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Altered intestinal permeability in multiple sclerosis patients: a pilot study

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Introduction

The microbiota and gut function are increasingly recognized as relevant in autoimmune disorders. Our group has reported the pathogenic relevance of proinflammatory CD161highCD8+ T cells in MS; further investigations showed overlap between these cells and mucosal-associated invariant T (MAIT) cells, that have recently received much attention as a gut-homing subset, responding to microbes and including interleukin 17 (IL17) helper T cells. An altered physiology of gut mucosa, and/or of the gut-associated lymphoid tissue may impact on intestinal permeability (IP), leading to an increase of epithelial paracellular space. A change in IP may be considered a biomarker of local or even distant immune-mediated disorders. We investigated gut permeability through a test that directly measures the ability of lactulose and mannitol (two non-metabolized sugar molecules) to permeate the intestinal mucosa

Subjects

	NON-TWIN PATIENTS	TWIN PATIENTS						HD
		TW1	TW2	TW3	TW4	TW5[a]		
Number	16	1	1	1	1	1	1	18 (14+4)
Female/Male	9/7	F	F	F	F	F		15/3
Age, years	36±9,91	45	54	44	43	32		38.5 ± 10.66
Disease type	RR	RR	RR	RR	RR	RR	RR	-----
Disease duration, years	0.5-20	15	9	6	14	16	10	-----
EDSS range	0-3,5	0	1	1,5	1	4,5	0	-----
DMT	12naive[b]	naive	yes[c]	naive	yes[c]	yes[c]	naive	-----

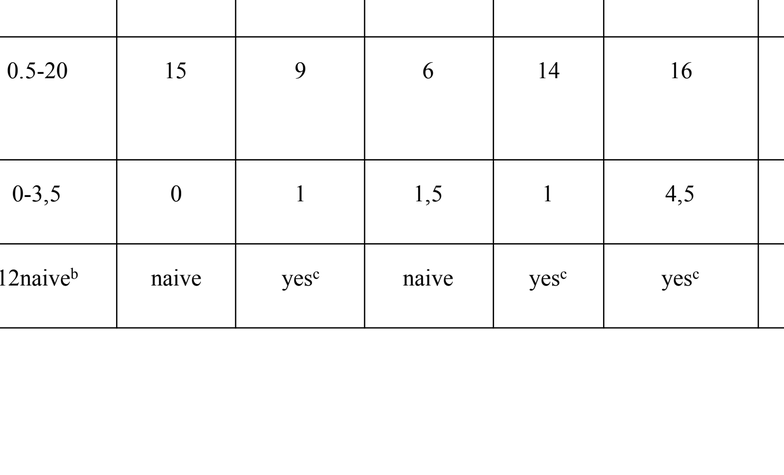
Intestinal permeability analysis

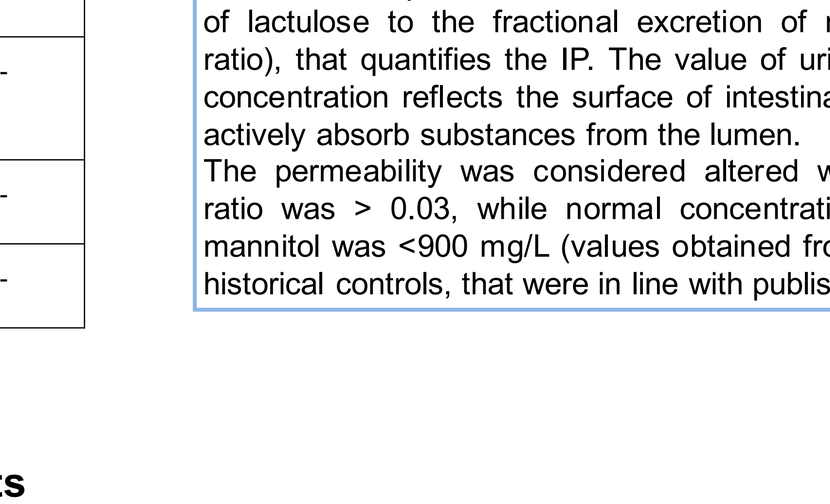
The fractional excretion of lactulose was calculated as a ratio (mg lactulose excreted/mg lactulose assumed). The lactulose excreted were obtained from mg/L lactulose × liters of urine. The same was for mannitol.
The values of lactulose and mannitol calculated in the pre-test urine as mg/L were subtracted from the same value obtained in the 6 h collected urine.
The urine concentrations of lactulose and mannitol were measured using a method based on liquid chromatography combined with mass spectrometry.
Results are expressed as a ratio of the fractional excretion of lactulose to the fractional excretion of mannitol (L/M ratio), that quantifies the IP. The value of urinary mannitol concentration reflects the surface of intestinal wall able to actively absorb substances from the lumen.
The permeability was considered altered when the L/M ratio was > 0.03, while normal concentration of urinary mannitol was <900 mg/L (values obtained from a group of historical controls, that were in line with published data).

Results

	PATIENTS			HEALTHY DONORS		
	Total (n=22),(%)	Non-twins (n=16),(%)	Twins (n=6), (%)	Total (n=18),(n%)	Non-twins (n=14), (%)	Twins (n=4), (%)
Increased IP	16 (73)*	13(81)**	3(50)	5 (28) *	4(28)**	1(25)
Normal IP	6 (27)	3(19)	3(50)	13 (72)	10(72)	3(75)

A significant difference in the proportion of participants with increased IP was observed: 16/22 (73%) in patients vs 5/18 (28%) in HD; p=0.001. The difference was even more significant without considering twin couples: 13/16 (81%) patients vs 4/14 (28%) HD; p<0.001. Urinary mannitol concentration was significantly lower in patients compared to controls, suggesting a deficit of the active mechanism of absorption from intestinal lumen.
We found no significant correlations between IP changes and the main clinical/radiological parameters of the patients.





Discussion

Our pilot study suggests that an alteration of IP is a relatively frequent event in MS. IP changes include a deficit of the active mechanism of absorption from intestinal lumen, as suggested by the significant decrease of urinary mannitol concentration in patients. These results warrant future investigations where the IP status is linked to other key variables, such as MAIT cells and microbiota. In this context, the possible relationship between blood-brain barrier and IP may be another intriguing object of future researches.