"Vertically acquired hepatitis C virus infection: correlates of transmission and disease progression"

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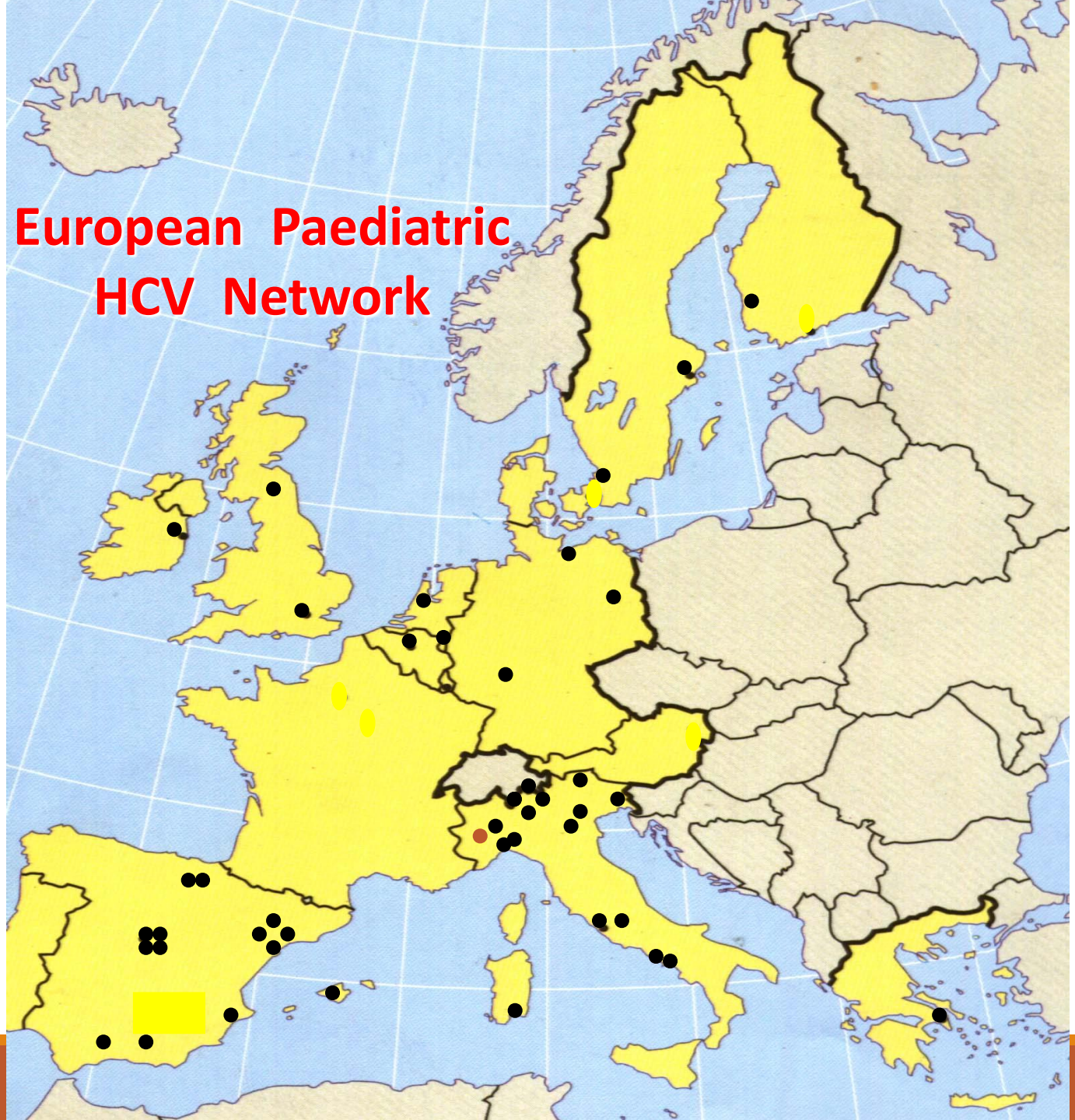
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Evolution of vertically acquired HCV-infection

