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学位論文題目	Long-term Prognosis and Genetic Background of the Patients with Left Ventricular Noncompaction (左室心筋緻密化障害の長期予後と遺伝学的背景に関する研究)
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論 文 内 容 の 要 旨

Objective

Left ventricular noncompaction (LVNC) is postulated to be caused by an arrest of the normal process of intrauterine endomyocardial morphogenesis. LVNC can occur from the fetal period to the adulthood. LVNC has since been classified as a primary genetic cardiomyopathy, but the natural history and genetic basis are not fully evaluated. So, in this study, we clarified the genetic background and analyzed the largest series of patients with LVNC via nationwide surveys, and compared the clini cal features and the long-term prognosis over 20 years between infantile and juvenile cases of LVNC.

Methods.

We conducted follow-up nationwide surveys to elucidate the clinical features and the prognosis of LVNC in Japanese children who had been identified in 1996-2015. The clinical features and anatomical properties of infantile cases of LVNC (age at present ation< 1 years: 108 cases, infantile type) were compared with juvenile cases (age at presentation 1-15 years: 97 cases, juvenile type). Echocardiographic data included left ventricular end-diastolic dimensions (LVDD); LV ejection fraction (LVEF); and the distribution and depth of prominent trabeculations in the left ventricle. N/C (noncompacted to compacted layer) ratios were measured in 5 wall segments of the left ventricle at end-diastole: 4 wall segments of the anterior, lateral, posterior walls, interventricular septum at the levels of papillary muscles in the short axis view, and one wall segment at apex in the long axis view. The thickness of compacted layer in LVPW (LVPWC) and LVDD were expressed as Z scores based on body surface area. We also compared the correlation between different echocardiographic parameter and LVEF.

On the genetic side, we targeted and sequenced 102 unrelated LVNC patients using next generation sequencing (NGS). NGS was performed using an IonPGM syst em strategy which included a total of 73 cardiac disorder-related genes associated wi th cardiomyopathies and channelopathies.

Results.

Clinical features.

Most patients in the infantile type had clinical signs or symptoms of heart failure at initial presentation (60%), the majority of juvenile (56%) cases were asymptomatic and identified only when screened for cardiac abnormalities. The number of patients with heart failure requiring hospitalization was significantly higher in the infantile type than that in the juvenile type (72% vs.30%, $p<0.0001$).

Echocardiographic findings.

Reduced LVEF at initial presentation was significantly more common in the infantile type than in the juvenile type. 56% of the patients in the infantile type had an

LVEF less than 50%. The maximum N/C ratio was observed at the apex, N/C ratio ≧2.0 in all patients, followed by the posterior wall, lateral wall, interventricular septum, and anterior wall. The N/C ratio of the posterior wall and apex, and the me an N/C of five segments were lower in the infantile type. There were no significant differences in noncompaction scores, LVPWC and LVDD Z-scores between the two types. LVPWC and LVDD Z-scores showed a moderate but significant correlation with LVEF. In the group of LVPWC Z-scores less than -1.5, LVEF were significantly lower than that in the group with LVPWC Z-scores greater than -1.5 (43.9±4.1 vs 55.0± 2.6%, p=0.02). There was not a significant correlation between mean N/C ratio of 5 segments, noncompaction score, N/C ratio of posterior wall and LVEF.

Prognosis and risk factors.

Survival analysis showed worse prognosis over the shorter term in the infantile type, the survival rate was similarly poor for both types after two decades. However, congestive heart failure at diagnosis was a significant risk factor for survival free of death, heart transplantation (HT) or implantable cardioverter-defibrillator (ICD) insertion. In the infantile type, event free rates were 80% at 5 years, 73% at 10 years, 64% at 15 years and 63% at 20 years after presentation. In contrast, in the juvenile type group the event free rate was 91% at 5 years, and decreased gradually to 81% at 15 years and 61% ultimately similar to the infantile type group at 20 years. Lower LVPWC Z-score was found to be the most significant risk factor for infantile type while decreased LVEF was for juvenile type. The multivariable proportional hazards model including echocardiographic parameter showed that congestive heart failure at diagnosis and lower LVPWC Z-score were independent risk factors for death, HT or ICD insertion but not age onset.

Genetic analysis.

102 patients had blood samples. Next generation sequencing of the 102 patients yielded 540830 ± 11986 sequence reads per person; the mean read length per sample was 163.6 ± 1.1bp; the mean depth of base coverage was 247.0 ± 5.8 reads; 95.23% had more than 10-fold coverage, 92.5% had more than 20-fold coverage. There were 45 pathogenic variants; 41 were missense, 1 deletion, 1 nonsense, and 2 splice site variants. Sarcomere gene variants accounted for 60%, while variants in genes associated with channelopathies accounted for 13%. Overall, *MYH7* was most commonly mutated (n=19, 42%), followed by *TAZ* (n=6, 13%), ANK2 (n=3, 7%) and *SGCD* (n=2). There was only one pathogenic variant in each of *MYBPC3*, *TNNC1*, *LMNA*, *KCNH2*, *KCNE3*, *JUP*, *HCN4*, *BMPR1A* and *TBX5*.

