

POINT-BY-POINT REPLY TO THE REVIEWERS

Reviewer #1

Specific Comments to Authors: Authors has reviewed the literature regarding Giant Cell hepatitis in detail. Overall the manuscript well-described the available literature with emphasis on pathophysiology and available treatment options. A table should be added summarizing the treatment options and response in infantile Giant Cell hepatitis. There are few grammatical and syntax errors which also be checked before consideration for publication.

- We thank the reviewer you for appreciating our manuscript. As mentioned by the reviewer, we aimed at providing an overview on infantile giant cell hepatitis associated to autoimmune hemolytic anemia. Rather than making a new table, we preferred to complete the current table with the detail that, in our opinion, is the main innovative therapeutic point for this clinical condition, namely the use of rituximab. Therefore, in the table, we added this information and highlighted those cases who received this treatment. Otherwise, as mentioned in the manuscript, the therapeutic regimens applied in the different case reports and small case series were widely heterogeneous, and such a description goes beyond the scope of this review. The manuscript has been extensively checked and edited, as regards the writing.

Moreover, we decided to add a short conclusion for this manuscript, in order to emphasize the main clinical and therapeutic messages.

Table I. Overview of the demographic features and outcome in patients with infantile GCH+AHA.

Authorship (country, year)	Clinical Case (n)	Age (months)	Gender	Outcome	Rituximab	Follow-up (months)	Cause of death
Before 2011 [case reports/series providing individual data]							
Bernard <i>et al.</i> (France, 1981)¹¹	1	10	F	Fatal	N	-	Liver Failure
	2	9	M	Fatal	N	-	Liver Failure
	3	24	M	Fatal	N	-	Liver Failure
	4	6.5	M	Alive	N	N/A	-
Imgrueth <i>et al.</i> (Switzerland, 1986)²³	5	5	F	Alive	N	9	-
Brichard <i>et al.</i> (Belgium, 1991)²⁴	6	8	M	Alive	N	24	
	7	7	F	Fatal	N	-	Encephalopathy with seizures

Weinstein <i>et al.</i> (USA, 1993)²⁵	8	5	F	Alive	N	30	-
Perez-Atayde <i>et al.</i> (USA, 1994)²⁶	9	23	F	Fatal	N	-	Sepsis
	10	9	M	Alive	N	8	-
Choulot <i>et al.</i> (France, 1996)²⁷	11	15	M	Alive	N	12 years	-
Mendelez <i>et al.</i> (UK, 1997)²⁸	12	8	M	Fatal	N	-	Liver and Renal Failure
Hartman <i>et al.</i> (Israel, 2001)²⁹	13	6	M	Fatal	N	-	Liver Failure
Gorelik <i>et al.</i> (USA, 2004)³⁰	14	4	F	Alive	Y	36	-
Kashyap <i>et al.</i> (India, 2006)³¹	15	4	F	Alive	N	2	-
Vajro <i>et al.</i> (Italy, 2006)¹²	16	10	F	Alive	N	36	-
Miloh <i>et al.</i> (USA, 2007)³²	17	2	M	Alive	Y	24	-

Rovelli et al. (Italy, 2007)³³	18	14	M	Alive	Y	48	-
Baran et al. (Turkey, 2010)¹³	19	3	F	Fatal	Y	-	Sepsis and Renal Failure
Unal et al. (Turkey, 2010)¹⁴	20	2	F	Fatal	Y	-	Sepsis
	21	6	M	Fatal	N	-	N/A
	22	11	M	Alive	Y	18	-
Maggiore et al. (2011) [largest case series providing aggregated data]							
Maggiore et al. (Italy, 2011)⁹	16 cases	2.5-17	M (n=9) F (n=7)	Alive (n=12) Fatal (n=4)	Y (n=2); N (n=10) N	2-28 years -	- OLT (n=1); Sepsis (n=3)
After 2011 [[case reports/series providing individual data]							
Raj et al. (USA, 2011)²²	1	6	F	Alive	N	30	-
Lega et al. (Italy, 2012)³⁴	2	8	M	Alive	N	6	-

Bouguila <i>et al.</i> (Tunisia, 2013)³⁵	3	9	N/A	Fatal	N	-	Sepsis
Whittington <i>et al.</i> (Canada & USA, 2014)¹⁸	4	22	F	Alive	Y	48	-
	5	14	F	Alive	Y	48	-
	6	6	F	Alive	N	48	-
	7	4	F	Fatal	N	-	N/A
	8	6	M	Alive	Y	36	-
Bakula <i>et al.</i> (Poland, 2014)³⁶	9	7	N/A	Alive	Y	30	-
	10	8	N/A	Alive	Y	26	-
	11	2	N/A	Alive	Y	5	-
	12	12	N/A	Alive	Y	76	-

	13	7	N/A	Fatal	N	-	Hemophagocytic Syndrome (after HSCT)
Paganelli M <i>et al.</i> (Italy, 2014)³⁷	14	3	F	Alive	Y	N/A*	-
	15	14	F	Alive	Y	N/A*	-
	16	12	F	Alive	Y	N/A*	-
	17	16	M	Alive	Y	N/A*	-
Marsalli <i>et al.</i> (Italy, 2015)³⁸	18	5	F	Alive	N	N/A*	-
	19	8	M	Alive	N	N/A*	-
	20	10	F	Alive	N	N/A*	-
	21	10	F	Alive	N	N/A*	-
	22	6	F	Alive	Y	N/A*	-

	23	7	F	Alive	N	N/A*	-
	24	8	M	Alive	N	N/A*	-
Cho et al. (South Korea, 2015) ³⁹	25	2	N/A	Alive	N	36	-
Matarazzo et al. (Italy, 2019) ⁴⁰	26	5	F	Alive	Y	141	-
	27	9	F	Alive	Y	91	-
	28	8	M	Alive	Y	76	-
Kim et al. (South Korea, 2020) ⁴¹	29	7	M	Alive	Y	19	-

*The authors do not provide the follow-up length for individual patients; however, they provide general information on the follow-up in their respective case series (Paganelli et al: “At last follow-up visit, all patients were alive with their native liver 2 to 16 years after disease presentation”; Marsalli et al.: “follow-up [median 17.4 months, range 7—24 months]”).

Abbreviations: GCH+AHA, Giant Cell Hepatitis and Autoimmune Hemolytic Anemia; N/A, not available; M, male; F, female; Y, yes; N, no; OLT, orthotopic liver transplantation; HSCT, hematopoietic stem cell transplantation.

