Patients' experience and perception of the diagnosis process of the rare disease, atypical Hemolytic Uremic Syndrome (aHUS)

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Abstract

Background

atypical Hemolytic Uremic Syndrome (aHUS) is a disorder of an intrinsic part of the innate immune system called Complement. aHUS is difficult to diagnose because of its ultra- rarity, varied presentation, confounding clinical manifestations, lack of specific clinical tests and vague disease name. Delay in diagnosis can cause death or significant organ damage and lasting physical and psychological harm.

Methods

We conducted an online survey of global aHUS patients. A questionnaire was devised which sought patients' experience of their aHUS diagnosis process from their first symptoms of an aHUS onset, through their health care pathway to receiving an aHUS diagnosis and its outcome. The questionnaire included process measures of time taken in key process steps, self-reported health status at each step and the perception the patients had about the overall process.

Results

The timelines revealed by 227 respondents to the questionnaire describe a disease that was variable in onset symptoms tolerability before medical advice was needed (mean 8 days, median 3 days). On seeking medical advice at primary healthcare level, most patients were quickly (mean 14 days , median 1 day) escalated to specialist healthcare while a minority experienced some delay in doing so. The longest process timeline (mean 32 days, median 7 days) was experienced in specialist care before a diagnosis was given. Self-reported health status of the patients dropped overall from a pre illness ,"Good to Excellent" status to "Poor to Very Poor" before seeking medical advice. It deteriorated further while waiting for escalation to specialist care and finally a diagnosis decision. Overall patient perception of the process was split between those who felt confidence in ,or a little anxiety about, it (56%) ; and those who were left with a feeling of high anxiety following the experience or damaged confidence in the process (44%).

Conclusion

aHUS presents a challenge for diagnosis. At primary care level a quick recognition is needed of an unexplained blood problem like anaemia, or a kidney function problem, to enable rapid escalation to specialist healthcare. It then needs specialists to identify a thrombotic microangiopathy (TMA) quickly and apply clinical tests and reasoning to determine the cause of the TMA. For most aHUS patients a correct and timely diagnosis is achieved. For around a third of patients there are significant delays in one or more of process steps before a correct diagnosis is arrived at. This often resulted in the worst of patient physical and mental health outcomes. More information is needed about patient reported symptoms, clinical tests performed , clinical specialisms encountered, working diagnoses given and impacts on outcomes and legacy treatment. This study has given aHUS patients the first opportunity to say collectively what the diagnosis process is like from their viewpoint.

Introduction

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 (1). 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 (2).

Rare diseases present a difficult challenge to the diagnosis process. Patients often present with symptoms of common conditions and to clinicians who may not have seen, or been aware of, a specific rare disease before (3).

Atypical Hemolytic Uremic Syndrome ,or aHUS, is one of 7,000 known rare disease conditions (4). It is exceptionally rare by any definition of a rare disease in the USA, UK, Europe, and Japan (5,6,7,8,9). Estimates of aHUS patient prevalence range from around two to ten per million of the population, depending on region and age, meaning potential prevalent numbers of patients range between 16,000 and 79,000 globally

Annual incidence rates are unknown but are estimated at between 0.23 to 1.9 per million of the population. At an incidence rate of 0.5 per million of the population there would be around 4,000 potential patients globally in need of an aHUS diagnosis each year(10).

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 (11). TMAs are a group of disorders characterized by microangiopathic hemolytic anaemia, thrombocytopenia and microthrombi leading to ischemic tissue injury . Though rare, thrombotic microangiopathies are life-threatening conditions that require urgent management. Presenting symptoms may be nonspecific, but basic laboratory tests reveal a specific constellation of thrombocytopenia and anaemia with red blood cell fragmentation on the blood film and evidence of haemolysis. (12)

aHUS is the rarest form of TMA (13) , which can occur in, and damage, the smallest blood vessels in vital organs, including the kidney and brain (14). It is one of a spectrums of TMAs that have different underling pathologies, and which have differing genetic and triggering causes including infection, pregnancy, malignancy, autoimmune disease, vaccinations, and medications (15). Secondary TMAs can also induce a temporary complement dysregulation with an overlap between both scenarios which can make a specific aHUS diagnosis difficult (16).

A TMA is a relatively rare condition but a medical emergency requiring immediate treatment intervention to avoid irreversible organ damage or death (17) . Late or misdiagnosis of an acute aHUS onset can result in a mortality of 8% and with 50%–80% of patients progressing to end-stage renal failure (18).