Conclusions.

A nationwide survey over 20 years of patients with LVNC revealed poor prognosis

both in infantile and juvenile types after two decades; therefore, on-going follow-up is recommended into adulthood. Heart failure at diagnosis and hypoplasia of the compacted layer of the LV wall are the major determinants of poor prognosis. Although N/C ratio is a useful criterion for diagnosis of LVNC, it may be not assessment predictor of severity of LVNC and cannot predict prognosis. NGS revealed a wide spectrum of genetic variations and a high incidence of pathogenic variants in LVNC patients.

学 位 論 文 審 査 の 要 旨

（論文審査の要旨）

左室心筋緻密化障害（Left Ventricular Noncompaction: LVNC）は胎生期の心室、特に左室の心内膜側の心筋が緻密化しない病態で、臨床的には拡張型心筋症の病態を示し血栓症や不整脈を合併することがあり、原発性遺伝性心筋症として分類されてきたが、自然経過および遺伝的根拠は完全には評価されていない。本研究では、全国調査を通じ、遺伝的背景を明らかにし、LVNC患者の全体像を分析し、幼児期と乳児期のLVNC症例の臨床的特徴および長期予後を比較した。

【方法】

日本国内の小児LVNC患者の臨床的特徴および予後を明らかにするために全国的な調査を行い、LVNCの乳児症例（出現年齢1歳未満：108例、乳児型）の臨床的特徴および解剖学的特徴を、若年症例（発表年齢1-15歳：97例、若年型）と比較した。心エコー検査所見として左室拡張末期径（LVDD）、LV駆出率（LVEF）および左心室における顕著な肉柱形成の分布および深さを比較した。N/C比（非緻密化層と緻密化層の比率）は拡張期の左心室の5カ所と乳頭筋のレベルでの短軸方向の前壁、側壁、後壁、心室中隔の4カ所、長軸方向では心尖部で比較した。LVPW（LVPWC）およびLVDDにおける緻密層の厚さは、体表面積に基づくZスコアとして評価した。遺伝的検討として、次世代配列決定（NGS）を用いて 102人のLVNC患者を標的とし、心筋症およびchannelopathiesに関連する合計73の心臓疾患関連遺伝子を含む IonPGM を用いて検討した。

【結果】

乳児型のほとんどの患者は、初期症状として 60%に心不全の臨床徴候・症状を有し、一方、若年型の 56%は無症候性でありスクリーニングで同定されていた。 入院を必要とする心不全患者の数は、乳児型 72%、若年型 30%で有意差を認めた（$p<0.0001$）。 LV 駆出率の低下は乳児型に多く、乳児型の 56%は LVEF が 50%以下であった。N/C 比の最大値は心尖部の 2.0 であり、以下、後壁、側壁、心室中隔、および前壁であった。乳児型では、後壁と心尖部の N/C 比および左心室の 5 カ所の平均 N/C が低かった。LVPWC および LVDD の Z スコアは、中等度であるが LVEF との有意な相関を示した。 -1.5 未満の LVPWC Z スコア群では、LVPWC Z スコアが-1.5 より大きい群（43.9±4.1 対 55.0±2.6%、p=0.02）よりも LVEF が有意に低かった。生存分析では、乳児型の短期間の予後が悪かったが、生存率は 20 年後の両方のタイプで同様に不良であった。しかし、診断時のうっ血性心不全は、死亡、心臓移植または埋め込み型心臓除細動器挿入の危険因子であった。 遺伝子分析では、45 の病原性変異体があった。 41 個は missense、1 個の deletion、1 個の nonsense、および 2 個の splice site variant であった。Sarcomere gene variants は 60%を占め、一方、channelopathies に関連する遺伝子

の変異体は 13%であった。全体として、MYH7 が最も多く（n=19.42%）、以下、TAZ（n=6.13%）、ANK2（n=3.7%）、SGCD（n=2）の順で変異を認めた。

【結論】
LVNC 患者の 20 年間にわたる全国調査で、乳児および若年型で 20 年後の予後は不良であり、長期間の追跡が推奨される。診断時の心不全および左室壁緻密層の低形成は予後不良の主要な決定因子である。 N/C 比は LVNC の診断のための有用な基準であるが、重症度の評価予測因子ではない。また、LVNC 患者において広範囲の遺伝的変異および病原性変異の発生を認めた。

以上のことから、本研究ではこれまで明らかでなかった左室心筋緻密化障害の自然経過および遺伝的背景を初めて明らかにした点は新規性があり、診断時の心不全および左室壁心筋緻密層の低形成は予後不良の主要な決定因子であることを示した点は、医学における学術的重要性も高く、今後の臨床的発展性が期待できる。

以上より本審査会は本論文を博士（医学）の学位に十分値すると判断した。