Pyrexia of Unknown Origin in Children in Singapore: A Twelve Year Experience

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Introduction

Pyrexia of unknown origin (PUO) is a diagnostic dilemma often faced in the pediatric setting. It is defined as daily fever more than 38.3 degrees Celsius for a minimum of 8 days, in whom no cause is apparent after initial outpatient or hospital evaluation that includes a careful history, physical examination and initial lab assessment.

Methods

We conduct a 12 year retrospective study of children admitted to KK Children's Hospital and first referred to the infectious disease (ID) service for PUO between December 2004 and May 2017, to determine the causes and outcomes of children referred for PUO.

Analysis was done using SPSS software version 20. Chi square test was used for categorical data, and Kruskal-Wallis test for continuous data. P values are considered statistically significant at < 0.05.

Results

Total of 257 children were identified.

Fig. 1: Number of children with PUO in each age group

History and Physical examination

•Duration of fever before diagnosis of PUO was made: 8 days-14 months.

Investigations

Diagnostic Group	Infection	Inflammatory	Malignancy	Others/Unknown	HLH	p value (chi square test)
Cough: n (%)	73 (53.7)	20 (39.2)	2 (18.2)	17 (32.7)	3 (42.9)	0.024
Mouth ulcer: n (%)	3 (2.2)	7 (13.7)	1 (9.1)	6 (11.5)	0 (0)	0.025
Joint pain: n (%)	4 (2.9)	9 (17.6)	1 (9.1)	2 (3.8)	0 (0)	0.005
Lymphadenopathy: n (%)	26 (19.1)	30 (58.8)	4 (36.4)	13 (25.0)	4 (45.1)	<0.0001
Hepatomegaly: n (%)	20 (14.7)	7 (13.7)	5 (45.5)	4 (7.7)	6 (85.7)	<0.0001
Splenomegaly: n (%)	9 (6.6)	2 (3.9)	3 (27.3)	1 (1.9)	5 (71.4)	<0.0001

Table 1: Comparison of symptoms and signs between the diagnostic groups for PUO

Diagnostic Group	Infection	Inflammatory	Malignancy	Others/Unknown	HLH	p value
Highest WBC count, x10 ⁹ /L: Median (IQR)	8.8 (6.0-14.6)	6.0 (4.2-12.0)	8.6 (3.4-12.4)	9.2 (5.2-13.3)	4.3 (1.9-9.5)	0.319
Highest ANC count, x10 ⁹ /L: Median (IQR)	4.6 (2.8-8.5)	3.8 (1.9-8.6)	3.2 (0.3-6.4)	4.4 (2.2-8.3)	2.7 (1.2-4.6)	0.675
Lowest PLT count, x10 ⁹ /L: Median (IQR)	285.0 (209.0-405.5)	265.0 (210.0-414.0)	158.0 (78.0-335.0)	302.5 (238.5-440.0)	132.0 (40.0-177.0)	0.043
Lowest Hb, g/DL: Median (IQR)	11.4 (10.3-12.3)	11.5 (10.2-12.6)	9.4 (7.4-11.3)	12.0 (10.9-12.7)	10.3 (8.6-11.3)	0.041
Highest CRP, mg/L: Median (IQR)	43.4 (7.9-106.8)	34.3 (16.3-100.5)	51.8 (36.8-96.2)	23.9 (7.2-63.0)	78.6 (70.9-231.9)	0.018
Highest ESR, mm/hr: Median (IQR)	60.0 (28.0-95.0)	63.0 (37.0-90.0)	82.0 (30.0-123.0)	39.0 (24.0-79.0)	80.0 (26.0-105.0)	0.349
Highest ALT, U/L: Median (IQR)	26.0 (15.0-53.0)	20.5 (16.0-47.3)	36.0 (11.0-61.0)	21.0 (14.0-40.3)	103.0 (50.3-248.8)	0.099
Highest AST, U/L: Median (IQR)	38.0 (26.0-62.0)	35.5 (28.8-52.5)	45.0 (35.0-63.0)	38.5 (26.0-50.3)	153.5 (49.0-758.5)	0.084
Highest LDH, U/L: Median (IQR)	504.0 (287.0-844.0)	586.0 (397.5-832.5)	451.0 (174.5-1207.0)	530.5 (308.0-806.3)	764.5 (481.3-6482.5)	0.22