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TOPIC HIGHLIGHT

2016 Hepatitis C Virus: Global view

Vertically acquired hepatitis C virus infection: Correlates of transmission and disease progression

Pier-Angelo Tovo, Carmelina Calitri, Carlo Scolfaro, Clara Gabiano, Silvia Garazzino

Evolution of vertically acquired HCV-infection

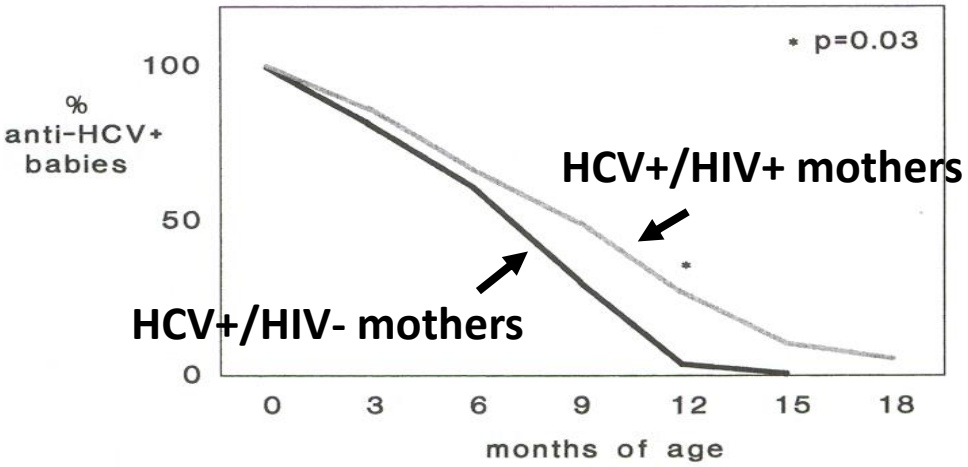
- Currently, mother-to-infant transmission of HCV is the most common cause of HCV infection amongst children in developed Countries

- Estimates of the risk of mother-to-child transmission of HCV range from 3% - 7%

Tovo PA, WJG 2016

Diagnosis of HCV infection in children born to seropositive mothers

- Persistence of HCV antibodies beyond 18 months of age
- Serum HCV-RNA in at least two separate determinations



Tovo PA, et al. Clin Infect Dis 1997

Manzini P, et al. *Hepatology* 1995

Primary HCV infection

At birth and in the first weeks of life:

- **no jaundice**
- **no HCV-associated signs → no clinical diagnosis of infection**
- **a substantial proportion of children has normal or mildly increased ALT levels → ALT activity is a poor surrogate marker of infection**

Sensitivity and specificity of HCV-PCR in 547 children born to seropositive mothers

Age	N° PCR	Sensitivity	Specificity
Birth	199	28 %	98 %
1 month	188	79 %	98 %
3 months	326	75 %	98 %
6 months	306	85 %	98 %
9 months	183	70 %	98 %

EPHN - J Med Virol 2006; 78: 305-10

Evolution of viraemia in infected children

- **Large fluctuations over time**
- **Non-viraemic children may have incresed ALT values and viceversa**
- **Possible spontaneous viral clearance**

  - Negative HCV-PCR at the last 2 or 3 consecutive tests at least 12 weeks apart

Spontaneous viral clearance in vertically infected children

	N° children	HCV RNA -
EPHN Clin Infect Dis 2005	238	20 %
Yeung LT J Viral Hepat 2007	34	25 %
Moriné-Borjoan E AIDS 2007	12	25 %
Garazzino S Eur J Ped	45	27 %
Bortolotti F Gastroenterology 2008	240	11 - 16 %
Abdel-Hady M J Viral Hepat 2011	65	9 %

