PSNMD CASE DISCUSSION

A 4-year-old Boy Presenting with Left Lower Extremity Weakness

October 29th, 2021

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CC: Left lower extremity weakness

Present illness

- Full-term delivery
- No past medical Hx. except admission d/t pneumonia

- 2021/01/03: fever
- 2021/01/04: Lt. cheek, both shoulder petechia
  → admission at 강동성심병원
  lab> WBC 11710(N3.6% ANC 421), Hb/Hct 6.4/18.7,
  PLT 21K , ESR 46, CRP 166.8 mg/L
  PT /aPTT 13.1/30.2
- 2021/01/07: AMC transfer → BM biopsy → diagnosis of ALL

A 4-year-old Boy Presenting with Left Lower Extremity Weakness

H20 말초 혈액 도말 판독 SPECIAL REPORT

H20 말초 혈액 도말 판독 SPECIAL REPORT(20210000-H20-BCM-I-00208)

♣ 01. CELL COUNT

WBC	12.6	x10³ /uL
RBC	2.46	x10^6/uL
HB	6.9	g/dl
HCT	20.6	%
MCV	83.7	fl
MCH	28.0	pg
MCHC	33.5	%
RDW	15.9	%
PLT	106	x10³ /uL
MPV	12.1	fl
PDW	12.5	fl
E-ALC	10090	/uL
E-NORMO	0	/100 WBC
IG	0.2	%
E-ANC	330	/uL

♣ 02. WBC DIFF.COUNT

BLAST	75	%
SEG NEU	3	%
LYM	21	%
MONO	1	%
E-NEUTROPHIL	2.9	%
E-LYM	80.3	%
E-MONO	16.5	%
E-EO	0.1	%
E-BASO	0.2	%

♣ 03. Findings

WBCNumber	Mild increase
WBCothers	Presence of blasts
RBCSize	Normocytic
RBCStainability	Normochromic
RBCAnisocytosis	Mild anisocytosis
PLTNumber	Mild decrease

♣ 04. 판독소견(Comments)

COMRBC I	Normocytic normochromic anemia
COMRBC II	Anisocytosis
COMWBC I	Mild leukocytosis
COMWBC II	Presence of blasts
COMPLT I	Mild thrombocytopenia

A 4-year-old Boy Presenting with Left Lower Extremity Weakness

H26 백혈병 및 림프종 세포표지검사 SPECIAL REPORT

Specimen : BM 21-50
Clinical information : r/o acute leukemia

Method :
- Immunofluorescence method by flow cytometry
- The monoclonal antibodies used in the tests are produced by the commercial manufacturer.

Result :

Monoclonal antibody	Positivity	Intensity	Specificity
CD 45	90.4 %	intermediate	Leukocyte Common Antigen
CD 34	5.4 %		Stem cell
TdT	13.3 %	dim	Terminal deoxynucleotidyl transferase
CD 13	52.3 %	intermediate	Myeloid
CD 33	0.9 %		Myeloid
CD 10	95.5 %	bright	J5,CALLA
CD 19	92.7 %	bright	B cell
CD 20	2.1 %		B cell
cCD 22	41.2 %	intermediate	B cell
CD 2	0.4 %		T cell
CD 3	0.1 %		T cell
cCD 3	0.1 %		T cell
CD 5	0.0 %		T cell
CD 7	0.4 %		T cell
CD 56	0.0 %		NK cell
Cy IgM	2.9 %		Cytoplasmic immunoglobulin
Sm IgM	5.4 %		Surface immunoglobulin
Anti-MPO	0.0 %		Myeloid

* Positivity defined as antigen expression by 20% or more of leukemic blast cells, except TdT positivity by > 10%.

Interpretation : A population of blasts with intermediate CD45 expression and low SSC is identified, which comprises approximately 90.4 % of cells in the specimen.

The blasts are positive for CD10, CD19 (bright), CD13, cCD22 (intermediate), and TdT (dim).

All myeloid and T lineage antigens tested are negative except for CD13.

