

## Clinical and laboratory studies of hospitalized children with typhoid fever in AL-Najaf

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### Abstract

Typhoid fever is a major public health problem in developing countries. In Iraq, where the sanitary infrastructures were severely damaged during the last (10) years because of illegal sanction, the high prevalence of typhoid fever creates a pressing need for rapid, reliable and non-costly diagnostic tool. This study aimed at investigating the clinical and laboratory findings of typical fever in Al-Najaf children and it was conducted mainly for reappraisal of the Widal test and its diagnostic utility in endemic area.

### الخلاصة

تعتبر حمى التيفوئيد من المشاكل الصحية الكبيرة في البلدان النامية والبلدان الفقيرة وفي العراق ونتيجة للحصار والحروب المتتالية أصبحت حمى التيفوئيد من الأمراض المتوطنة وأصبح المعنيين بحاجة إلى وسائل تشخيصية سريعة ودقيقة ورخيصة وأن هذه الدراسة تهدف بشكل أساسي إلى تقييم فحص (ويدال) كوسيلة تشخيصية يعتمد عليها في تثبيت تشخيص حمى التيفوئيد لدى الأطفال في مدينة النجف. أخضعت هذه الدراسة (92) طفلاً من المصابين بحمى التيفوئيد والذين دخلوا مستشفى الولادة والأطفال التعليمي في النجف للفترة الواقعة بين آذار 2002 وأيلول 2003 للبحث والتحليل وقد تم عمل استمارة تفصيلية لكل طفل تحتوي على الملاحظات السريرية المختلفة بالإضافة إلى تحليل زرع الدم، تحليل حمرة الدم التفصيلية واختبار (ويدال). تم تصنيف الأطفال إلى ثلاثة فئات عمرية أساسية وكانت نسبة الفئتين العمرية (5-8) سنة هي الأكبر حيث شكلت (26 و 2) % كانت نسبة الذكور من الأطفال التي شملتهم دراسته (65 و 5) % بينما شكلت الإناث (43 و 5) % ومن الملاحظات السريرية المهمه التي ظهرت في هذه الدراسة أن الأطفال الذين كان لديهم تضخم الكبد (54 و 3) % أكثر من نسبة الأطفال الذين كان لديهم تضخم الطحال (41 و 3) % أما شكل الحمى فكان من نوع الحمى المتناوبة في أغلبية الأطفال (82 و 6) % وكانت من النوع المستمر في (17 و 4) منهم. أظهرت نتائج تحاليل الدم بأن (83 و 3) % من الأطفال كان لديهم نقص تام في عدد الكريات البيضاء وكانت نسبة الذين لديهم نقص نسبي في الكريات البيضاء (52 و 2) % بينما كان عدد الكريات البيضاء طبيعياً في (13) % من الأطفال. لقد خلصت هذه الدراسة إلى أن تحليل (ويدال) وبلرغم من محدودية استخدامه في البلدان المتقدمة ما زال يمثل وسيلة تشخيصية ذات قيمة وأهمية كبيرة في تشخيص حمى التيفوئيد في البلدان النامية.

### Patients and methods

(92) children with typhoid fever were studied in Al-Najaf maternity children hospital between March 2002 and September 2002. A performed sheet with demographic data, medical history and clinical findings were filled in addition to complete blood count: Blood culture and slide agglutination test for O and H antigens were done for all patients; and patients were grouped into blood culture negative (Typ-CN) and blood culture positive (TYP-CP) typhoid Fever 50 patients (54.3) % and 42 patients (45.06) % respectively. A slide widal test were done for all patients in addition to 50 children with non typhoidal febrile illness as a control group. The cut-off value that defines a positive widal test is 1/180 and 1/160 for O and H antigen respectively.