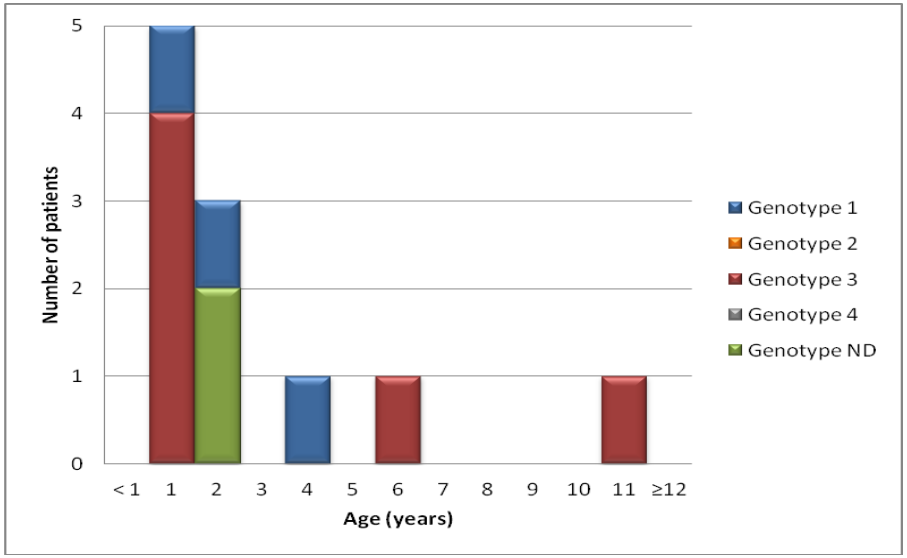
- SVC is associated with biochemical remission of hepatitis

- SVC usually occurs by 7 years of age (Ref:[Yeung LT, Farmand S, Garazzino S)

  → "conventional" antiviral therapy should be postponed beyond the preschool age, apart from selected cases

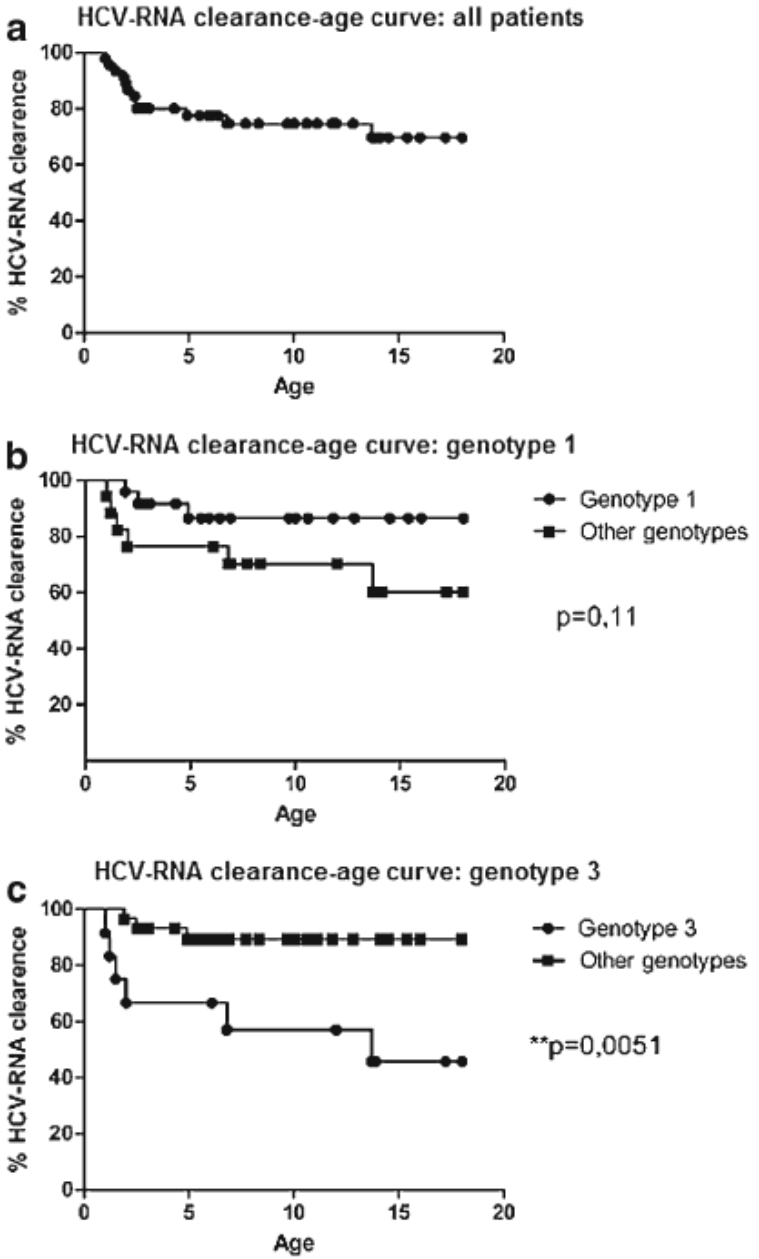
Turin cohort:
907 children born to HCV-infected mothers followed from birth

