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aHUS Diagnosis Process – patients' experience from first symptoms to escalation into specialist care.

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Abstract

Background

atypical Hemolytic Uremic Syndrome, aHUS, is a rare disease which results from uncontrolled regulation of the innate part of the immune system, called Complement, causing endothelial damage which results in a thrombotic microangiopathy (TMA). Diagnosis of aHUS presents a challenge to health care professionals resulting in misdiagnosis and treatment delay. Clinicians and patients believe that the aHUS diagnosis process could be improved.

Methods

We conducted an online survey of global aHUS patients using a questionnaire which sought patients' experience of their aHUS diagnosis process. In one section of the Questionnaire, patients' experience of the subprocess from experiencing first symptoms of an aHUS onset, to first seeking medical advice from primary care and the outcome of that advice was sought.

Results

We found that most (89%) patients reported their health state becoming rapidly (mean of 14 days) distressed. A wide range of presenting symptoms was reported, but only one symptom, nausea/sickness, was reported by more than 50% of patients. Together with incomplete use of the most common, but nonspecific, clinical tests, the outcome was that no patient was given an aHUS diagnosis in primary care, though other TMAs were suspected in five patients. For two thirds of patients the outcome was a quick passage to specialist care but with diagnostic uncertainty with half entering intensive care. Deferred patients were eventually escalated to specialist care after an average of 3 iterative diagnosis consultations. Some significant differences in age, health state, care provider and aHUS family history were observed between the two groups.

Conclusion

The failure to receive an aHUS diagnosis in primary care, although understandable, would be a shock to aHUS patients. A rapid escalation of care when their health was deteriorating fast was the next best outcome for most. The key missed opportunity for a diagnosis for a small number was a known family history of aHUS. A disease alert card may be beneficial for those predisposed, or with aHUS familial links, as evidence to help primary care professionals' in their diagnostic decisions.

Key points

1. **No patient received an aHUS diagnosis at primary health care level, although five were suspected of having other thrombotic microangiopathies, TMAs.**
2. **Patients presented with a diverse range of common symptoms and all but one, nausea/sickness, were experienced by less than 50% of patients.**
3. **There is still no specific clinical test to diagnose aHUS, also making it difficult to distinguish from other TMAs.**
4. **66 % of patients present in such a poor health state that they are rapidly escalated into specialist care after their first visit but with diagnosis uncertainty.**
5. **54% of all patients entered directly into intensive care after seeking primary care medical advice.**
6. **An aHUS alert card for patients with predisposition to, or a known family history of, aHUS could avoid some missed diagnosis opportunities.**

Introduction

atypical Hemolytic Uremic Syndrome, or aHUS, is a primary disease due to a disorder in an intrinsic part of the innate immune system called Complement. The disease manifests because of dysfunction of control within the alternative pathway of Complement which leads to self-damage to the endothelial cells lining small blood vessels, or capillaries, which triggers a micro thrombotic event known as Thrombotic Microangiopathy, or TMA (1).

aHUS is the rarest form of primary TMA (2) , which can occur in, and damage, the smallest blood vessels in vital organs, including the kidney and brain (3). It is one of a spectrum of TMAs that have different underlying pathologies, and which have differing genetic and triggering causes including infection, pregnancy, malignancy, autoimmune disease, vaccinations, and medications. Secondary TMAs can also induce a temporary complement dysregulation with an overlap between both scenarios which can make a specific aHUS diagnosis difficult (4).

A TMA is a rare condition but a medical emergency requiring immediate treatment intervention to avoid irreversible organ damage or death (5). Late or incorrect diagnosis of an acute aHUS onset can result in a mortality of 8% and with 50%–80% of patients progressing to end-stage renal failure (6).

