Histological features of very early-onset compared to later-onset inflammatory bowel diseases: A multicenter retrospective study

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【背景】IBD（炎症性腸疾患）は潰瘍性大腸炎（UC）、クローン病（CD）、分類不能型（IBD-U）が含まれ、小児・思春期に約 25%が発症する。小児 IBD の中でも、6 歳未満で発症する型を VEO-IBD（Very Early-Onset IBD）と呼び、全小児 IBD の 3～15%を占める。発症率は年々増加している（7.2%/年）。VEO-IBD の病因には遺伝的要因の関与が強く、100 以上の単一遺伝子異常（monogenic IBD）が報告されている。過去には「若年発症＝重症」という見方もあったが、すべての VEO-IBD が重症ではなく、最近では「monogenic 例が重症化を規定しており、non-monogenic 例は比較的穏やか」という報告が増えている。Infantile IBD（2 歳未満）は特に重症で、手術・感染リスクが高いが、これは monogenic 性による影響が大きいとされている。また、VEO-IBD の重症化には monogenic 変異が強く関与していることが明らかになっているが、全ての VEO-IBD が monogenic ではなく、遺伝異常を伴わない non-monogenic VEO-IBD も多数存在する。この non-monogenic VEO-IBD の臨床的・組織学的特徴は十分に解明されておらず、その炎症の程度や病態が年長児発症例（LO-IBD）と、どのように異なるのかは明確ではない。

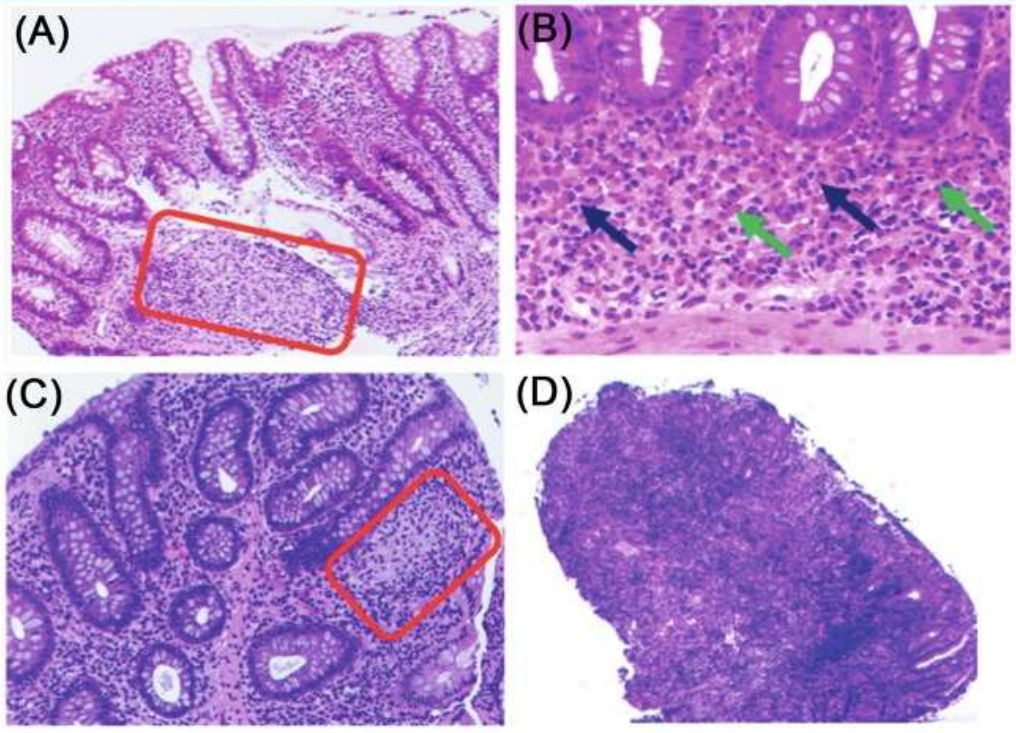
【目的】非遺伝性の極早期発症炎症性腸疾患（non-monogenic VEO-IBD）の内視鏡所見と組織学的所見を、LO-IBD と比較して明らかにする。**【方法】**小児 IBD 専門施設 2 か所（伊）による多施設後ろ向き観察研究。VEO-IBD 患者は、疾患表現型が近い LO-IBD 対照と対応させた（潰瘍性大腸炎〔UC〕は 1:1、クローン病〔CD〕は 1:2）。臨床/内視鏡/組織の各データを後ろ向きに収集）。**【結果】**VEO-IBD 53 例（UC 42、CD 11）、LO-IBD 68 例（UC 44、CD 24）を同定。VEO-CD は LO-CD より大腸限局型が有意に多く（p=0.002）、VEO-UC は全結腸炎がより多い傾向（p=0.05）。組織学的には、基底部形質細胞浸潤（好酸球混在）、杯細胞減少、活動性炎症、陰窩構築異常が、VEO-UC より LO-UC で有意に高頻度（それぞれ 83.7% vs 61.9%, p=0.021；100.0% vs 73.8%, p<0.001；86.4% vs 66.7%, p=0.028）。CD ではスキップ病変が LO-CD で多かった（83.3% vs 45.5%, p=0.031）。