## Results and Discussion

Of the total 92 cases (65.2) % have aged (5-80 years: (65.5) % were male and (43.5) % were female. One of unexpected result was that (73.9) % were from urban area while (25.1) % from rural area. The Frequency of clinical and laboratory events are similar in both groups apart from duration of fever which was longer in (Typ-CN) group. (54.3)% have hepatomegoly while (41.3) % have splenomegaly. (82.6)% have intermittent pattern of fever and (17.4) % have sustained type. Hematological profile revealed that (34.8) % have absolute leucopenia, (52.2) % with relative leucopenia and (13) % have normal W.B.C .count.

## Conclusions

Despite its well known limitation the widal test remains a valuable toll for diagnosis of typhoid fever in endemic area and reliance on somatic (O) antigen only will result in missed diagnosis

## Introduction

Typhoid fever (T.F) ; the most frequent and best studied type of enteric fever, which is a systemic clinical syndrome produced by *Salmonella typhi* . because humans are the only natural reservoir of *S. typhi* ; direct or indirect contact with an infected person is necessary for infection<sup>(1)</sup> Typhoid fever is an important public health problem in many parts of the world especially in developing countries in which the disease is endemic<sup>(2,3)</sup> . The incidence of typhoid fever has decreased markedly in developed countries reaching less than 0.2/100,000 while still it is one of the considerable threat in developing countries with an incidence that can reach 500 per 100,000 (0.5)% and high mortality rate ,the World Health Organization has estimated that 12.5 million cases occur annually worldwide (excluding china)<sup>(4,5)</sup> . Water borne and food borne outbreaks due to poor sanitation and direct fecal-oral spread due to poor personal hygiene are seen , mainly in developing countries<sup>(6)</sup> . Unlike most other gastrointestinal infections ; which predominantly affect children aged<sup>(6)</sup> months to<sup>(3)</sup> years ; the incidence of typhoid fever peaks between<sup>(5)</sup> and<sup>(12)</sup> years.<sup>(7)</sup> According to hospital –based data and limited information from field studies that used passive surveillance for case detection; typhoid fever is infrequent under three years of age<sup>(8,10)</sup> these findings are repeated in standard medical texts<sup>(11)</sup> Several factors may explain the low rate detection of typhoid fever in preschool years . Typhoid fever is surprisingly milder and a typical in-presentation at this age ; and as such ; it may be under – reported when case detection is , as was the case in most previous studies<sup>(12,13)</sup> . Subclinical or a typical presentation may be the result of underdeveloped reticuloendothelial system; the nidus for multiplication of *Salmonella typhi* .difficulties in collecting the recommended 5ml blood for conventional blood culture methods used in endemic area ; prior use of antibiotics and technical obstacles in materials and personals also lead to more under diagnosis<sup>(14,15)</sup> . For these reasons we undertook a prospective study depending on widal test ; which is cheap ; easy to do , and sensitive and it has proved to be of diagnostic value in connection with clinical data particularly in endemic areas in which differentiation of typhoid fever

from other similar other illness is quite important<sup>(16,17)</sup> This study also conducted to find out comparative study between simple sild widal test and blood culture for isolation of *S. typhi* which is time consuming ; requiring well equipped lab and sometimes unobtainable due to intermittent presence of micro-organism in blood stream<sup>(18)</sup> In spite the importance of typhoid fever as very common infectious disease in Najaf city ; very few studies have been done particularly in pediatric age group ; so that this study proposed to be fruitful and it will high light the diagnostic value of widal test which was regarded as a crude screening test long time