The single most important event that will determine the successful treatment and resolution of a health problem is a correct diagnosis. A clinical diagnosis is a process that begins when someone recognises ill health symptoms and will include a team of experts working to identifying the cause of such symptoms (7). The clinical diagnosis process involves complex patient centred information gathering and clinical reasoning steps which result in an explanation of the patient's ill health and Clinicians have recognised diagnosis of rare diseases as a topic of interest (8).

aHUS patients too have identified diagnosis as a problem and believe that the process can be improved and therefore regard it as a priority for research (9,10). Late referral aHUS patients are less likely to receive

interventions that could alter the progression of Chronic Renal Failure or reduce its associated co-morbidity and be in a worse state at the start of renal replacement therapy, with longer hospitalisation and poorer survival (11).

aHUS alliance Global Action has undertaken a global study of aHUS patients' experience and perception of the aHUS diagnosis process. A report on the reasons for the study, the method used, and the results of the high-level process measures of timeline, health status and perception has been published (12).

The purpose of this study is to provide more insights into the experience of patients from first experiencing symptoms of illness , through their first seeking medical advice to receiving a first working diagnosis, and the resulting care outcome from that diagnosis.

Methods

An online questionnaire was used to gather patient's experience and perception of the aHUS Diagnosis Process and was based on the diagnosis process model as adopted by the Committee of Diagnostic Error in Health Care as illustrated in Figure 1 (13) . A section was included in the questionnaire for the patient experience of entering the primary care pathway for a diagnosis (14). There were 227 respondents, either patients or carers of patients, to the questionnaire from whom data was gathered and analysed. Characteristics of respondents are given in Appendix A.