Special stain : MPO - negative on leukemic blasts
PAS - block dot positive on leukemic blasts
ANBE - negative on leukemic blasts

Conclusion : Acute Lymphoblastic Leukemia, common cell, group III

A 4-year-old Boy Presenting with Left Lower Extremity Weakness

H24 골수검사 SPECIAL REPORT

Clinical information (1/7): r/o acute leukemia

Peripheral Blood Smear(12600-6.9-106k, 83.7fL, reti: 0.73%)
RBC : Normocytic Normochromic, Anisocytosis (+), Polychromasia (-), Poikilocytosis (+):schistocyte
WBC : Slightly increased in No.
Differential - Blast 75%, Metamyelocyte 1%, Seg neutrophil 4%, Lymphocyte 19%, Monocyte 1%
Platelet : Slightly decreased in No.

Marrow Aspiration and Touch Print (specimen quality; adequate)
Bone Marrow Differential Count

Myeloblast	%	Monoblast	%
Promyelocyte	%	Promonocyte	%
Myelocyte	%	Monocyte	%
Metamyelocyte	%	Eosinophil	%
Band form	%	Basophil	%
Segmented form	%	Plasmablast	%
Neoplastic cell	%	Plasma cell	%
Neoplastic lymphocyte	94.4 %	Pronormoblast	%
Lymphoblast	%	Basophilic normoblast	%
Immature lymphocyte	%	Poly normoblast	1.6 %
Lymphocyte	2.4 %	Ortho. normoblast	1.6 %
		Histiocyte	%

Megakaryocytes: Rarely found
Granulocytic : Decreased in No.
Erythroid : Decreased in No.
Storage Iron : Not interpretable due to insufficient marrow particles
Note : Lymphoblasts (94.4%) show medium to large size, round to irregular shaped nuclei, inconspicuous nucleoli and scanty cytoplasm. Some blasts have vacuoles.
Special stain : MPO - negative on leukemic blasts
PAS - block dot positive on leukemic blasts
ANBE - negative on leukemic blasts
FAB score : +2

Marrow Biopsy and Clot Section (quality; adequate, length: 0.6cm)
Cellularity : Variable, average 60% (40~90%) Focal fibrosis or squeezing artifact (+)
Megakaryocytes : Rarely found
Nucleated cells: Mostly leukemic blasts

DIAGNOSIS : Bone marrow, iliac crest, left, aspiration and biopsy :

Acute Lymphoblastic Leukemia

(IP[M21-57]: Acute lymphoblastic leukemia, common cell, group III with aberrant expression of CD13)
(Hemavision: pending)
(Chromosome: pending)

H90 Acute Leukemia Profile 검사 SPECIAL REPORT

◆SPECIMEN : Bone marrow (2021.01.07.)

◆SPECIMEN & NUCLEIC ACID PREP. QUALITY : Acceptable

◆INDICATION FOR TESTING :

◆RESULT :

1. Major BCR-ABL1 rearrangement, Nested RT-PCR	--- Negative
2. Minor BCR-ABL1 rearrangement, Nested RT-PCR	--- Negative
3. PML-RARA rearrangement, Nested RT-PCR	--- Negative
4. TEL-AML1 (ETV6-RUNX1) rearrangement, Nested RT-PCR	--- Positive (174 bp)
5. AML1-ETO (RUNX1-RUNX1T1) rearrangement, Nested RT-PCR	--- Negative

[Internal Control (BTD) - Positive]

◆INTERPRETATION :

t(12;21)(p13;q22)에 의해 발생하는 ETV6-RUNX1 융합유전자는 RUNX1의 transcription factor로서의 기능을 방해하여 백혈병이 발현됩니다. B 계열 급성림프모구백혈병의 약 25%에서 보이며, 유아기 백혈병에서는 검출되지 않습니다. 빈도는 환아 연령이 증가할수록 감소하여 성년기 백혈병에서는 드물게 검출됩니다.

본 융합유전자는 매우 양호한 예후와 연관되어 있습니다. 특히 다른 양호한 예후인자를 동반한 환아는 90% 이상에서 완치를 획득합니다. 질환 경과상 주로 후기에 재발하며, 이는 본 융합유전자가 아닌 추가적인 분자유전학적 변이에 의한 것으로 추정되고 있습니다.