48 children diagnosed to be HCV-infected
45 HCV+ children enrolled
Median age at last visit**: 12 years**



Garazzino S, et al. Eur J Pediatr (2014) 173:1025–1031

Genotype-3 infection is an independent predictor of SVC



Garazzino S, Eur J Ped 2014

Spontaneous resolution of viremia – host factors

- Positive IFN-γ responses against structural and nonstructural recombinant HCV-antigens (El-Kamary SS, 2013)
- Altered NK cells number and phenotypes (Indolfi G, 2016)
- Presence of the rs 12979860 single-nucleotide C/C of the interleukin 28B gene, particularly with genotype 1 infection (Indolfi G, 2014)

→It is noteworthy that IL-28B elicits the transcription of IFN-stimulated genes that are responsible for antiviral activity

Tovo PA, WJG 2016

ALT levels are highest in the first two years of life then decline. They are poorly predictive of the underlying liver damage.

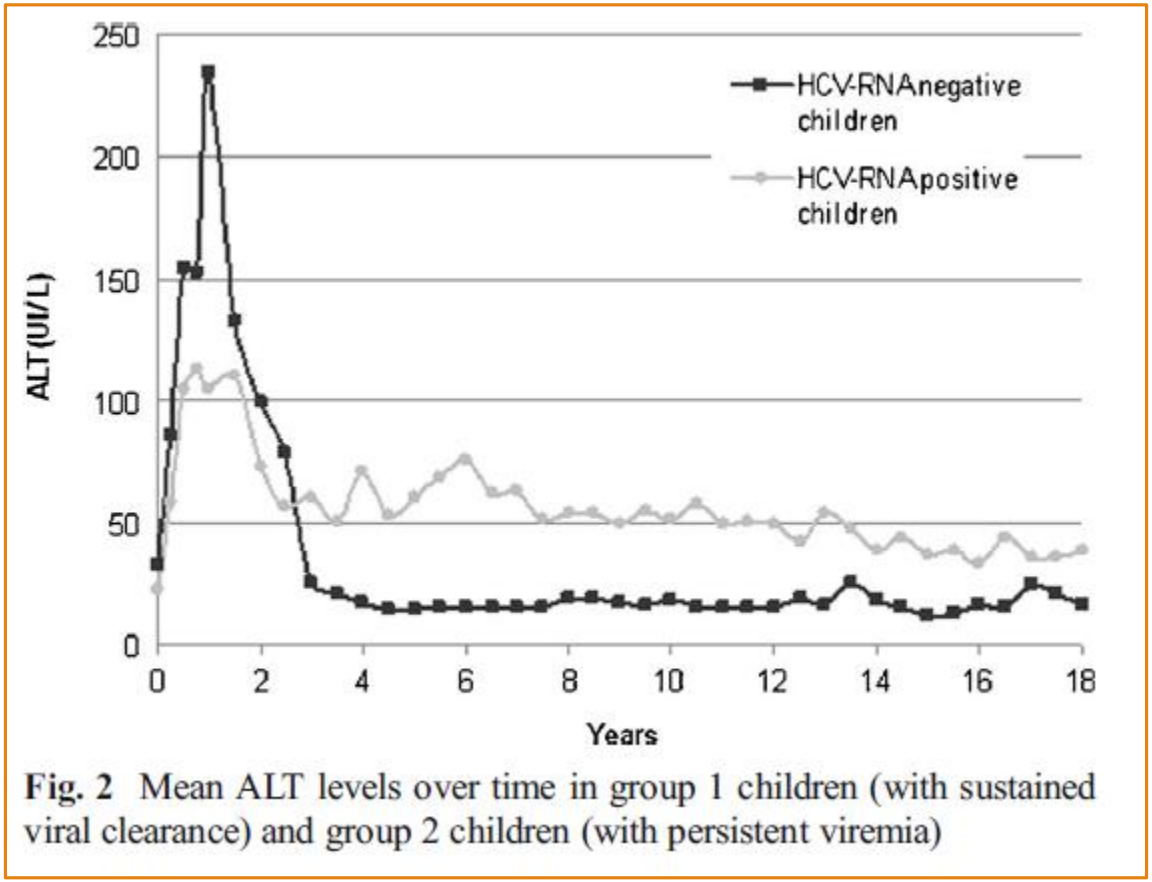
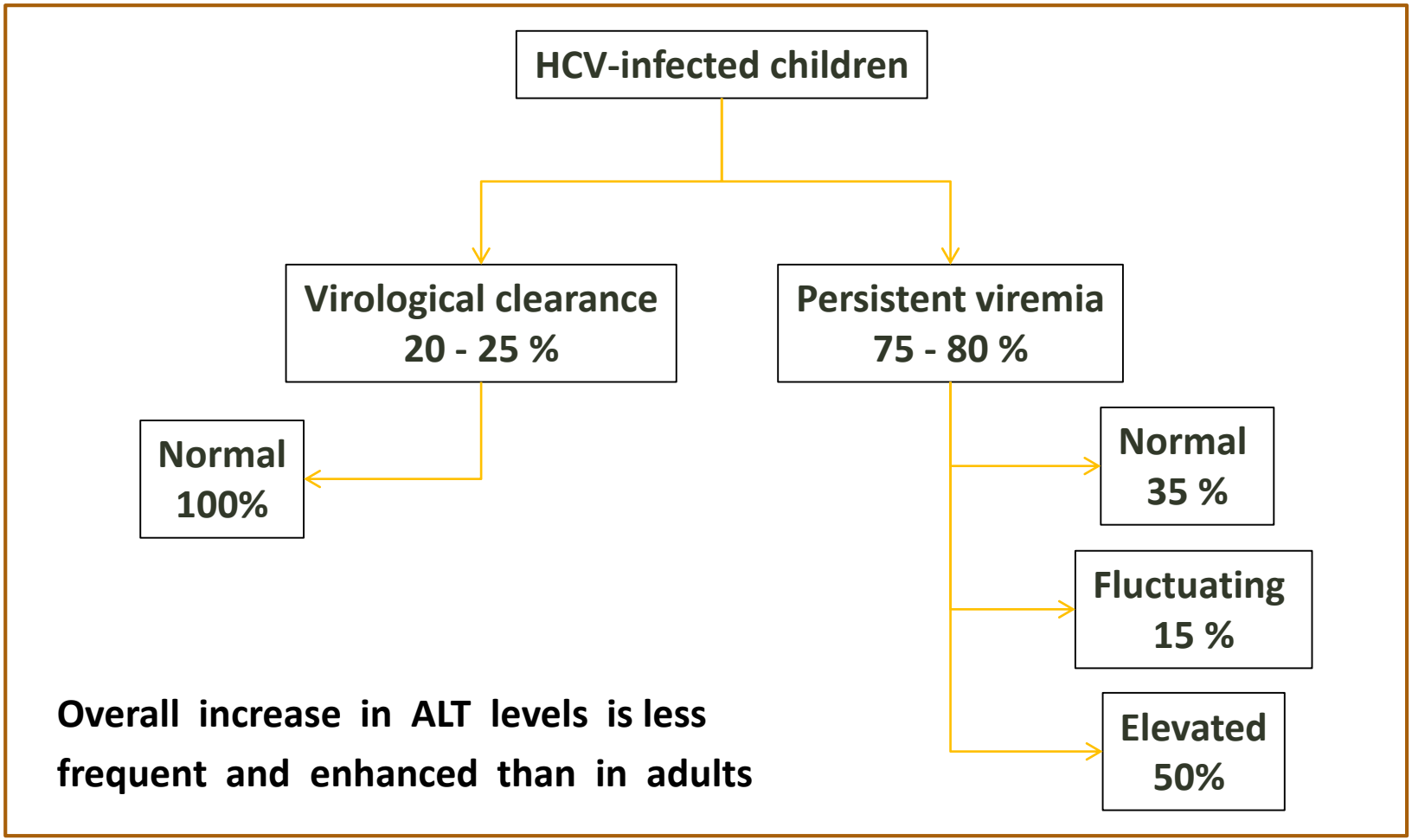


