitis and its complications reported as one of the most common causes for hospital admission among pediatric population in our country (26–30). At least one report showed bacterial meningitis as a malignant complication of pediatric rhino sinusitis ( based on PNS-CT scan ) in Iran (26).

This case control study designed to compare the incidence of rhino sinusitis ( based on PNS-CTScans), in KD cases with control group was admitted by history of head trauma.

## Methods

During 2013–2018, this prospective, case control study had done in pediatric ward of Rasul Akram Hospital as a 3th referral educational hospital affiliated by Iran University of Medical Sciences (IUMS) in Tehran, Iran. This study was approved by the Ethical Committee in the Research Center of Pediatric Infectious Diseases,IUMS. All project partners adhere to the principles of the Helsinki Declaration. Written informed consent was obtained from the parents of all children enrolled in the study. Performing all clinical examinations and diagnostic tests will be at the expense of the plan.

Initially, a check list was completed for each case by an authorized physician. Personal information (eg :sex, age, examination and illness progression) for each patient were completed and data collection covering different aspects ( e.g., lab tests ;presence and site of sinusitis; type of sinusitis (chronic, acute) according to the CT scans were written in questioner .

Imaging studies: PNS- CT scan (spiral modified) had done in all cases and controls and reported by one expert radiologist ( blind) .Rhino sinusitis finding were considered (eg; Opacification, Mucosal thickening; retention cyst ) also site of sinus involvement ;type of sinusitis (acute or chronic) were evaluated. The PNS CT-scan changes compared between 2 groups respect to their ages ,gender, site and type of sinusitis.

Statistical analysis: All analysis were conducted by SPSS-13.5. Chi-square were calculated for all categories The Student's t test was used to determine significant differences in means of all continuous variables. Chi-square values (CI 95%, p < 0.05) were calculated for all categories. *P value < 0.05 was considered significant.*

Case definition: Inclusion criteria for KD : During 5 years, KD diagnosed in 43 children ( mean age :6.49 ± 4.16 years ) fulfilled criteria of KD according to diagnostic criteria in literature(1) Presence of fever > 5 days, and four of five following criteria : bilateral bulbar conjunctivitis, changes in the mouth(erythema of oropharynx, fissuring, and crusting of the lips, strawberry tongue); change in the peripheral extremities(erythema of the palms and soles with edema of dorsum of the hands and feet with later desquamation), polymorphous erythematous rash; enlarged cervical lymph node( $\geq$  5 cm)

Exclusion criteria: A preliminary tests and standard examination were requested after initial examinations by a pediatrician for excluding other etiologic causes except KD .We excluded all known infectious causes except KD ( eg; bacterial meningitis ,sepsis ,pneumonia, osteoarthritis, toxic shock syndrome, scarlet fever, Stevens Johnson, viral infection ; measles, rubella, HHV6 ,EBV,...) and other noninfectious causes ( eg; malignancy ,rheumatologic diseases) .

Control Group: included 43 children (mean age: 7.81 ± 4.19 years; p = 0.1) with head trauma during 48 hours after admission in emergency ward.

All of controls were healthy before trauma (without infection or URI); *The Controls with abnormal findings in the sinuses (due to edema, hematoma or,brain hemorrhage ( brain CT scan )are excluded.*

## Results

KD cases were male 62.76% (n = 27), 37.2% (n = 16) female. The mean age was not different between 2 groups ( $6.48 \pm 4.15$  years vs.  $7.81 \pm 4.19$  years ; $p$ -value = 0.14).