【結論】VEO-IBD と LO-IBD は、病変局在や組織像で異なる表現型を示す。若年児 UC では LO-UC に比べ組織学的負荷が低い一方、VEO-CD では CD に典型的な特徴が出にくい。

Take Home Messages

1. 単一遺伝子異常に基づく VEO-IBD は独特で重症化しやすいが、非遺伝性 VEO-IBD は十分に特徴づけられていない。
2. VEO-IBD と LO-IBD では病変範囲が異なり、広範囲な大腸病変がより一般的にみられる。
3. 非遺伝性 VEO-UC では、顕微鏡的疾患活動性を示す組織学的特徴が LO-UC より少なく、組織学的負荷が低いことを示唆。
4. CD の典型所見（スキップ病変や小腸の絨毛鈍化）は LO でより多く、肉芽腫など一部の所見は発症年齢に依存しない可能性がある。

Fig 1: Histological features of very early-onset compared to later-onset inflammatory bowel diseases: A multicenter retrospective study



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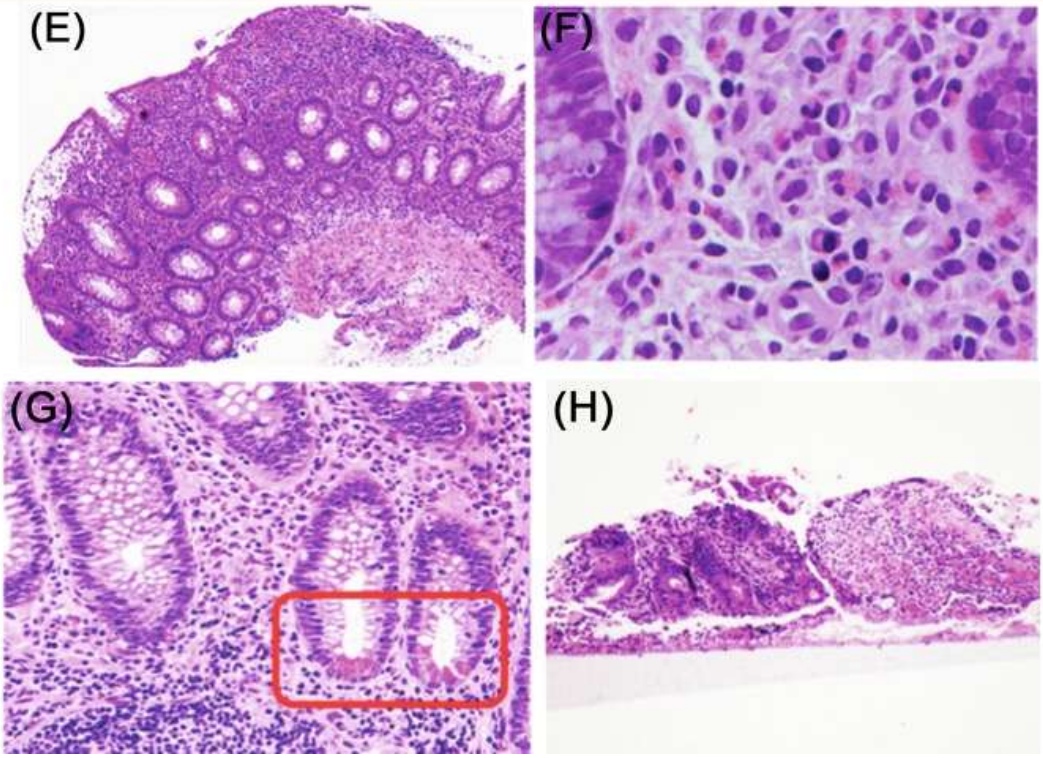

Table 1. Demographic and clinical characteristics of the study population, VEO-IBD versus LO-IBD.