Fig. 2 Mean ALT levels over time in group 1 children (with sustained viral clearance) and group 2 children (with persistent viremia)

Children with SVC have higher ALT levels in the first two years of life when compared to those with persistent infection
[Resti M 2003; Garazzino S 2014]

ALT levels


HCV-infected children
Virological clearance
20 - 25 %
Persistent viremia
75 - 80 %
Normal
100%
Normal
35 %
Fluctuating
15 %
Elevated
50%
Overall increase in ALT levels is less frequent and enhanced than in adults

Chronic HCV infection (I)

- Different clinical course in children as compared to adults.
- In children HCV progression is minimal or mild, generally asymptomatic
- HIV co-infection accelerates progression
- Other influencing factors: ethnicity, obesity, toxins, co-morbidities (hemolytic anemias, chemotherapy, immunosuppression) and genetic factors such as IL-28B genotype

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Chronic HCV infection (II)

- 30-40% of children → chronic active infection

  = persistent viraemia, abnormal ALT values and sometimes hepatomegaly (1/4 in the first decade of life)

- severe hepatic damage is rare but liver transplantation may be required

- Hepatocellular carcinoma is extremely rare

Chronic HCV infection (III)

- Children grow regularly without variations from normal height and weight ranges
- A wide spectrum of histopathological alterations has been found in the liver
- The grade of disease varies from minimal to moderate - pictures of overt cirrhosis are rare
- Liver biopsy is not a routine procedure but still the gold standard to quantify liver damage; transient elastography may help monitoring the evolution of liver fibrosis over time
- New biomarkers of liver injury (ITIH4, C4a, arginase 1) have been shown to reflect liver fibrosis and steatosis

Transient elastography

32/45 patients

Stiffness 4 - 5 kPa 7 HCV RNA-negative

14 HCV RNA-positive

Stiffness 5.1 - 6.7 kPa: 9 HCV RNA-positive

Stiffness of 8.1 and 8.6 kPa in 2 viremic children respectively

Humoral immunity

Virtually all vertically infected children develop specific antibodies against HCV. Some pts with SVC can serorevert after many years

A few HCV RNA-positive, antibody-negative asymptomatic children have been described

Tovo PA, WJG 2016

Extrahepatic manifestations

Mixed cryoglobulinemia is the most frequent HCV-related extrahepatic manifestation in adults

→uncontrolled clonal expansion of B-lymphocyte whith membranoproliferative glomerulonephritis, purpura, arthralgia, peripheral neuropathy and ultimately non-Hodgkin's lymphoma

Mixed cryoglobulinemia had not been previously described in children.