### Patients and methods

All patients admitted to Al-Najaf maternity and children hospital between 20th of March 2002 and September 2003 who were presented with clinical pictures strongly suggestive of typhoid fever ; all of them were contralled in this study except those treated with antibiotics prior to the time of admission . A performed sheet with demographic data; medical history and clinical findings were filled by one of the investigators. Many events were filled including duration of fever before preseration; history of change in bowl habits, Headach, abdominal pain, history of chills and neuropsychiatric features. One examination we looked for beaks of temperature, evidence of acute abdomen, hepatomegaly and splenomegaly. Beside blood picture and Widal test, total and deferential count were done for all patients. (92) patients qualified for the study were grouped into blood culture positive typhoid fever (typ-cp) constituting (50) children and (42) children with clinical picture highly suggestive of typhoid fever but culture negative (typ-cn) .50 cildren with non typhoidal febrile illness were randomly chosen as control group . For all patients, blood culture and agglutination test for (O) and (H) antigens have been done. Blood culture was carried out on admission by collecting (5) ml of whole blood; it was incubated directly in blood culture media of brain, hart infusion borth and was incubated for (7) days. *Salmonella typhi* identification by biochemical reaction including Kligler iron agar, triple sugar test and urea production test .All the procedures was performed by well qualified bacteriologist. A slide Widal test were done for all cases including (TYP-CP) , (TYP-CN) and non typhoidal febrile patients using commercially prepared stained antigens produced by Omega-diagnosed limited company , Scotland , U.K. . It was carried out on the following steps;

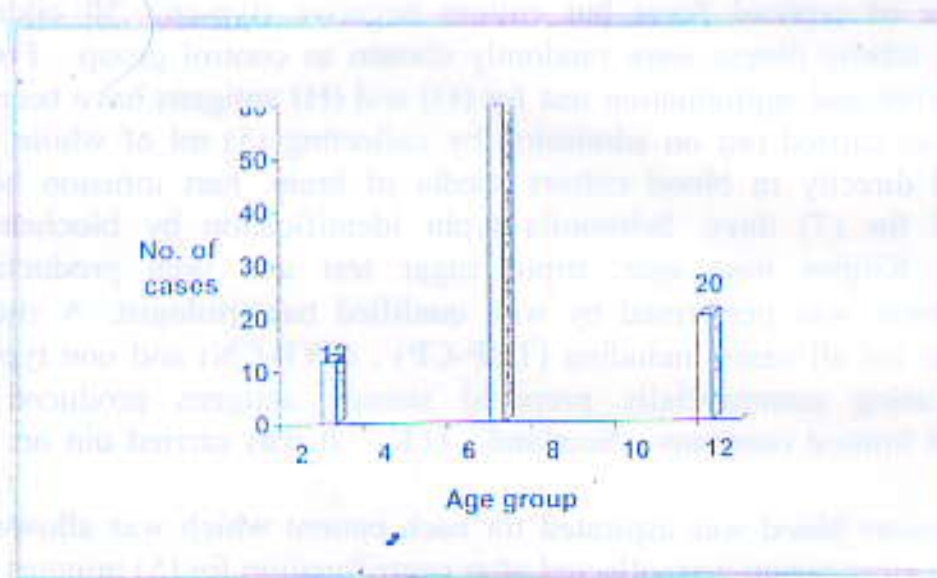
1. (3) ml venous blood was aspirated for each patient which was allowed to clot and retracted . clear serum was collected after centrifugation for (5) minutes at (2500) R / minutes .
2. Using microtiter pipette to deliver 0.08 , 0.04 , 0.02 , 0.01, 0.005 and 0.0025 m l of undiluted serum into a row of 3cm diameter circles on a white tile .
3. Add one drop (0.05) ml of appropiate well shaken suspension to each serum circle.
4. Mix drops and spread to cover the entire circle by using wooden applicator sticks for each circle.

5. Gently and evenly rocks and rotate the tile for one minute while examining for agglutination.
6. Results obtained corresponding to tube agglutination titer of 1:20, 1:40 , 1:80 , 1:160 , 1:and 1:640 respectively .

The study design which was implemented is a sort of Sectional study which measures the ability of a test to identify patients with specific disease<sup>(19)</sup>. The cut off value that defines a positive Widal test diagnostic for typhoid fever is 1/80 and 1/160 for O (somatic antigen ) and H (flageller antigen) respectively . The data were coded and processed in department of community medicine, medical college, Kufa univernity, chi-square to ascertain the association between two or more categorical variables. The level of (p value <0.05) was considered as the cut off for significance.