◆METHOD :

1) RNA extraction from mononuclear cells
2) Nested RT polymerase chain reaction by Hemavision kit
3) Electrophoresis and staining
4) 유전자재배열의 위치
   t(9;22)(q34;q11); BCR-ABL1, t(15;17)(q22;q11.2-12); PML-RARA, t(12;21)(p13;q22); ETV6-RUNX1,
   t(8;21)(q22;q22); RUNX1-RUNX1T1
5) 참고값: Negative
6) 기타: Hemavision kit has CE marks for IVD.
7) 참고문헌

Olesen LH, Clausen N, Dimitrijevic A, Kerndrup G, Kjeldsen E, Hokland P. Prospective application of a multiplex reverse transcription-polymerase chain reaction assay for the detection of balanced translocations in leukaemia: a single-laboratory study of 390 paediatric and adult patients. Br J Haematol 2004;127:59-86.

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H90 Hempanel gene,혈액암,165 gene (서술)[차세대 염기서열분석] SPECIAL REPORT

Specimen Type
Bone marrow aspirate (blasts: 94.4% by microscopy, 90.4% by flowcytometry)

Indication for Test
B-lymphoblastic leukemia (Karyotype: 47,XY,add(5)(p14),add(8)(q22),der(9)add(9)(p22)add(9)(q22),add(10)(q21),
der(11)t(1;11)(q12;q22),+mar[11]/46,XY[19])

Potential Pathogenic Variants

Gene	Chr position	RefSeq	Nucleotide	Amino acid	Read depth	VAF	Categorization
None detected							

Tier I: Variants of strong clinical significance
Tier II: Variants of potential clinical significance
Tier III: Variants of unknown clinical significance
Cut-off value of VAF: 2.0%

Results of Must-call Genes

Potential pathogenic variants가 검출되지 않은 must-call 유전자들
: FLT3-TKD, NPM1, KIT, RUNX1, TP53, IDH1, IDH2, NRAS, KRAS, RB1, IKZF1, ASXL1, CALR, CSF3R, DNMT3A, SETBP1, SF3B1, SRSF2, TET2, MYD88, BRAF, JAK2, CEBPA, MPL
Potential pathogenic variants가 검출된 must-call 유전자들
: 없음

Low Coverage Regions
염기서열 coverage의 깊이는 일부 표적부위에 대해 가변적일 수 있습니다. 낮은 coverage를 보인 영역은 다음과 같습니다: CRLF2

References
1. J Mol Diagn 2017;19:4-23.
2. Revised WHO classification 2016.

Appendix

HemPanel Gene List version 2.0
ABL1, ABL2, AKT1, ALK, ANKRD26, ARID1A, ASXL1, ATM, ATR, ATRX, B2M, BCL2, BCL6, BCOR, BCORL1, BIRC3, BMI1, BRAF, BTG1, BTK, CALR, CARD11, CBL, CBLB, CCND1, CCND2, CCND3, CCR4, CD28, CD58, CD79A, CD79B, CDK4, CDKN1C, CDKN2A, CDKN2B, CDKN2C, CEBPA, CHD4, CIITA, CKS1B, CRBN, CREBBP, CRLF2, CSF1R, CSF3R, CTLA4, CUL4B, CUX1, CXCR4, DDB1, DDX3X, DDX41, DIS3, DKK1, DNMT1, DNMT3A, EBF1, EED, EGR1, EP300, EPHA7, EPOR, ERG, ETNK1, ETV6, EZH2, FAM5C, FAM46C, FAS, FBXW7, FLT2, FLT3, GATA1, GATA2, GATA3, GNAS, HNRNPK, HRAS, IDH1, IDH2, IKZF1, IKZF2, IKZF3, IL2RB, IL7R, IRAK1, IRAK4, IRF4, JAK1, JAK2, JAK3, KDM5A, KDM6A, KIT, KMT2A (aka MLL1), KMT2C, KMT2D (aka MLL2), KMT2E, KRAS, LTB, LUC7L2, MALT1, MAP2K1, MEF2B, MPL, MTOR, MYC,MYD88, NCKAP5, NF1, NOTCH1, NPM1, NR3C1, NRAS, NT5C2, NTRK3, PAX5, PDGFRB, PHF6, PIGA, PIK3CA, PLCG1, PML, POT1, PPM1D, PPP3CA, PPP3CB, PPP3CC, PRPF40B, PTEN, PTK2B, PTPN11, RAD21, RARA, RB1, RUNX1, SETBP1, SETD2, SF1, SF3A1, SF3B1, SH2B3, SMC1A, SMC3, SRSF2, STAG2, STAT3, STAT5B, SYK,TAL1, TET2, TNFAIP3, TNFRSF14, TP53, TSLP, TYK2, U2AF1, U2AF2, VAV1, WHSC1, WT1, XPO1, ZFHX4, ZRSR2