Table 2: Comparison of blood results between the diagnostic groups for PUO

Fig. 2: Boxplot comparisons of Lowest platelet counts between the diagnostic groups for PUO

Fig. 3: Boxplot comparisons of Highest C-reactive Protein levels between the diagnostic groups for PUO

Table 1 shows the comparison of the symptoms and signs between the various diagnostic groups for PUO. Table 2 shows the comparison of blood results. Figures 2 & 3 show the boxplot comparisons of lowest platelet counts and highest CRP levels between the various diagnostic groups for PUO respectively. As illustrated by Table 1 and 2 and Figures 2 and 3, patients with Haemophagocytic lymphohistiocytosis (HLH) are more likely to have hepatomegaly, splenomegaly, and have lower platelet counts and higher CRP.

Diagnoses

Table 3 shows the causes of PUO identified. Infective causes accounted for 52.9% of PUO cases, followed by inflammatory causes (19.8%), malignancy (4.3%), HLH (2.7%), others (0.8%).

Cause	Frequency	Cause	Frequency	Cause	Frequency
Infective causes	136 (52.9%)	Infective causes (Cont)	136 (52.9%)	Malignancy/Haematology	11 (4.3%)
Typhoid	19	Influenza A	1	Leukemia	4
Mycoplasma infection	13	H1N1 virus infection	1	Lymphoma	2
Rickettsia/scrub typhus	12	Infectious mononucleosis (non-EBV, non CMV)	1	Liver embryonal sarcoma	1
Tuberculosis**	12	Mediastinal mass with paraneoplastic infection	1	Neuroblastoma	1
Urinary tract infection	11	Melioidosis	1	Adrenal gland highly proliferative mesenchymal tumor	1
EBV infection	10	Mycoplasma and EBV infection	1	Multisystem Langerhans cell histiocytosis	1
Sinusitis	8	Occult bacteremia	1	Severe aplastic anemia	1
Non-typhoidal salmonella	6	Osteomyelitis/osteopetrosis	1	Others	2 (0.8%)
Pneumonia	4	Retropharyngeal abscess	1	Evan's syndrome	1
HIV infection	3	Rotavirus infection	1	Acute demyelinating encephalomyelitis	1
Otitis media	3	Tuberculous paraventricular leprosy	1		
Group A Streptococcus infection	3	Malaria	1		
Infective endocarditis	3				
Parainfluenza 3 virus	3	Inflammatory causes	51 (19.8%)		
Bacterial enterocolitis	2	Kikuchi disease *	25		
CMV infection	2	JIA/Still's disease	13		
Salmonella and typhus infection	2	SLE	4		
Disseminated BCG infection	2	Kawasaki disease	3		
Enterovirus infection	2	Inflammatory bowel disease	2		
Adenovirus and rhinovirus	1	Systemic vasculitis (TA/PAN)	1		
RSV and enterovirus	1	Ulcerative colitis, primary sclerosing cholangitis, undifferentiated CTD	1		
RSV infection	1	DRESS syndrome	1		
Adenovirus	1	IgG4 disease	1		

Table 3: Causes of PUO in the study children

A similar Canadian study by Chow et al showed that the commonest causes for PUO were infection for 832 (51%), collagen vascular disease for 150 (9%), malignancy for 93 (6%), miscellaneous non-infectious conditions for 179 (11%) and no diagnosis in 384 (23%) children.[1]

Treatment and Outcomes

Most children had resolution of fever with treatment of underlying disease and were discharged well. Those with unknown cause of fever had a self-limited course of their illness. Death occurred in 8 children.

Conclusion

PUO in children was mostly due to infective or inflammatory causes. Attention to uncovering exposures, symptoms, signs or laboratory findings is the most fruitful approach to finding the cause of PUO.

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