### Results and Discussion

Fig. (1) Illustrated the distribution of (92) cases of typhoid fever who were enrolled in this study according to their age. Itrevealed that 12 patients (13%) were included in the first group ranging from (1-4) years , 60 patients (62.2%) in the second group (5-8) years and 20 patients (21.8%) in the third group (9-12)years . the mean age was 6.95 . this indicates that the incidence of typhoid fever is at its peak in the age group of (5-8)years , which is consistant withj data in standard text of peditric<sup>(11)</sup>, on contrast to data of Indian studies which have revealed unexpected results of age specific incidence .<sup>(6)</sup>



**Figure (1)** Emphasize the age group distribution of (92) children with typhoid fever in nagaf .

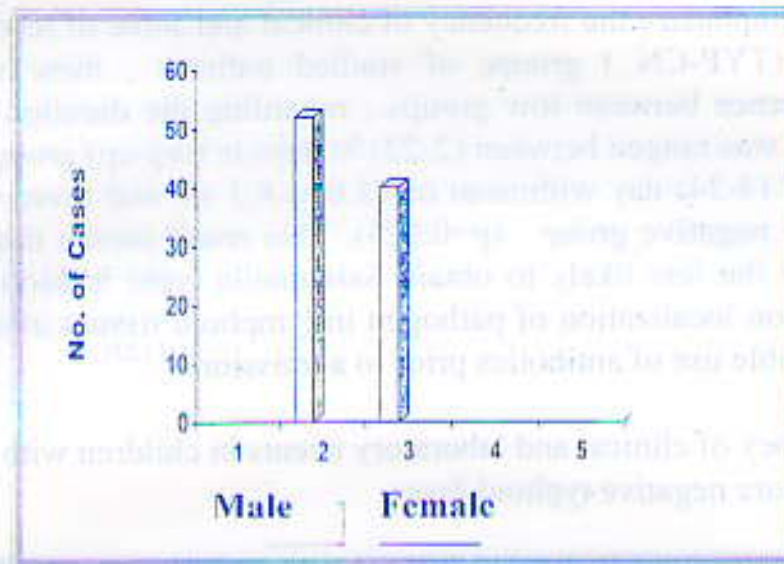


Figure (2) demonstrate the sex distribution of studied subjects which showed 52 patients (65.5)% were male and 40 patients (43.5)% were female which reveal significant sex difference compared with another study<sup>(20)</sup>

### Results

The study has shown that number of cases from rural areas was much less than that from urban areas. Figure (3) revealed that 68 patients (73.9%) were from rural areas while the remainder(24) patients (26-1%)were from rural area ; this unexpected result can be explained on the environmental, social, and financial and community health system changes that occurreds during last 10 years because of illegal sanction impacton our country



Figure (3) Distribution of typhoid Fever of children in rural and urban areas in Najaf city.

Table (1) emphasize the frequency of clinical and some of laboratory events in (AYP-CP) and (TYP-CN ) groups of studied patients , there was statistically significant difference between tow groups ; regarding the duration of fever before admission which was ranged between (2-22) % days in (typ-cp) group with a mean of 8.2565.25D and (4-34) day withmean of 13.05+ 8.3 sD and fever wassignificantly longer in culture negative group . (p=0.025). This result means that the longer the duration of fever the less likely to obtain Salmonella typhi in blood culture which canbe explained on localization of pathogen in lymphoid tissues after the first week of illness or possible use of antibiotics prior to admission. <sup>(13,22)</sup>

**Table(1)** Frequency of clinical and laboratory events in children with culture positive and cult ure negative typhoid fever