Method Summary
1) Genomic DNA was extracted from bone marrow.
2) Genomic DNA was sonicated into fragments of 200bp on average and QC was performed to ensure fragment size.

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G10 Chromosome analysis 2021-01-07 125018

[Referral Reason]
Common cell ALL

Specimen Type : BM
Adequacy : Good
Sampling Date :

Method : 24-hour culture/48-hour culture, GTL-banding
No. of cells counted : 30
No. of cells analyzed : 30
No. of karyotypes : 3
Resolution : 300-400 band

[Result]
47,XY,add(5)(p14),add(8)(q22),der(9)add(9)(p22)add(9)(q22),add(10)(q21),der(11)t(1;11)(q12;q22),+mar[11]/46,XY[19]

[Summary]
Abnormal with complex chromosomal abnormalities

[Interpretation]
본 환자는 Common cell ALL로 진단받았고, 골수 염색체 검사에서 5p, 8q, 9p, 9q, 11q 등의 complex chromosomal abnormalities 클론이 관찰되었습니다.

ALL FISH 검사에서 ETV6/RUNX1 rearrangement 소견과 함께 CDKN2A(9p21)의 heterozygous deletion, KMT2A(MLL) deletion이 관찰되었습니다.
ETV6/RUNX1 rearrangement의 t(12;21)은 cryptic translocation으로서 염색체 검사에서 확인이 어렵고, CDKN2A(9p21)의 heterozygous deletion, KMT2A(MLL) deletion은 골수 핵형과 부합하는 소견입니다.

A 4-year-old Boy Presenting with Left Lower Extremity Weakness

G22 FISH, 종양 2021-01-07 160232

[Referral Reason]
Common cell ALL

Sampling Date :

[Hybridization probe]
1) CDKN2A(9p21)/CEP9 dual color : CDKN2A(Orange)/CEP 9(Green), Vysis 2) KMT2A (MLL), dual color break apart : 5'KMT2A(Green)/3'KMT2A(Orange), Vysis 3) ETV6/RUNX1 ES dual color : ETV6(Green)/RUNX1(Orange), Vysis 4) IGH, dual color break apart : 3'IGH(Orange)/IGHV(Green), Vysis

[Result]
nuc ish(CDKN2Ax1,CEP9x2)[180/200],(KMT2Ax1)[170/200],(ETV6x2,RUNX1x3)(ETV6 con RUNX1x1)[180/200],(3'IGHx2,5'IGHx1,5'IGH dimx1)(3'IGH con 5'IGHx1)(3'IGH con 5'IGH dimx1)[180/200]

% cells with CDKN2A deletion : 90.0 % (180/200)
% cells with KMT2A(MLL) deletion : 85.0 % (170/200)
% cells with ETV6/RUNX1 rearrangement: 90.0 % (180/200)

[Summary]
Abnormal with CDKN2A deletion, KMT2A(MLL) deletion, and ETV6/RUNX1 rearrangement

[Interpretation]
본 환자는 Common cell ALL로 진단받았고, 골수 염색체 검사에서 complex chromosomal abnormalities 클론이 관찰되었습니다.

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Present illness

- 2021/01/08: Induction CTx
- 2021/02/05: discharge

- He then continued consolidation chemotherapy on an outpatient basis.

- 2021/04/24: left foot drop and gait disturbance
- 2021/05/04: his parents noticed that he didn't use his left hand very well.