PNS-CTscan finding: Sinusitis was diagnosed in 41.8% (18/43) of KD cases (mean age  $7.44 \pm 0.89$  years); 60.46% (n = 26) were male, 39.53.2% (n = 17) female.(table-1) Sinusitis diagnosed in 20.9% (9/43) of controls (mean age  $7.88 \pm 2.44$  years). Sinusitis was more frequent in KD cases ( $P$  value = 0.036).The mean age of children with sinusitis had not significant difference between 2 groups ( $7.44 \pm 0.89$  vs.  $7.88 \pm 2.44$   $p$  = 0.176) : table-2

Table-1: prevalence of sinusitis in cases and controls

Sinusitis	Kawasaki cases	Control	Total
Positive	18(41.8%)	9(20.9%)	26
Negative	25(59.2%)	34(79.1%)	59
Total	43	43	86
P value = 0.036			

$P$  value < 0.05 was considered statistically significant.

Chronic type of sinusitis was reported in 50% (n = 13) of all cases.

The site of paranasal sinus involvement showed in Table 2

Presence of sinusitis in cases and controls were not related to age, sex and site of sinusitis ( $p$  = 0.71; 0.80; 0.63).

Table-2: Para nasal sinus involvement in cases and controls

Paranasal sinus involvement	Group		Total
	Cases	controls	
Maxillary	6	2	8
Maxillary + Ethmoid	2	1	3
Maxillary + sphenoid	3	3	6
Maxillary + Ethmoid + sphenoid	5	3	8
Maxillary + Ethmoid + frontal	2	0	2
Total P value = 0.63	18	9	27

P value < 0.05 was considered statistically significant.

## Discussion

Here, we studied the PNS CT scan in 43 proven KD and 43 controls ; without significant difference in mean age(p value = 0.14.). Sinusitis (PNS CT scan based) confirmed totally in 26 children: 41.8% (18/43) of KD; 20.9% (9/26) of controls. Sinusitis observed more frequent in KD (p-value = 0.036). Most KD cases with sinusitis were male (60.46%); with mean age =  $7.44 \pm 0.89$  years. But the mean age between KD cases with and without sinusitis was not different ( $7.44 \pm 0.89$  vs.  $7.88 \pm 2.44$ y; p = 0.176).

Results of present study emphasizes a prominent role for sinusitis in progression to KD in pediatric group. The positive correlation between KD and infectious diseases are likely help to recognize the role of super-antigens involving the heart and blood vessels(2,3) Sinusitis confirmed in 26 studied children regardless of KD, is very close to Sherman et al and Slavin et al studies, they found community acquired sinusitis as one of the most common infections for medical attention and visited by pediatrician (10,11,13,14 ) like previous studies, this study determined the probable role for infectious etiologies in pediatric group (eg: otitis media with effusion; sinusitis ,pneumonia, septic arthritis, and other diseases ) [7–9] Shermin et al defined sinusitis was a common upper respiratory infections in pediatric diseases (11)

In deed ,Lloyd et al showed KD caused by an infectious agent(10). Hypothesis of super antigens is one of the most important explanations for many diseases including rhino sinusitis and KD( 7–10). Obstruction of the external meatus of para nasal sinuses and eustachian tube due to inflammation, hypertrophic mucosa, accumulation of secretions in the respiratory tract and metaplastic changes can lead to more severe and longer infection (16,17 ). Several studies have been conducted to verify this hypothesis. Some of these studies suggest that the difference in timing of the evaluation of super antigens leads to different results (1, 2,11,12 ). The bacterial infections (due to super antigens ) simply do not treat. In these disease inflammatory process and will continue pointlessly leading to increase the susceptibility to infection later (10,16,17 )The study was done on PNS -CT scan, although the CT scans in childhood is an aggressive procedure and doesn't recommend for diagnosis of acute sinusitis ,and uncomplicated situation(12,13). Chronic type of sinusitis was reported in 50% (n = 13) of studied children. So, it might be helpful in sub acute or chronic sinusitis cases (12). Although use of CT scan recommended for chronic sinusitis, here chronic symptoms are not noticeable, PNS- CT scan make a confounding role in judging the relationship the KD and sinusitis, But in the control group who underwent CT scans for other reasons, were probably cases of sub acute and chronic sinusitis has been mixed although the sub-acute cases are less likely to change thickness. Diagnosis of sinusitis upon symptom and physical examination in pediatric population is not value (12–14) it is possible to diagnose base on endoscopic procedures or imaging studies ( 12,13,14). PNS CT is the best imaging for diagnosis of sinusitis in children (19,20). It allows better soft tissue differentiation and high spatial resolution images depicting fine details in compare with MRI (20) The most common site of paranasal sinus in KD was maxillary(6) pan sinusitis depend on age (n = 5) ;Maxillary + sphenoid (n = 3). Here, except maxillary sinus, sphenoid sinus was a common site for involvement in KD cases. According to Gualtieri et al, PNS- CT scan is recommended in