	TheEvent	(Typ-CP)	(Typ-CN)	Total
1.	Duration of Fever			
	(5-9)days	31(33.7)%	25(27.2)%	56(60.8)%
	(10-14)days	6(6.5)%	10(10.9)%	16(17.4)%
	(more than2weeks)	5(5.4)%	15(16.3)%	20(21.8)%
2.	chills	20(21.7)%	8(8.7)%	28(30.4)%
3.	Nochills/NoRigor	30(32.6)%	34(36.9)%	64(69.6)%
4.	Diarrhea	20(21.7)%	24(26.1)%	44(47.8)%
5.	Constipation	8(8.7)%	8(8.7)%	16(17.4)%
6.	Headache	32(34.8)%	28(30.4)%	60(65.2)%
7.	Abdominal pain	30(32.6)%	38(41.3)%	68(73.9)%
8.	Peak of temperature More than 39°C	42(45.6)%	38(41.3)%	80(87)%
9.	Type of fever			
	a)Contuinuous	10(10.9)%	6(6.8)%	16(17.4)%
	b)Remittent	40(43.5)%	36(39.1)%	76(82.6)%
10.	Hepatomegal	24(26)%	26(28)%	50(54.3)%
11.	Splenomegaly	18(19.5)%	20(21.7)%	38(41.3)%
12.	Acute Abdomen	4(4.3)%	4(4.3)%	8(8.6)%
13.	Neuropsychiatric Manifstation	2(2.2)%	Nil	2(2.2)%
14.	Cough	15(16.3)%	13(14.1)%	28(30.4)%
15.	Leukocyte COUNT			
	Wbc<4000/mm3	17(18.5)%	15(16.3)%	32(34.8)%
	WBC<7000/mm3	25(27.2)%	23(25)%	48(52.2)%
	WBC<7000/mm3	7(7.6)%	5(5.4)%	12(13)%

There is a significant difference between the two groups regarding the presence of chill: table (1) shows that (20) patients (21.7)% and (8) patients (8.7) % have chills in (typ -cp) group and (typ-CN)group respectively. Diarrhea were found in (44)cases (47.8)while (16)cases (17.4)% were suffered from constipation , this rate of diarrhea is much less than figures reported in other studies which was exceeding 70%(20)(21) Headache was appeared as a common symptoms and it has reported in (60) patients (65.2)% which is consistent with other studies (20)(22).Abdominal pain was found in (68) patients (73.9)% which was comparable with previous studies , and it was more common in (typ-CN) patients as shown in table (1)(23) . The patients were divided into three groups according to the duration of fever before admission , the first group (5-9) days were (56) patients (60.8)%, second group(10-14) days constitute (16)patients (17.4)% and third group more than 2weeks was including (20) patients (21.8)%. regarding this aspect table (1) again revealed that the number of cases with fever more than 2 weeks were 15(16.3)% in (typ-CN)compared with 5(5.4)% in (typ-CP) group which support the result that with progress of illness , the blood culture yielding less positive results (13,22,23)This results make Widal test more useful diagnostic tool during this week of illness and later (22).Regarding the degree of temperature table (1)showed that(80) patients(87)%have high grade fever temperature  $\geq 39^{\circ}$  while only12patients(13)%have moderate and low grade fever $<39^{\circ}$  there was no significant difference between the two groups but this figure confirm the fact that most of patients have high grade fever (1,23)Analysis of organic enlargement revealed that 50 patients (54.3)% have hepatomegaly while 38 cases (41.3)% have splenomegaly and the remainder 4 patients (4.3)%have neither hepatic nor splenic enlargement. Table (2) illustrate the the difference between our study and another study which was done in Ras- AL- Kaima U.A. E. in 1996, it was concluded that organic enlargement were much more common in our study 88 of patients(95.6)% while only 19 patients (37.2)% in Ras AL- Kaima study; moreover in our study hepatic enlargement appeared more than splenic enlargement (1,20,22).