When creating their research agenda, aHUS patients included the following research topic:- "*Is there a diagnosis sweet spot which can be found before a developing thrombotic microangiopathy turns into a catastrophic episode of aHUS?" (19)* . Underlying concerns were expressed to support priorities for research by an International aHUS Registry, including: "Is *there a "golden period" for diagnosis which can predict more favourable outcomes for patients with aHUS?"*, *"Can the degree of kidney function recovery be predicted by the time between aHUS onset and diagnosis/treatment?"* and "*What are the barriers to diagnosis, and how can they be overcome?"* Thereby suggesting from experience that there is a point within the diagnosis process timeline beyond which kidney damage becomes chronic and a poorer health outcome follows (20).

Increasingly patient advocacy organisations are gathering information from patients themselves about their experience and perception of their disease diagnosis to raise awareness and inform of unmet needs resulting in incorrectly/untimely treated disease following misdiagnoses and diagnosis delays (21).

The purpose of this research is to describe and measure performance of the aHUS diagnostic process from the aHUS patient's perspective; and to provide insights into the timelines, health state changes, and outcome perceptions of steps in the aHUS diagnosis process.

Methods

An online questionnaire was used to gauge patients' experience and perception of their aHUS diagnosis process. It was completed by aHUS patients , or aHUS care givers on behalf of the patients.

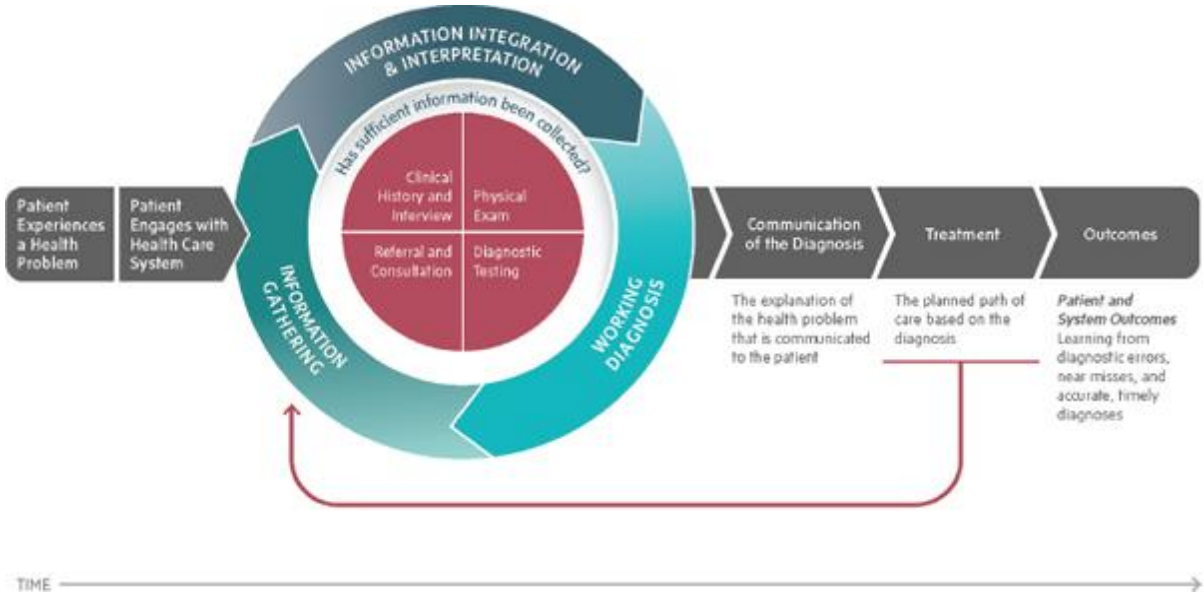

Figure 1 Conceptual Model of the Diagnosis Process (2)

The questionnaire included questions structured around the steps in a clinical diagnosis process model (Fig.1) conceptualised by USA institute of Medicine Committee on Diagnostic Error in Health Care (2). These included the process steps from first experiencing a health problem, seeking medical advice , escalation to specialist care, through to gaining and the outcome of an aHUS diagnosis. It did not seek examples of their treating clinicians' reasoning, the palliative treatments received or the quality of care before a diagnosis was made.