HCV RNA	Cryoglobulins	Other extrahepatic manifestations
Negative (n=12)	2	0
Positive (n=33)	13	Renal impairment (2) diabetes mellitus (1)
Total	15	3

median age 6.6 years

Garazzino S, Eur J Ped 2014

Non-organ specific autoantibodies (NOSAs)

	a	b	c	d	e	f
N° of children	47	51	40	37	39	80*
NOSAs +	34%	65%	32.5%	16%	8%	40%
Anti-smooth muscle	17%	51%	17.5%	3%	5%	40%
Anti-LKM1	15%	8%	10%	5.5%	2%	0
ANA	9%	10%	7.5%	5.5%	-	0

a: Muratori P Clin Infect Dis 2003; 37:1320-6
b: Gregorio G Clin Exp Immunol 1998; 112: 471-6
c: Bortolotti F J of Hepatology 1996;25:614–620
d: Camarero C Eur J Pediatr 2008;167:219–224
e: Gehring S Word J Gastroenterol 2006;12:5787-92
f: Hamed ME Saudi J Gastroenterol 2013;19:262-70

*only genotype 4

LKM-1 positivity, even if not the most common, was the most peculiar autoimmune feature of children with chronic hepatitis C (not found in controls)

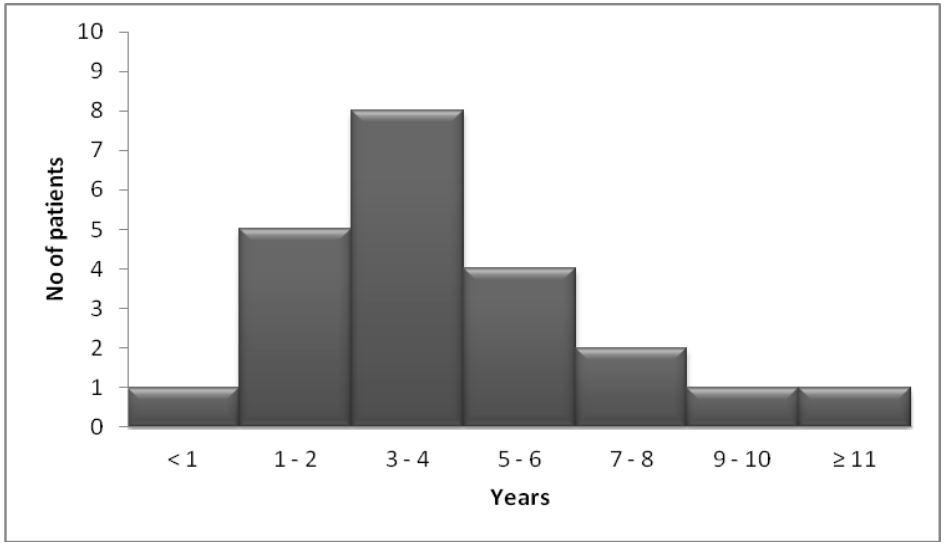
Table 1 Genotype and HCV-related phenomena according to virological status

HCV RNA	Genotype					NOSAs			
	1	2	3	4	NA	ANA	SMA	ANA + SMA	LKM
Negative (n=12)	3	0	6	0	3	0	5	2	0
Positive (n=33)	21	3	6	3	0	4	8	3	2
Total	24	3	12	3	3	4	13	5	2

> 50%

Autoantibodies do not predict liver fibrosis progression!

Age distribution at first detection of NOSAs



Garazzino S, Eur J Ped 2014

Conclusions

Vertically-acquired HCV infection is characterized by a high chronicity rate, but mild livery injury for most

This subclinical evolution does not rule out long-term negative outcome

NOSAs and cryoglobulins may be an occasional finding in children with chronic infection, independently from viremia, but autoimmune diseases or HCV-associated extrahepatic manifestations are rare

In the era of DAAs, optimal timing for treatment in children should be defined

Treatment of HCV-infected women in childbearing age (or earlier?) is crucial to prevent vertical infection

Thank you for your attention