**Table(2)** outline the difference between Al.-Najaf and Ras- AL-Kaime study in concern with organic enlargement

Sign	Hepatomegaly	Splenomegaly	Nil	Total
Najaf study	* 50(54.3)%	38 (41.3) %	4(4.3)%	92(100)%
Ras -AL- Kaima Study	10(19.6)%	9(17.6)%	32(62.7)%	51(100)%

\*P< 0.001

Regarding types of fever table (3) shows the differencebetween our study and Shianga study which has been carried out in China in 1997 ; it revealed that intermittent fever was more common in our patients76(82.6)% compared with 60 (33>7) % in Shiagya study patients (23).

**Table (3)** demonstrate the difference between Al-Najaf study and shiangya study regarding type of Fever

Type of Fever	Intermittent	Sustained	Total
Najaf study	*76(82.6)%	16(17.4)%	92(100)%
Shiangya study	60(33.7)%	118(66.3)%	178(100)

$$X^2=62.7 \text{ df}=1 * P<0.001$$

Although the gastrointestinal manifestations are common particularly with progress of the disease but only 4patients (4.3)% were presented with acute abdomen : one child only had perforation of small bowl . The hematological profile of patients revealed that 32(34.8) % have absolute neutropenia (WBC<4000/mm<sup>3</sup>) and 48(52.2) % have relative leukopenia (WBC<7000/mm<sup>3</sup>) and (12) patients (13) % have normal leukocyte count >7000/mm<sup>3</sup>; a result which is comparable with other studies (23) (24) . As illustrated in table (4); all patients with non typhoid febrile illness have had negative O agglutination and (4) patients (8) % have had H agglutinin titer of 1:80. In (type-CP) group Widal test was positive in (48) patients (98)% and it was fals negative in two patients (4) % > In ( typ- CN) group Widal test was positive in (40) patients (95.2) % which is more or less similar to (typ- CP) group. Analysis of sensitivity and specificity of Widal test in predicting a positive cases showed that the best model to be an O and / or H titer of  $\geq$  or = 1: 160 (sensitivity 92%; specificity 89%). While the negative predictive value of this model is high (99.2) %; the positive predictivevalue was below 805 even for very high tite of O and H> 1:320; at this point the specificity was, sapporung the oh nical view the high proportion of (TYP- CN ) patients realy were typhoid cases but were missed by culture . This result bring out the fact that choosing a cut off value of 1: 160 and more for O and / or H agglutinine is quiet useful as a single diagnostic test of typhoid fever (25). This study showed that the difference in poitivity of widal test in bacteriological proved tyhoid and clinically suggestivebut culture negative patients compared to the non tyhoidal febrile patients was highly significant (P<0.0007).

**Table (4)** out line records of anti O+ anti H agglutinins titersOf children in three studied groups

Group of patients	Negative	1/80		1/160		1/320		1/640		Total
		O	H	O	H	O	H	O	H	
Typ(CP)	2(4%)	4(8%)	16(32)%	20(40) %	8(16)%	50(100)%				
		0 (zero)	18(36) %	20(40) %	12(24)%	50(100)%				
Typ (CN)	2(4.7)%	4(9.5)%	12(28.5)%	18(42.8)%	6(14.2)%	42(100)%				
		1(2.3)	14(33.03)%	16(38)%	9(21.5)%	42(100)%				
Non typhoidal Febril illness	46(92)%	0(zero)				50(100)%				
		4(8)%				50(100)%				



### Conolusion The study concluded

Importance in diagnosis of typhoid fever in endemic area further more reliance on somatic (O) antigen only will result in missed diagnosis<sup>(26)</sup>. In addition the slide agglutination widal test offers the advantages of simplicity , speed , early diagnosis , economy and flexibility<sup>(27,28)</sup> .This study is supporting the clinical view that a high proportion of (typ-CN) Patients really were typhoid cases but missed by blood culture It also showed a similar clinical and laboratory profiles of ( typ-CN) and (typ-CN) patients apart from duration of fever which does not affect the initial widal titer.

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