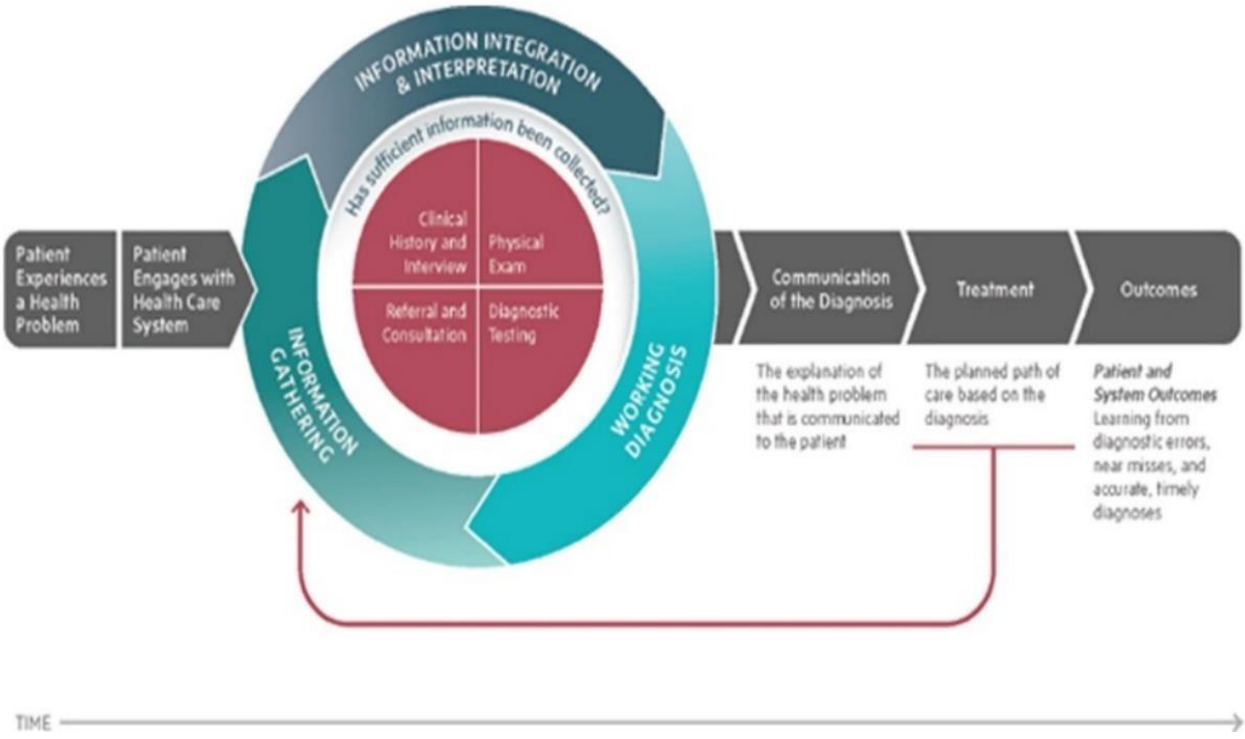

Fig 1 The diagnosis Process Model

Results

Sub-process measures

Self- declared health status

In Table 1 details of patients' self-declared health state prior to illness and on seeking medical advice are presented. Prior to illness 201 (88%) patients reported their health status as "Good to Excellent", which converted to an average health state index of 3.8/5. By the time patients decided to seek medical advice, 221(98%) patients reported their health status had fallen to " Good to Very Poor", which converted to an average health state index of 1.9/5. Similar before and after health states were reported by all age groups.

Table 1 Patients self-declared health state at the start and end of the sub process stage.

	Prior to first symptoms				**On first seeking medical advice**		
Self/proxy reported health state	**No**	**%**	**Cum %**		**No**	**%**	**Cum %**
Excellent	72	32	32		1	0	0
Very Good	78	34	66		5	2	2
Good	51	22	88		41	18	20
Poor	15	7	95		99	44	64
Very Poor	11	5	100		81	36	100
Deceased	0	0			0	0	
Total	227	100			227	100	
Average Health State Index* All	3.8				1.9		
Infants (36)	3.9				1.9		
Older children (42)	3.7				1.8		
Adults (149)	3.8				1.9		

*Health status index derived from health state reported and based on scoring excellent = 5, Very good = 4 , Good =3 , Poor= 2 to Very Poor =1

Timelines

In Table 2 the timelines from noticing first symptoms to patients first seeking medical advice and time taken to escalate health care from primary care level to specialist are shown.

89% of patients reported that it took up to 14 days to seek medical advice with a median delay of 3 days. It took up to 31days for the care of 89% of patients to be escalated to specialist level but with a median of 1 day. Three and thirteen patients, respectively, reported it took more than six months to go through the same sub steps. Their outlier timelines, including some reporting it took decades, materially affecting mean results.

Table 2 Timelines for sub process steps

	To seeking medical advice			To escalation of care		
Days	**No.**	**%**	**Cum.%**	**No.**	**%**	**Cum. %**
1	73	32	32	104	46	46
2-3	57	25	57	35	15	61
4-7	51	22	79	30	13	74
8-14	22	10	89	23	10	84
15-31	11	5	94	10	5	89
32-183	10	4	98	12	5	94
184-365	2	1	99	6	3	97
366- 5 years	1	0	100	4	2	99
Over 5 years	0	0	-	3	1	100
Total	227	100	-	227	100	-
	Gross	Net*		Gross	Net*	
Mean	14	8		70	14	
SD	62	20		413	101	
Median	3	3		1	1	
Range	1-730	1-365		1-4379	1-365	

*__excludes patients with more than 365-day timeline__

Correct Diagnosis

In Table 3 the first working diagnoses made by Primary Care/ General Practitioners (PCP/GPs) and ER Practitioners (ERPs) are shown. No patients received an aHUS diagnosis at this stage. Five patients were suspected of having other TMAs and 38 were given diagnoses of more common illnesses. For most (nearly 80%) the outcome was diagnosis uncertainty.

Table 3 First working diagnosis in primary care

Diagnosed with:	No	%
aHUS	**0**	**0**
Other TMA	**5**	**2.4**
Other Illnesses	**38**	**18.4**
None/uncertainty	**164**	**79.2**
Total	**207***	**100**

*** 20 patients reported to be already in specialist care. Two of these patients received an immediate aHUS diagnosis.**

Care pathway route

Table 4 shows the chosen routes to first seeking medical advice. 20 (9%) of patients reported already being at specialist care level. 207 (91%) patients reported their initial route for advice was at primary health care level. 107 (47%) patients visited their Primary Care Practitioner(PCP) /General Practitioner (GP), and 100 (44%) patients went to Emergency Room (ER)/ Accident & Emergency (A &E) hospital departments

Table 4 - Initial routes into health care

Advice from	No.	%
ER/A&E	100	44
PCP/GP	107	47
Already in specialist care	20	9
Total	227	100

Information gathering

Presenting symptoms

In Table 5 details of patients' symptoms on presentation are shown. 221 patients (6 patients reported no symptoms) reported presenting with one, or more, of eighteen separate symptoms. Nausea (including vomiting) was the most reported symptom, by 142 patients (63%). Each of the other symptoms were reported by 41% or less of all patients.