The resulting draft questionnaire was tested on six patient advocates, patients and clinicians and any suggested amendments were made prior to draft approval.

Information about the confidentiality, care and use of the participants data was published in the survey launch article on the aHUS alliance Global Action website (22). It was repeated in the questionnaire to gain participants' positive informed consent before the main questionnaire was entered.

To encourage global participation attention was drawn to the survey questionnaire via international patient organisations, social media networks and direct mail to patients who have contacted the investigators in the past. The questionnaire, however, was only available in the English language.

The survey questionnaire was launched on 25 November 2020 and remained open until 19 January 2021. Once closed the SurveyMonkey file of questionnaire responses was downloaded to a master Excel spreadsheet. Initial examination revealed that of the 270 respondents in the SurveyMonkey file, 11 respondents had answered no more than the informed consent question. Further examination revealed that 32 respondents had only partially completed the questionnaire and were excluded because their data did not extend to the whole of the diagnosis process. The research results would therefore be based on 227 respondents. The website page with the portal to the online questionnaire had 654 views during the time that it was open to view, 227 participants , therefore, represents a response rate of 35%.

Prior to analysis, responses were checked for completeness and need for corrections to qualitative and quantitative responses to permit application of analytical formulae. Subsequently tables were produced for the process quality measures of timelines of, patient health status during, and perception about, the diagnosis process.

Results

Characteristics and Demographics of participants

The characteristics and demographics of the 227 patients participating in the study are shown in Table 1. The study participants included 149 (66%) aged 18 and over, and 78 less than 18 years of age. The highest number of patients 127 (56%) were aged between 18 and 54 years. 156 (69%) were female, and 69 (30%) were male, with 2 (1%) reporting they were of another gender. 40 (58%) of the male participants were less 18 years old, 29 (42%) were older, whereas only 37 (24%) of female participants were less than 18 years and 119(76%) were older. Of those reporting "other" gender 1 (50%) was under 18 years, and 1 (50%) was over 18 years.

Table 1 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

Table 1 Continued

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

143(63%), 58 (26%) and 26 (11%) reported they were from the North Americas, Europe, and the Rest of the World, respectively.

Prior to their diagnosis 36 (15 %) of under 18- year- olds were infants and the other 42 (19%) were studying. 21 adults were also studying. 107 (47%) adults were working and 10 (4%) were retired. There were 11 (5%) otherwise occupied as homemakers, ill, on maternity leave or unemployed.

36 (16%) patients were diagnosed with aHUS prior to 2011, 61 (27%) between 2011-2015 and 130 (57%) were diagnosed after 2015. 12 (5%) patients knew of a family history of aHUS at the time of their diagnosis and 9 (4%) found out later but did not know at that time. 40 (18%) were aware of kidney disease in their family at the time of being diagnosed, whereas 9 (4%) did not know. 206 (91%) and 178 (78%) respectively reported that there was no family history of aHUS or kidney disease.

168 (74%) patients reported that they had tested positive for aHUS predisposing genetic factors Male patients reported the highest positive genetic predisposing rate, 87% compared with 64 % for females. Patients less than 18 years old similarly had a positive genetic predisposing rate of 87% , which was much higher than the rate for adults at 68%.

Process Measures

Timelines

In Tables 2 the reported timelines for the overall process and each of the sub process steps,(i.e., from first symptoms to seeking medical advice, escalation to specialist care, and time from entering specialist care to being given a diagnosis) are shown. A time interval analysis, from 1 day upward to over 5 years, across the process is provided. Table 2a shows the mean and median results from the reported timelines including adjustments for outliers.

Table 2 Over all Process and Sub Process Timeline Experience reported by participating patients

	Overall Process				To seeking medical advice				To escalation of care				To aHUS diagnosis		
Days	**No.**	**%**	**Cum. %**		**No.**	**%**	**Cum.%**		**No.**	**%**	**Cum. %**		**No.**	**%**	**Cum. %**
1	0	-	0		73	32	32		104	46	46		29	13	13
2-3	8	4	4		57	25	57		35	15	61		37	16	29
4-7	34	15	19		51	22	79		30	13	74		41	18	47
8-14	41	18	37		22	10	89		23	10	84		26	12	59
15-31	40	18	55		11	5	94		10	5	89		25	11	70
32-183	50	22	77		10	4	98		12	5	94		28	12	82
184-365	10	4	81		2	1	99		6	3	97		11	5	87
366- 5 years	27	12	93		1	0	100		4	2	99		16	7	94
Over 5 years	17	7	100		0	0	-		3	1	100		14	6	100
Total	227	100	-		227	100	-		227	100	-		227	100	-