- 2021/05/29: outpatient clinic of PRM (consultation from PHO)
- 2021/06/08: EMG/NCS

Review of System

General	Fever (-)	Chill (-)
Cardiovascular	Chest pain (-)	Orthopnea (-)
Respiratory system	Cough (-)	Sputum (-)
	Rhinorrhea (-)	Dyspnea (-)
Gastrointestinal system	Anorexia (-)	Nausea (-)
	Vomiting (-)	Constipation (-)
	Diarrhea (-)	Abdominal pain (-)
Urinary system	Dysuria (-)	Frequency (-)
	Anuria (-)	

Physical examination

Incomplete physical examination d/t poor compliance

General appearance	Not so ill looking	
Head and neck	Pharyngeal injection (-)	Paratonsilar hypertrophy (-)
	Tympanic membrane: intact	Palpable LN (-)
Thorax	Breathing sound: clear	Substernal retraction (-)
	Heart beat: regular	
Abdomen	Flat and soft	Tenderness (-)
	Bowel sound: normoactive	Splenomegaly (-)
	Hepatomegaly (-)	

Physical examination

Incomplete physical examination d/t poor compliance

Motor function

Tone: normotonous on both upper extremities

Power :

	Rt	Lt
Shoulder F/E	G/G	G/G
Elbow F/E	G/G	G/G
Wrist F/E	G/G	G/G
Finger F/E	G/G	F/F
Hip F/E	G/G	G/G
Knee F/E	G/G	G/G
Ankle DF/PF	G/G	P/F
Big toe DF/PF	G/G	P/F

Physical examination

Incomplete physical examination d/t poor compliance

Sensory function

Rt: Intact

Lt: Impaired (Left hand, leg, foot)

Reflex

DTR

Biceps reflex +/+ Knee reflex +/+

Pathologic reflex (-/-)

Laboratory Study

(▼)WBC (Qn)[ChemR-I],Blood 2.6 x10³/uL
(▲)E-neutrophil (Qn)[ChemR-I],Blood 58.8 %
(▼)E-lymphocyte (Qn)[ChemR-I],Blood 14.0 %
E-ANC (Qn)[ChemR-I],Blood 1500 /uL

Hb (Qn)[ChemR-I],Blood 11.4 g/dl
Platelet (Qn)[ChemR-I],Blood 229 x10³/uL

PT(sec) (Qn)[ChemR-I],Blood 11.8 sec
aPTT (Qn)[ChemR-I],Blood 28.0 sec

(▲)AST(SGOT) (Qn)[ChemR-I],Blood 57 IU/L
(▲)ALT(SGPT) (Qn)[ChemR-I],Blood 59 IU/L
(▲)Alkaline phosphatase (Qn)[ChemR-I],Blood 176 IU/L

Sodium (Qn)[EM],Blood 140 mmol/L
Potassium (Qn)[EM],Blood 4.5 mmol/L
Chloride (Qn)[EM],Blood 103 mmol/L

(▲)CRP (Qn),Blood 0.81 mg/dL

NCS/EMG (2021/06/08)