Table 5 Patients' presenting symptoms on first seeking medical advice

	Patients with	No.	%			Patients with	No.	%
1	**Nausea**	142	63		10	**Cold and sore throat**	29	13
2	**Headache**	94	41		11	**Bruising /Rash**	23	10
3	**Pallor/Paleness**	88	39		12	**Urine issues**	20	9
4	**Diarrhoea**	76	33		13	**Fever**	15	7
5	**Facial/Limb swelling**	58	26		14	**Pain Stomach/Back**	12	5
6	**Breathlessness**	52	23		15	**Jaundice**	10	4
7	**Confusion and Memory**	43	19		16	**Bleeding**	9	4
8	**Aching Joints**	37	16		17	**Loss of appetite**	7	3
9	**Fatigue**	37	16		18	**Dizziness**	2	1

Clinical Tests Undertaken

In Table 6 the clinical tests recalled by patients are presented. Of the four most reported clinical tests taking temperature was the highest , by 177 (78%) patients. It was closely followed by measuring blood pressure by 171 (75%) patients. Then blood tests/counts were reported by 157(69%) and 119 (52%) patients reported having their urine dipped. Another nine clinical tests were reported; but few patients experienced them. 13 (6%) of patients recalled no tests being done on first clinical visit

Table 6 Clinical Tests undertaken on first seeking clinical advice.

Tests done:	No.	%		Tests done:	No	%
Temperature	177	78		**Biopsy**	3	1
Blood pressure	171	75		**ECG**	2	1
Blood tests	157	69		**Blood culture**	1	0
Urine dip	119	52		**Lumbar punch**	1	0
Scan	9	4		**Oxygen levels**	1	0
Stool sample	5	2		**COVID**	1	0
X Rays	4	2		**None**	13	6

Working diagnosis and outcome care pathway decision.

Table 7 presents the care pathway outcome after first seeking medical advice and an initial diagnosis

114 (50%) patients were admitted to hospital following their first primary care visit. Eleven (5%)were already in hospital. Of these patients 55 (24%) went into regular hospital care, whilst 70 (31%) were admitted into intensive care. Immediate admission to hospital was 50% more likely if the patient's first visit was to an Emergency Room/A& E Department rather than to a PCP/GP, i.e., 70 (30%) patients compared with 45 (20%) respectively.

30 (13%) patients' care was escalated by referral to a specialist. 13 (5%) of those patients would subsequently be admitted to hospital with 12 (6%) of them into intensive care. The remaining 5 (3%) reported that they were treated as outpatients.

72 (32%) of patients were not immediately referred and returned home 39 (17%) either with a misdiagnosis or no diagnosis 33 (15%).

Table 7- Care pathway outcome after first working diagnosis

	Admitted to hospital		Referred to specialist		Sent home with a diagnosis		Sent home without diagnosis		Total	
Advice from	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
ER/A&E	69	30	9	4	11	5	11	5	100	44
PCP/GP	45	20	13	6	28	12	21	9	107	47
Already in care	11	5	8	4	0	0	1	0	20	9
Total	125	55	30	13	39	17	33	15	227	100
Into regular hospital	55	24	13	5	21	9	11	5	100	44
Intensive care	70	31	12	6	18	8	22	10	122	54
Outpatient	0	0	5	2	0	0	0	0	5	2
Total	125	55	30	13	39	17	33	15	227	100

Non-Escalated patient characteristics and experience

Tables 8a and 8b provide comparisons of the characteristics and experience of the 72 patients whose care was not immediately escalated with those who were escalated for specialist care.

Table 8a shows there is no significant difference (*p*-value .288598 , *p* > .05) in the comparative gender mix of those not escalated /escalated. However, there was a significant difference in the age mix (*p*-value .000017,*p*> .05). Thirty-six percent of older children were not immediately escalated. This was much higher than the 10% of older children in the escalated group.