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Table 2a Average timelines for Overall Process and Subprocesses

Days	Overall (gross)	Overall (net)*		To seeking medical advice (gross)	To seeking medical advice (net)		To escalation of care (gross)	To escalation of care (net)		To aHUS diagnosis (gross)	To aHUS diagnosis (net)
Mean	381	29		14	8		70	14		295	32
SD	956	52		62	20		413	101		856	62
Median	23	16		3	3		1	1		10	7
Median range	3-5293	3-365		1-730	1-365		1-4379	1-364		1-5110	1-365

*net i.e., excluding undiagnosed/misdiagnosed and slower symptom development over 365 days.

123 (55%) of patients reported that they received an aHUS diagnosis within 31 days of noticing symptoms. For 104 (45%) patients it took more than 32 days. 42 (19%) patients reported a rapid diagnosis process timeline of 7 days or less, whereas 44 (19%) patients reported it took more than one year to get an accurate diagnosis.

The average time reported for the whole process was 381 days (std dev 956), whilst the median time taken was 23 days (3-5293). Excluding the long-time undiagnosed and misdiagnosed (outliers, taking more than one year) the results were 29 days (std. dev 52) and 16 days (3-365) respectively.

203 (89%) of patients reported a rapid onset of illness with symptoms only tolerable for up to 14 days before first seeking medical advice.

The average time taken by patients to seek advice following symptom onset was 14 days (std. dev. 62), with a median time of 3 days (1-730). Excluding the outlier patient with very slow (i.e., taking more than one year) symptom development, the mean time is 8 days (std. dev. 20) with the median remaining at 3 days (1-365). Three patients took a year or more to make a first visit for medical advice.

Having sought medical advice, the care for 169 (74%) patients was escalated to specialist level in the following seven days, for 104 (46%) it was immediate. It took more than a year for 7 (3%) patients to be referred to specialist care.

The mean time to care escalation was 70 days (std dev. 413) and a median time of 1 day (1-4379). Excluding long term undiagnosed and misdiagnosed (outliers more than one year), the mean time for care escalation was 14 days (std. dev. 101) and an unchanged median of 1 day (1- 364).

Once in specialist care 107 (47%) patients were given an aHUS diagnosis within 7 days or less; and 30 (13%) patients remained undiagnosed/misdiagnosed for over 365 days, including 14 (6%) who were misdiagnosed for more than 5 years. The mean time to diagnosis in specialist care was 295 days (std.dev 856) and with a median of 10 days (3-5110 days). The results excluding the long-term misdiagnosed patient revealed a mean time to diagnosis of 10 days (std dev.62) and a median of 7 days (1-365).

Health Status

Table 3 gives the health states reported using a version of the EQ-5D instrument before, within, after the process. Prior to first feeling symptoms 201 (88%) patients reported their health was "Good to Excellent" on the five-point scale from "Very poor" to "Excellent" health. Using a numerical scale from 1 for "Very Poor" to 5 for "Excellent", their reported health converted to a health state index of 3.8, which would be the top end of a "Very Good" health rating.

On seeking medical advice 221 (98%) of patients reported their health to be "Good to Very Poor" which converted into a health state index of 1.9, i.e., at the top end of a "Poor" health state. In the time taken to achieve an aHUS diagnosis 224 (99%) of patients were reporting health to be "Good to Very Poor" with an average health state of 1.4 dropping into the lower end of "Poor" health state.

Table 3 aHUS Diagnosis Process – Patients self-declared health state at key stages with conversion to a health state index

	Prior to first symptoms			On first seeking medical advice			At time of diagnosis			At time of study participation		
Self/proxy reported health state	**No**	**%**	**Cum %**	**No**	**%**	**Cum %**	**No.**	**%**	**Cum %**	**No.**	**%**	**Cum %**
Excellent	72	32	32	1	0	0	0	0	0	25	11	11
Very Good	78	34	66	5	2	2	3	1	1	77	34	45
Good	51	22	88	41	18	20	13	6	7	96	42	87
Poor	15	7	95	99	44	64	53	23	30	23	10	97
Very Poor	11	5	100	81	36	100	158	70	100	4	2	99
Deceased	0	0		0	0		0	0		2	1	100
Total	227	100		227	100		227	100		227	100	
Average Health State Index* All	3.8			1.9			1.4			3.4		
Infants (36)	3.9			1.9			1.5			3.8		
Older children (42)	3.7			1.8			1.3			3.8		
Adults (149)	3.8			1.9			1.4			3.1		