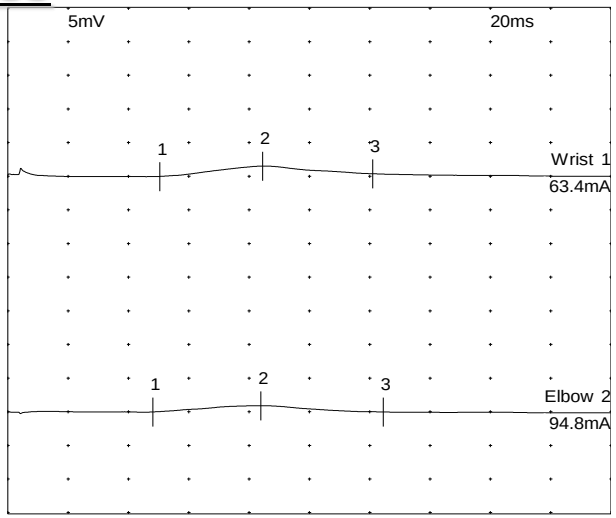
Motor NCS

Nerve / Sites	Rec. Site	Onset Lat ms	B-P Amp. mV	P-P Amp. mV	Dist. cm	Vel. m/s
L Median - APB						
Wrist	APB	5.04	1.6			
Elbow	APB	4.81	0.9			
L Deep peroneal (Fibular) - EDB						
Ankle	EDB	NR	NR	NR		
Fib Head	EDB	NR	NR	NR		
L Peroneal - TA						
Fib head		2.83	1.6	2.2		
Fib head		3.13	1.2	2.0		
Knee		4.17	1.0	1.6	3	30.8
R Peroneal - TA						
Fib head		2.92	1.5	2.0		
Fib head		3.08	1.7	2.2		
Fib head		3.02	2.0	2.7		
Fib head		2.98	1.9	2.5		

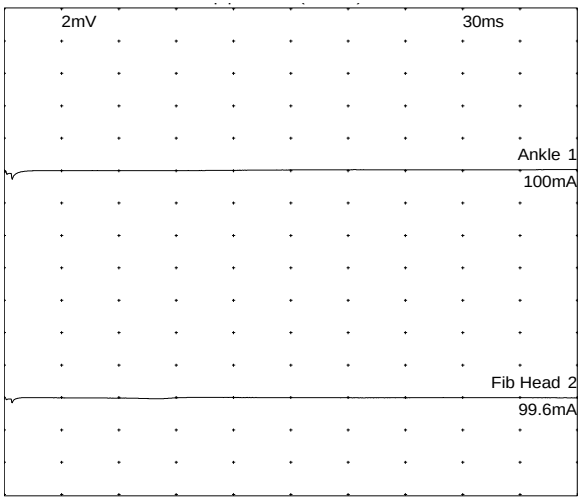
NCS/EMG (2021/06/08)