Surprisingly, those with a known aHUS family history were significantly (*p*-value .039054, *p*>.05) less likely to be escalated. There was no significant difference for those with a family history of kidney disease *(p*-value .73741, *p*>.05).

There was no significant differences (*p*-values .752751 and .417636 , *p* >.05, respectively) in experience between eras when diagnosis was made, or the regions where patients lived.

Table 8 a Comparison of the characteristics of non-escalated and escalated patient.

		Not escalated	Not escalated	Escalated	*p*-value*
		No.	%	%	
	N = 72/155				
Gender					.288598
	Male	19	26	32	
	Female	51	71	68	
	Other	2	3	0	
Age					.000017
	Infant	13	18	15	
	Older child	26	36	10	
	Adult	33	46	75	
Era					.752751
	Before 2011	13	18	15	
	2011-2015	20	28	26	
	After 2015	39	54	59	
aHUS FH**					.039054
	No	64	89	92	
	Yes	7	10	3	
	Not known	1	1	5	
Kidney Disease FH**					.73714
	No	56	78	78	
	Yes	14	19	17	
	Not known	2	3	5	
Region					.417636
	North Americas	39	54	63	
	Europe	22	31	26	
	Rest of world	11	15	11	

*Chi-square test, *p*-value significance at *p* >.05 **FH- Family History

Table 8(b) shows that 90% (65) of patients, who were not escalated to specialist care, reported that their health state was "Poor" or "Very Poor". Whereas only 74 % of those who were to enter immediate specialist health care reported that health state. The difference is significant (*p*-value .020326 *p* > .05). Consequently, their relative health state index their average health scores of 1.8 and 1.9 respectively reflects the difference.

Sixty-eight percent (49) of non-escalated patients' first visit was to PCP/GPs care compared with 47% of patients, whose care was immediately escalated after one visit to ER/A&E. The experience of care provider chosen has a significant difference (*p*-value .001942 , *p* > .05)

Non escalation made no significant difference (*p*-value .7766, *p* > .05) to entering directly into intensive care i.e., 55% (40) and 53% respectively.

Table 8b -Comparison of experience of non-escalated and escalated patients.

	Not escalated (72)	**Not escalated**	**Escalated/In care (155)**	***p*-value**
	No.	%	%	
Health State:				.020326
Excellent	0	0	1	
Very good	0	0	3	
Good	7	10	22	
Poor	42	58	37	
Very Poor	23	32	37	
Average Health Score:	1.8		1.9	
Care Provider:				.001942
PCP/GP	49	68	47	
ER/A&E	22	31	44	
Outpatient	1	1	9	
Average No. of Visits	3.3			
Time to escalation (days)	12			
Specialist entry level:				.7766
Hospital	32	45	47	
Intensive Care	40	55	53	

Discussion

With no access to patients' medical records, this study is reliant on self, or carers' proxy reporting of events, timelines and outcomes of patients who have been through an aHUS diagnosis process. Bias can result, as much of it depends on recall of events, which occurred in some cases years or decades before, as well as subjective and retrospective reporting . In such an approach it is likely that timelines may differ from actual and may be approximate estimations (15).

Bias may also result from the way in which patients participated in the study(16). Although participants were unselected volunteers, they were from those who were connected in some way with the organisation and website of the aHUS alliance Global Action, either directly or via international aHUS patient social networks that interface with the website. The characteristics and demographics of the study participants is presented in Appendix A . A higher proportion of North American patient experiences, as well as a higher number of female patients, may have participated as a result. The experiences and perceptions of this study group may be more

reflective of the developed world and a female patient viewpoint.

Overall, however, the age and gender characteristics of study participants do not differ significantly from expected results derived from the sum of other aHUS Global Registry/ Patient Global Poll reports (17,18,19,20). There are more aHUS adults than children; and there are more females with aHUS than males. The gender/age differences are also consistent because there are more boys than girls in the infant age group, whereas in older children there is no gender difference. In adulthood aHUS women are much more prevalent than men.