Self-reported health state index based on Excellent=5, Very Good =4, Good=3 Poor =2, Very Poor=1 Deceased=0

At the time of participating in the study 198 (87%) patients reported their health state had reached "Good to Excellent" levels with an average health score of 3.4, i.e., in the mid lower end of "Very Good". Similar trends in self-reported health scores across the diagnosis steps were observed in 36 infant patients, 42 older children and 149 adults. Older children reported the lowest health state index of 1.3 prior to an aHUS diagnosis ,and adults had the

lowest outcome health state index, 3.1, at time of study participation. The reported health recovery for under 18s was almost at (infants) , or better than (older children) , their reported pre illness health state.

Perception of aHUS diagnosis process

In Table 4 the results of 225 (99%) patients who gave an opinion on how they felt about their diagnosis process experience as described for them in four given prepared statements in descending order of favourability. 127 (56%) patients agreed with statements A and B , 43 (19%) and 84 (37%), reflecting a relaxed and confident perception in the way their diagnosis process had been handled. 98 (44%) of patients agreed with statements C and D. 56 (25%) and 42 (19%), having been extremely anxious and having had their confidence shaken by the process they had experienced.

Table 4 – Patients perception of their aHUS diagnosis experience

		No.	%
Statement A	**It was not approached any differently from other healthcare issues, so I felt relaxed about getting info & options**	43	19
Statement B	**It was a little more complicated than I thought it would be to get an explanation, but felt confident about it**	84	37
Statement C	**I was extremely anxious that doctors did not seem to know what I had and what to do**	56	25
Statement D	**I did not know how hard and prolonged it would be to get a diagnosis of what was wrong with me, my confidence was really shaken**	42	19
	Total	225	100
	No opinion	2	-

Discussion

Participating patients' characteristics

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 (23). In such an approach it is likely that timelines may differ from actual and may be approximate estimations (24).

Another source of bias may result from the way in which patients participated in the study. 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. 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 participants do not differ significantly from expected results derived from the sum of other aHUS Global Registry Patient Poll reports (25, 26, 27,28). 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. Among the respondents in this study there was a substantially higher gender

difference in the 55 and older age group, there were 20 women and only 2 men. This may also explain the relatively higher female patients than males participation in the study because without the older patients, the young and middle-aged patients have a gender mix of 66F:33M which would fall within expected gender parameters.

Prior to symptom onset, all patients reported an active lifestyle. 80% were occupied, either in employment(47%), in education (28%) or domestically (5%) respectively. 20% were either preschool infants (16%) or retired (4%). A serious and severely debilitating health problem would seem to have a marked impact on their previously active lifestyle.

A smaller number of patients reported being aware of a family history of aHUS at the time of their diagnosis than having been reported before in aHUS research (26); There was more awareness of kidney disease in the family, which is a factor in aHUS disease. For most aHUS patient there was no known family history of aHUS or kidney diseases to help in making a diagnosis.

High level diagnosis process measures

The three high level measures of the process and sub steps with the process:

- The timeline it takes to be given an aHUS diagnosis .
- The quality of health status during and following the process.
- The perception of patients about the process they experienced.
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Timeline

The overall mean time from first symptoms to receiving a diagnosis is 381 days. There was a mean time of 14 days before patients sought medical advice initially, a mean time of 70 days before there was an escalation of care to specialist care and a mean time of 295 days while in specialist care to receive an aHUS diagnosis. If typical of the quality of the process, aHUS patients would almost certainly have the worst of clinical outcomes. However , the mean results disguise the more typical experience revealed by the median results – an overall median timeline of 23 days from symptoms being noticed to diagnosis, and sub process steps median timelines of 3, 1 and 10 days respectively which confirms an abrupt onset, swift escalation and then most time spent in specialist care waiting for a diagnosis.