Motor NCS

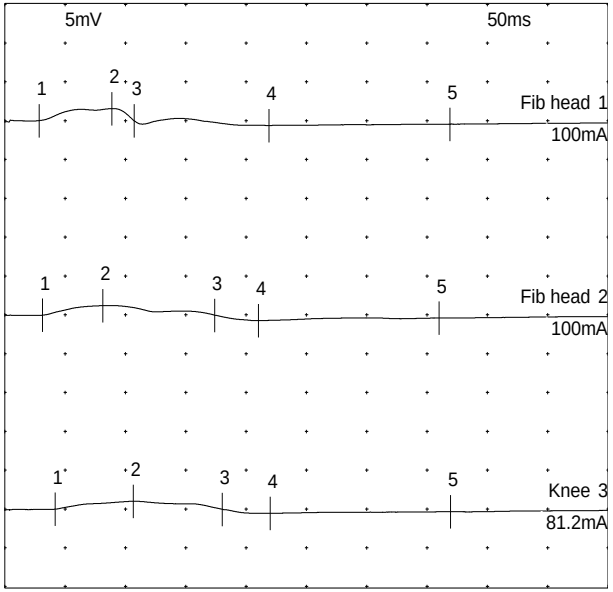
L Median - APB



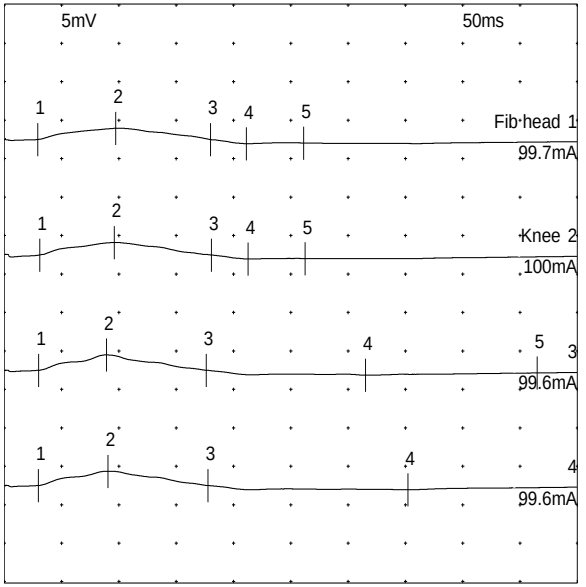
L Deep peroneal - EDB



L Deep peroneal - TA



R Deep peroneal - TA

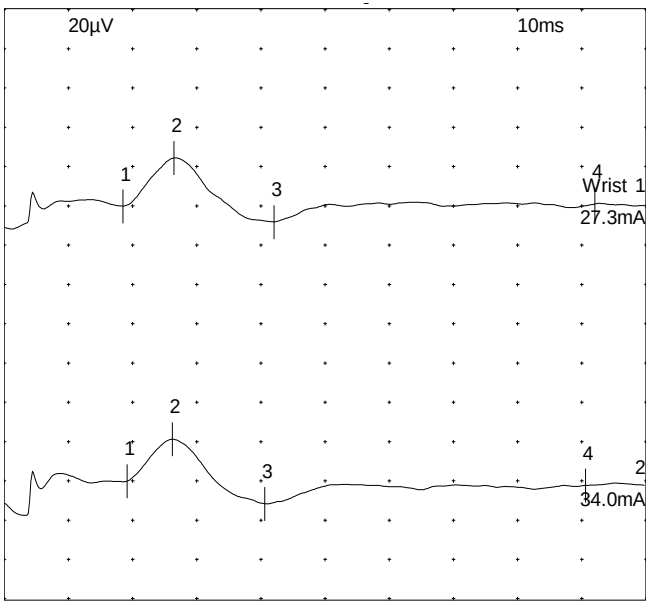


NCS/EMG (2021/06/08)

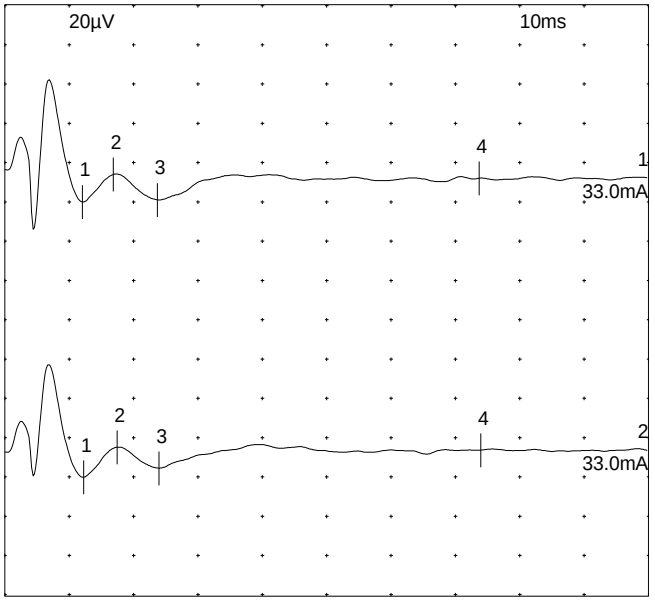
Sensory NCS

Nerve / Sites	Rec. Site	Onset Lat ms	Peak Lat ms	O-P Amp. μV	P-P Amp. μV	Dur. ms	Stim.
L Median - Digit III							
Wrist	Digit III	1.85	2.65	24.7	32.7	2.35	27.3mA
Wrist	Digit III	1.92	2.63	21.4	33.1	2.15	34.0mA
L Sural - Lat Malleolus							
Calf	Lat Malleolus	1.21	1.69	14.2	13.1	1.17	33.0mA
Calf	Lat Malleolus	1.23	1.75	15.4	10.9	1.17	33.0mA

L Median – Digit III



L Sural- Lat Malleolus



NCS/EMG (2021/06/08)

Needle EMG

EMG Summary Table										
	Spontaneous					MUAP			Recruitment	Interference
Muscle	IA	Fib	PSW	Fasc	CRD	Amp	Dur.	Phase	Pattern	Pattern
L. Tibialis anterior	N	2+	2+	None	None	NL	NL	Polys	Reduced	Reduced
R. Tibialis anterior	N	2+	2+	None	None	NL	NL	NL	Reduced	Reduced

What is the possible diagnosis?