Most patients reported a substantial drop in personal health status from first noticing symptoms of an illness up to seeking medical advice about its cause. Apart from 20 patients who reported that they were already in specialist care (due to pregnancy, transplant or cancer) , 207 patients entered at primary care level with visits to PCP/GP/ERPs in almost equal numbers (47% v 44%). Most patients reported an abrupt and rapid onset of illness. A small number of patients reported they had experienced symptoms for months or a year or more before, which, when looking back, they think may have been indicative of a slowly developing form of aHUS.

None of the patients were to receive an aHUS diagnosis at this level. So, the issue is whether there were missed opportunities at this level of care for PCP/GP/ ERPs to have made an aHUS diagnosis.

PCP/GPs acknowledge that their methods and practices are geared towards looking for the common causes of patient health problem rather than those of rare diseases (21). In some countries PCPs/GPs collectively may undertake hundreds of millions of doctor/patient consultations, but among that number there may only be dozens of interactions with patients presenting with aHUS (22,23). There are estimated to be 7000 rare diseases (24), and whilst there is expectation of receiving an accurate explanation of the patient's health problem, it is unrealistic to expect PCP/GP/ERPs to be aware of the symptoms for each low prevalence disease and so a diagnostic uncertainty could be a most likely outcome (25,26).

The diagnosis process in primary care is not solely aimed at reaching a definitive diagnosis but also to be a gateway to more specialised management of the patient. With overlapping and unexplainable symptoms, together with low value predictive tests at hand, the process becomes a combination of short cuts , loops and sometimes dead ends, in the time between presentation and the final working diagnosis (27).

Together, 221 aHUS patients recalled an array of 18 symptoms, of which each patient experienced one or more. None of the patients reported all. Only one, nausea/being sick, was reported by more than half of patients.

As the analysis in Table 9 shows the symptoms reported by aHUS patients are also common to other illnesses (28 29,30,) depending on timing of first visit, presenting symptoms could be of the aHUS precipitating condition and before displaying the physical effects of a manifesting thrombotic microangiopathy (31,32,33).

Typically for colds, influenza, and gastroenteritis it could take three to seven days for symptoms to develop after an infection, and their effects may continue to be felt for 7 to 14 days before abating (28,29,34).

There is very little in the literature about how long it takes for the unregulated complement in aHUS to trigger a TMA. Or for the TMA to be symptomatic and become a medical emergency. In those patients re-onsetting with aHUS after remission following a complement inhibitor withdrawal (35), or a renal transplant, clinical signs may be apparent with 24 hours of a previous negative urine or blood test because of close patient monitoring. Symptoms in naïve aHUS onsets may not reveal themselves for another 2 to 3 days or more, the TMA taking even longer to become an emergency health problem to the patient.

A COVID infection has been found to be a trigger of an aHUS onset (36). Symptoms of COVID 19 appear within 2 to 12 days following an infection and in mild cases can be present for up to a further 14 days (37). In a study of five aHUS patient onsets, two patients were found to have COVID at the time of their TMA diagnosis, whilst three patients who had been diagnosed with COVID had their TMA manifestations recognised and diagnosed between 10, 12 and 30 days later. In all cases patients' COVID episodes had been mildly symptomatic (38)

Of the triad of clinical manifestations of aHUS symptoms shown in Table 9 , acute kidney injury , anaemia, and thrombocytopenia, eight of the symptoms reported could be evidence of acute kidney injury, eight of them

anaemia and only four of them thrombocytopenia (low platelets). However, they were not consistently present in all patients. This would make a suspicion of aHUS more unlikely.