Most patients reported symptoms up to 14 days before seeking medical advice and that timeline would include symptoms from any triggering condition such as viral or bacterial infections which can be present for 7 to 14 days. In that time any uncontrolled complement amplification may start to trigger the damaging TMA. There is little data in literature about the time it takes for a TMA to become an emergency. A TMA can be traceable within 24 hours of a prior negative test , through haemoglobinuria appearance in a urine dip by those self-monitoring patients who have withdrawn from treatment (29). It could take a further 48 hours before significant thrombocytopenia is evident and in those who have a naïve onset, it might take another 36/48 hours for the TMA to become the haematological emergency (30, 31) . Seven days from identifying " manifestation" of a TMA and a diagnosis of aHUS has been stated to be the pivot point to avoid the more harmful of outcomes (32).

The results also reveal that for some patients there is a prolonged onset with symptom severity more tolerable , or possibly intermittent, for a long time before medical advice is sought. For some patient a significantly longer time may be experienced before a care escalation decision is made. For some in specialist care the working diagnosis falls short of an aHUS diagnosis and results in a long-term misdiagnosis with an alternative TMA. A long-term diagnosis delay of 31 days or more was reported by 81 (36%) patients in one or more of the sub steps of the aHUS diagnosis process.

The timeline of an aHUS diagnosis is influenced by the natural course of precipitating conditions, followed by TMA development up to symptoms becoming intolerable and the quality the overall care pathway experience.

Health Status

Using an adapted version of EQF-5L instrument, the health state reported prior to symptom appearance shows that most aHUS patients report they were in "Good to Excellent" heath, which was reflected in the active lifestyle reported before the disease on set. Their self- reported health state index score drops rapidly from of 3.8/5 pre onset to 1.9/5 by the time medical advice is sought, when most patients self-reported that their health had become "Good to Very poor". After entering specialist healthcare, the health state of patients is reported to have declined by a further 25% to 1.4/5 in the time taken to decide what the patient health issue was due to. During this longest timeline in the aHUS diagnosis palliative care, or interim treatment, would partially offset further deterioration in health state.

Following the diagnosis and treatment patients report a recovery to a similar health state before illness onset for under 18-year-olds, 3.8/5; but there is a longer adverse impact on adults'. Adults' health state index had reached only 3.1/5, just above "Good" in the "Good to Very Good" step. Fewer reported that post illness they had "Excellent" health with more reporting just "Good" health.

Patients' Perception

The third high level process measure is about patients' thoughts about their experience after going through the diagnosis process, based on their choice from four statements which reflect the complexity of what they had experienced and how confident or anxious they felt about it during and after. Just over half of patients agreed with statements that reflected confidence and lower anxiety about the process they had gone through which was only slightly more complicated than they thought it would be. Just under half of patients thought otherwise and with elevated feelings of anxiety and loss of confidence from an experience in which clinicians appeared not understand nor know what to do for their care resulting taking longer to arrive at a diagnosis, sometimes after a long-term misdiagnosis..

Conclusion

From the recalled experience of patients, aHUS is described as a disease which can onset suddenly and unexpectedly, becoming rapidly life threatening; but which, in a small number of cases, can also have a prolonged insidious onset. A rapid diagnosis is needed when it is in its crisis state and when patients present in poor to very poor health. Once escalated to specialist healthcare the time taken to identify a TMA manifestation, and the cause of that manifestation, becomes vital as patients' health continues to deteriorate further.

Most of the diagnosis process timeline is spent in specialist care. Eventually, for all the participants, a clinical diagnosis of aHUS was made, but for some their initial working diagnosis was wrong and those patients reported a misdiagnosis for a long time, sometimes for many years or decades.

Patients' opinion was almost equally divided on the lasting perception of their experience of the aHUS diagnosis process, between those who felt confident and relaxed about the process that they had been through and those who faced uncertainty in their clinician's diagnosis delays and found it more traumatic with a lasting shaking of confidence in, and elevated anxiety, about it.

More data about patients' experience during the process sub steps is required to better understand the results of the high-level process measures presented. Including presenting symptoms, clinical tests, care pathways and clinical specialisms involved, working diagnoses, and legacy treatments.

aHUS patients are known to share anecdotes about their lived experience of an aHUS diagnosis in social media and at aHUS patient gatherings. To the best of our knowledge this is the first study of the aHUS diagnosis process relying on patients recalled experience, rather than medical records. Its assembly and analysis shifts anecdotes to shared perception of health care practice in a very difficult time. It collectively reflects the reality of what it is like to go through the process to be diagnosed with the rare disease, aHUS.

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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 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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