pediatric group especially in isolated sphenoid sinusitis (20). Presence of sinusitis in cases and controls were not related to age, sex and site of sinusitis ( $p = 0.71; 0.80; 0.63$ ). Question whether PNS CT-scan is needed for all KD? The disadvantages of doing this procedure for all children with KD and intervening factors mentioned above.

Limitation of study: absence of clinical information such as clinical course, response to previous treatment .The next factor that was not considered in this study is the microbiological data. However, there are still rooms to study the relationship between infectious factors, KD, and the central role of super antigens..

## Conclusion

The result of this investigation shows the high prevalence of rhino sinusitis in KD which suggest the sinusitis as an important factor for developing the KD. Although, the presence of sinus pathology on a PNS –Ct CT scan does not establish the causality between sinusitis and *KD*, but due to high prevalence of rhino sinusitis in our pediatric population, we recommend PNS CT-scan for KD cases with prolonged URI symptoms ( $> 2$  weeks). In KD cases with confirmed sinusitis, antibiotic treatment is recommended to prevent relapses and complications of the KD treatment

## List Of Abbreviations

Kawasaki disease (KD); PNS CT-scan (para nasal sinus- computed tomography scans ); URI( Upper Respiratory Tract Infection); American Heart Association (AHA); chronic rhino sinusitis ( CRS).

## Declarations

Ethics approval and consent to participate: This study was accredited by Ethical Committee of Iran University of Medical Sciences. Helsinki Declaration was respected across the study and the informed consent to participate form was signed by the parents.

Consent for publication: All authors confirm Consent for publication

Competing interests: The authors declare no conflict of interest in preparing this study.

Availability of data and material: All authors confirm the availability of data and material

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Authors' contributions: Samileh Noorbakhsh designed and supervised the study, visited and interpreted the patients data, writing the initial report.

Zahra movahedi; Recheck the cases, rewriting and English editing the manuscript

Sarvenaz Ashouri: methodologist, analyze data, statistics

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1. All authors confirmed that the manuscript has not been and will not be published elsewhere or submitted elsewhere for publication
  - All figures of our manuscripts are original.
  - Conflict of interest

All authors declare to have no conflict of interest.

All Authors including confirmed that they have not any relevant financial interests or financial conflicts within the past 5 years and for the foreseeable future. They have no financial interests related to the material in the manuscript.

- Ethical Considerations:

This study was approved by the Ethical Committee in the research center of pediatric infectious diseases in Iran University of medical sciences.

Authors declaring that the study complies with current ethical considerations. An informed consent was obtained from each patient included in the study and (2) the study protocol conforms to the ethical guidelines of the [1975 Declaration of Helsinki](#) as reflected in a priori approval by the institution's human research committee.

Ethical Committee in the Research Center of Pediatric Infectiuos Diseases (affiliates by Iran University of Medical Sciences) has reviewed and approved the Waiver of Authorization for use of protected health information (PHI) for research purposes for the following study.

Principal Investigator: Dr Samileh Noorbakhsh, MD associate professor, Pediatric Infectious Disease; Research Center of Pediatric Infectious Diseases, Iran University of Medical Sciences.

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