Table 9 Analysis of presenting symptoms for other conditions and aHUS

	Other conditions					aHUS			
Symptoms	**Patients Reporting**								
Patients with	**No.**	**%**	**Gastro-enteritis**	**Influenza**	**UTI**	**Evans Syndrome**	**Anaemia**	**AKI**	**Platelets low**
Nausea/vomiting	142	63	X	X				X	
Headache	94	41	X	X			X		
Pallor/Paleness	88	39				X	X		
Diarrhoea	76	33	X	X					
Facial/Limb swelling	58	26						X	
Breathlessness	52	23				X	X	X	
Confusion and memory	43	19						X	
Aching joints	37	16		X					
Fatigue	37	16	X	X		X	X	X	X
Cold and Sore throat	29	13		X					
Bruising/Rash	23	10				X			X
Urine issues	20	9	X		X	X		X	
Fever	15	7	X	X	X	X			
Pain Stomach/Back/Chest	12	5	X		X		X	X	
Jaundice	10	4				X			
Bleeding	9	4							X
Loss of Appetite	7	3		X					
None	6	3							
Dizziness	2	1	X			X	X		
Seizures*	0	0						X	
Palpitations*	0	0				X	X		
Tinnitus*	0	0		X					
Blood in stools*	0	0	X						X
Cold hands/feet*	0	0					X		

8* not reported by patients

Information was gathered from clinical tests to assist the determination of the cause of illness. Table 10 shows that 211 (94%) patients' recollection is of having one or more of twelve different clinical tests. No patient reported having all clinical tests. Only four clinical tests were recalled by more than 50% of patients. The most common test reported by 78% of patients was taking the patient's temperature, followed by measuring their blood pressure (75%) , taking a blood sample (69%) and a urine dip (52%). Table 10 maps the typical tests for the signs of common conditions and the aHUS triad (39, 40, 41,42,43, 44,45). A blood test is the most likely to reveal the triad of aHUS signs and rule out more common conditions. Blood pressure might reveal anaemia and urine dip a kidney problem but other reasons for abnormal results are possible. An elevated temperature may only be indicative of an infection which might be caused by a precipitating viral/bacteria condition.

Table 10 Clinical tests undertaken on first seeking clinical advice.

Tests done	No.	%	Gastro-enteritis	Influenza	UTI	Evans Syndrome	Low platelets	AKI	Anaemia
Temperature	177	78	**X**	**X**	**X**				
Blood pressure	171	75							**X**
Blood tests	157	69				**X**	**X**	**X**	**X**
Urine dip	119	52			**X**			**X**	
Scan	9	4					**X**	**X**	
Stool sample	5	2	**X**						
X Rays	4	2							
Biopsy	3	1				**X**		**X**	
ECG	2	1							
Blood culture	1	0	**X**						
Lumbar punch	1	0							
Oxygen levels	1	0							**X**
COVID	1	0		**X**					
None	13	6							

With the evident distressed health state in most patients but with non-specific presenting symptoms and clinical tests, PCP/GP/ERP interpretation of the data gathered resulted in an initial working diagnosis and decision on what to do.

The decision for two thirds of patients was to escalate care immediately to specialist care, mostly with uncertainty of diagnosis but with five patients suspected of having another TMA. For those not referred, the advice was to return home with a misdiagnosis, or no diagnosis. Those patients would have to wait longer, with an average of three further visits to their PCP/GP/ERP before a referral to specialists. A few patients reported twenty or more revisits.

Some significant differences in age, health state, care provider and aHUS family history were observed between the referral groups. Most surprising was that more patients with a family history of aHUS were not immediately referred to specialists. Nor did the family history of those referred raise a suspicion of aHUS. This could be viewed as a missed diagnosis opportunity. Awareness of someone with a known genetic predisposition to aHUS, or who has familial links to an aHUS patient, could be helpful in explaining a manifesting TMA. In some countries an "alert card" has been distributed to such people so they can present to doctors to ask them consider an aHUS onset if the patient feared a possibility of aHUS (46.47).

Conclusion

Most aHUS patients rapidly seek medical advice at primary care level on the cause of their ill health. Presenting in a poor health state but with a broad range of disparate common symptoms and receiving non-specific clinical tests, no patient was given an aHUS diagnosis at primary care level. Although five patients were suspected of having other TMAs (TTP, HUS and Evans Syndrome).

Whilst primary care professionals were unable to diagnose aHUS, fortunately they were sufficiently concerned about their patient's unexplainable distressed state and clinical signs to refer most of them immediately to specialist care level. The remaining patients received no diagnosis or a misdiagnosis and were sent home to revisit for an average of three occasions before their care was escalated too.