	VEO-IBD (n = 53 (%))	LO-IBD (n = 68(%))	p
Sex (male)	27 (50.9%)	37 (54.4%)	0.422
Ethnicity			
Caucasian	45 (84.9%)	64 (94.1%)	
Other ethnicity[a]	8 (15.1%)	4 (5.9%)	0.085
Median age at onset (years, IQR)	3.3 (1.9–4.1)	12.0 (9.8–14.0)	<0.001
Median age at diagnosis (years, IQR)	3.7 (2.3–4.5)	12.5 (10.3–14.7)	<0.001
Symptom duration before diagnosis (years, IQR)	0.3 (0.2–0.6)	0.3 (0.1–0.7)	0.615
Initial diagnosis of IBD-U[b]	10 (18.9%)	6 (8.8%)	0.089
Type of disease			
UC	42 (79.2%)	44 (64.7%)	0.060
CD	11 (20.8%)	24 (35.3%)	
IBD-U	0 (0.0%)	0 (0.0%)	
Autoimmunity			
ASCA (109/121)	3 (6.7%)	14 (21.9%)	0.026
ANCA (109/121)	20 (44.4%)	31 (48.4%)	0.415
Extraintestinal manifestations[c]	3 (5.7%)	13 (19.1%)	0.026

Table 2. Demographic, clinical, endoscopic, and histological features of children with VEO-UC versus LO-UC.

	VEO-UC (n 42) (%)	LO-UC (n 44) (%)	p
Sex (male)	21 (50.0%)	23 (52.3%)	0.502
Autoimmunity (75/84)			
ASCA	0/36 (0.0%)	3/41 (7.3%)	0.146
ANCA	18/36 (50.0%)	28/41 (68.3%)	0.081
Signs and symptoms at disease onset, laboratory data			
Diarrhea	31 (73.8%)	27 (61.4%)	0.158
Bloody stools	39 (92.9%)	40 (90.9%)	0.526
Abdominal pain	33 (78.6%)	40 (90.9%)	0.097
Anemia	14 (33.3%)	11 (25.0%)	0.270
Failure to thrive/weight loss	8 (19.0%)	11 (25.0%)	0.343
Extraintestinal manifestations[a]	3 (7.1%)	6 (13.6%)	0.266
Erythrocyte sedimentation rate (mm/h, IQR)	34 (23–43)	33 (20–57)	0.759
C-reactive protein (mg/dL, IQR)	0.8 (0.6–1.0)	0.6 (0.5–1.7)	0.701
Fecal calprotectin (mg/g)	465 (243–1300)	800 (478–2000)	0.262
Albumin (g/dL)	4.0 (3.8–4.2)	4.2 (3.9–4.3)	0.213

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	VEO-UC (n 42) (%)	LO-UC (n 44) (%)	p
Paris classification			
E1, E2, E3	13 (31.0%)	22 (50.0%)	0.057
E4	29 (69.0%)	22 (50.0%)	
Atypical phenotypes			
Rectal sparing	0 (0.0%)	1 (2.4%)	0.500
Backwash ileitis	7 (16.7%)	11 (25.0%)	0.247
Cecal patch	3 (7.1%)	4 (9.1%)	0.526
Upper gastrointestinal	0 (0.0%)	1 (2.3%)	0.512
Mayo endoscopic score (80/84)			
1	7/40 (17.5%)	5/42 (11.9%)	0.343
2	26/40 (65.0%)	28/42 (66.7%)	0.529
3	7/40 (17.5%)	9/42 (21.4%)	0.433
Median Mayo endoscopic score (IQR)	2 (2–2)	2 (2–2)	0.466
Median PUCAI (IQR)	33 (25–40)	40 (20–60)	0.200
Histopathology			
Skip lesions	1 (2.4%)	2 (4.5%)	0.518
Granulomas	3 (7.1%)	0 (0.0%)	0.112
Deep ulcers	3 (7.1%)	1 (2.3%)	0.291
Eosinophilic inflammation (82/86)	31/41 (75.6%)	36/41 (87.8%)	0.126

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	VEO-UC (n 42) (%)	LO-UC (n 44) (%)	p
Lymphocytic infiltrates (83/86)	37/42 (88.1%)	39/41 (95.1%)	0.226
Crypt architectural distortion	28 (66.7%)	38 (86.4%)	0.028
Small intestine villous blunting	1 (2.4%)	2 (4.5%)	0.518
Active inflammation (85/86)	31/42 (73.8%)	43/43 (100.0%)	<0.001
Crypt epithelial apoptosis	1 (2.4%)	0 (0.0%)	0.488
Paneth cells metaplasia (82/86)	8/42 (19.0%)	7/49 (13.2%)	0.542
Goblet cells depletion (85/86)	26/42 (61.9%)	36/43 (83.7%)	0.021
Basal plasmacytosis (84/86)	40/42 (95.2%)	42/44 (95.5%)	0.454
Nancy Histological Index (IQR)	3 (3–3)	3 (3–3)	0.093

Table 3. Demographic, clinical, endoscopic, and histological features of children with VEO-CD versus LO-CD.

	VEO-CD (n 42) (%)	LO-CD (n 44) (%)	p
Sex (male)	21 (50.0%)	23 (52.3%)	0.502
Autoimmunity (75/84)			
ASCA	0/36 (0.0%)	3/41 (7.3%)	0.146
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