Whilst more awareness of rare diseases in medical education would be beneficial, awareness of TMA as a medical emergency would, as has been shown in a small number of cases, be beneficial to get naïve aHUS patients access to care needed. For those predisposed to, or with a known family history of aHUS, the availability of an alert card may be of help to primary care professionals in arriving at an aHUS working diagnosis.

This research topic could also benefit from a study using the medical records of PCP/GP/ERPs whose patients were ultimately diagnosed with aHUS.

More data is needed about aHUS patients' experience during the next process sub steps of specialist care, including clinical manifestations , clinical tests, care pathways and clinical specialisms involved in making aHUS working diagnoses.

aHUS patients are known to share anecdotes about their first encounter with the healthcare services and the anxieties of both being very ill and facing clinical uncertainty. To the best of our knowledge this is the first study of the aHUS diagnosis process relying on patient's recalled experience, rather than medical records. Its assembly and analysis shifts anecdotes to shared perception of health care practice in a very difficult time for them.

Appendix A Characteristics of patients participating

	Under 18 years									
	Infants		Older children		All under 18		All 18 and over		All patients	
	No .	%	No.	%	No.	%	No,	%	No	%
Age (years) :										
0 to 18	36	16	42	18	78	34	-	-	78	34
18 to 54	-	-	-	-	-	-	127	56	127	56
55 and over							22	10	22	10
Total	36	16	42	18	78	34	149	66	149	100
Gender:										
Female	16	7	21	9	37	16	119	53	156	69
Male	20	9	20	9	40	18	29	12	69	30
Other	-	-	1	0.5	1	0.5	1	0.5	2	1
Regional territory:										
N. America	20	9	20	9	40	18	103	45	143	63
Europe	6	3	15	7	21	9	37	17	58	26
Rest of World*	10	4	7	3	17	7	9	4	26	11
Lifestyle:										
Infant	36	16	-	-	36	16	-	-	36	16
Studying	-	-	42	18	42	18	21	10	63	28
Working	-	-	-	-	-	-	107	47	107	47
Retired	-	-	-	-	-	-	10	4	10	4
Other**	-	-	-	-	-	-	11	5	11	5
Diagnosed:										
Pre-2011	10	4	8	3	18	7	18	7	36	14
2011-2015	6	3	11	4	17	7	44	21	61	28
Post-2015	20	9	23	11	43	20	87	38	130	58

Family History:										
aHUS Known	4	2	1	0.5	5	2.5	7	2.5	12	5
aHUS not known	1	0.5	2	1	3	1.5	6	2.5	9	4
No history	31	13.5	39	16.5	70	30	136	61	206	91
Kidney Disease Known	6	3	4	2	10	5	30	13	40	18
Kidney disease not known	2	1	2	1	4	2	5	2	9	4
No history	28	12	36	15	64	27	114	51	178	78
Genetic predisposition***										
All Yes	32	14	35	15	67	29	101	45	168	74
All No	3	1	7	3	10	5	48	21	58	26
Overall +ve %	91	-	83	-	87	-	68	-	74	
By Gender										
Female -Yes	14	6	16	7	30	13	76	34	106	47
Female- No	1	0.5	5	2	6	2	43	20	49	22
Female +ve %	93	-	71	-	83	-	64	-	68	
Male -Yes	18	8	19	8	37	16	23	10	60	26
Male – No	2	1	2	1	4	2	5	2	9	4
Male +ve %:	90	-	90	-	90	-	82	-	87	
Other Yes	-	-	1	-	1	-	1	-	2	1
Other +ve %	-	-	100	-	100	-	100	-	100	

Africa-2 Asia-10 Oceania-12 South America-2 ** homemaker-2 ill-2 maternity-5 unemployed-2

*** 1 no response

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Authors contributions.

LW, LB, KS conceptualised and designed the study. LW, LB, KS designed the data capture instrument and KS set it up online. LW and KS undertook the intial analysis and LW drafted the initial version of the manuscript. All authors contributed to the revision of the manuscript and have read and approved the final reports. All authors read and approved the final manuscript.

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