Movement Disorders
CLINICAL PRACTICE
RESEARCH ARTICLE

Electrocardiogram Abnormalities Suggest Aberrant Cardiac Conduction in Huntington's Disease

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Abstract: **Background:** There is increasing evidence that the effects of Huntington's disease (HD) extend beyond the central nervous system. In particular, significant cardiac dysfunction has been described in transgenic mouse models and suggested in symptomatic patients, in whom cardiac involvement could provide an independent risk for sudden cardiac death.
Methods: Standard 12-lead electrocardiograms (ECGs) obtained at screening from 590 early symptomatic (Stage 1 and 2) HD patients participating in a multi-site Phase III study were analyzed.
Results: Evaluating only those ECGs in individuals not on medications or with potentially contributing medical conditions, the prevalence of bradycardia was 28.3% (marked in 5.8%), prolonged QRS 4.9%, intraventricular conduction delay 3.4%, right bundle branch block 1.3%, and QTc prolongation 3.7%.
Conclusion: Significant cardiac abnormalities, characterized primarily by conduction abnormalities, were found in a larger than expected number of patients. Abnormal intraventricular conduction may lead to increased risk for arrhythmia and may be compounded by prescription of QT-prolonging medications.

Introduction

Huntington's disease (HD) is a dominantly inherited, progressive neurodegenerative disorder characterized by a CAG triplet repeat expansion in the huntingtin gene, translated to a pathogenic polyglutamine expansion in the ubiquitously expressed huntingtin protein. The characteristic clinical features of HD include chorea, dystonia, bradykinesia, eye movement abnormalities, cognitive decline, and behavioral disturbances such as depression, irritability, and volatility. However, there is growing evidence that HD can also include peripheral manifestations, which may be clinically relevant.[1] Cardiac causes are the second most common cause of death in HD (second only to pneumonia) affecting as many as 25% of HD patients.[2] Cardiac abnormalities have been described in transgenic mouse models of HD, including dysregulation of the baroreceptor reflex, decreased heart rate variability, increased sympathetic activity, and in some cases severe arrhythmias, leading to sudden cardiac death.[3,4]

We conducted a retrospective study of a large, unique electrocardiogram (ECG) dataset to evaluate the baseline characteristics of a cohort of early symptomatic HD patients participating in the Creatine Safety, Tolerability, & Efficacy in Huntington's Disease study (CREST-E), an international, multi-site Phase III clinical trial. We sought to evaluate the prevalence of ECG abnormalities in a representative HD patient sample.

Methods

Subjects

Screening ECGs collected from a cohort of 590 subjects participating in CREST-E were assessed retrospectively. Inclusion crite-

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ria: 18 years of age and older, genetically confirmed HD, and stage I or II (early) disease denoted by a total functional capacity (TFC) score of ≥ 7. The study was performed in compliance with guidelines on human experimentation. The protocol was approved by the Partners Human Research Committee/Institutional Review Board and monitored by an independent data and safety monitoring board approved by NINDS.

Standard 12-lead ECG Recording

Participants underwent standard 12-lead ECGs. Intervals assessed included heart rate, PR interval, QRS duration, and corrected QT interval (QTc), calculated using the Bazett formula. Abnormal QTc defined as ≥ 450ms for men and ≥ 460ms for women.

Results

Demographics

The ECGs from 590 individuals (285 male and 305 female) with early HD were included. The mean total functional capacity was 10.1 ± 2.1; 271 individuals were in Stage 1 (TFC 11-13) and 319 in Stage 2 (TFC 7-10).

ECG Abnormalities

Abnormal ECGs were found in 256 (43.3%) of the study population; 231 (39.2%) were unexplained by medical risk factors or inciting drugs and 139 (23.6%) when subjects with relative bradycardia (heart rate 50-60 beats per minute) were excluded. We present our findings based on the population without specific risk factors tailored to each ECG abnormality. Table 1 summarizes the ECG abnormalities that were not attributable to cardiac risk factors or medications. Supporting Table 1 provides rates in the general population as a general point of comparison.

Heart Rate Abnormalities

Bradycardia was very common in our cohort and present in 178 (30.2%) patients. Of the 502 subjects without risk factors for bradycardia, including sino-atrial (SA) nodal blocking drugs, hypothyroidism, coronary artery disease (CAD), or hypertensive heart disease, 142 (28.3%) had unexplained bradycardia (heart rate < 60 bpm) and 29 (5.8%) had unexplained marked bradycardia (heart rate < 50 bpm), which did not correlate with advancing age or disease severity.

Ectopy and Rhythm Abnormalities

In the 553 without known risk factors for ectopy, including CAD, hyperthyroidism, or the use of stimulants, 22 (4.0%) patients had ectopic beats, including 2.0% with premature ventricular contractions (PVCs).

Conduction Abnormalities

Conduction abnormalities were frequent: 70 (11.9%) had evidence of atrioventricular (AV) block, prolonged QRS, cardiac axis abnormalities or fascicular block, or QTc prolongation unexplained by specific disease risk factors or relevant medications.

Atrioventricular (AV) Block

Of the 543 without CAD or AV nodal blocking drugs, 23 (4.2%) had unexplained AV block. One subject had Mobitz Type I Wenckebach and the remainder had first degree AV block. Advancing age, but not HD severity, was associated with a higher incidence of altered AV conduction.

Prolonged QRS

Of the 555 without QRS prolonging drugs or CAD, 27 (4.9%) had unexplained intraventricular conduction abnormalities with QRS prolongation ≥ 110 ms, 19 (3.4%) had intraventricular conduction delay (IVCD), and 7 (1.3%) had right bundle branch block (RBBB).

Cardiac Axis Abnormalities and Fascicular Block

Of the 541 without CAD, hypertensive heart disease or obstructive sleep apnea, unexplained left axis deviation (LAD) was seen in 20 (3.7%) and left anterior fascicular block (LAFB) in 15 (2.8%).

QT Prolongation

QTc-prolongation was found in 11 (3.7%) of the 294 subjects not on medications known to prolong the QTc interval or with CAD. Supplorting Table 2 provides prescription rates of medications associated with QTc prolongation, categorized as known or possible risk for torsades de pointes (http://www.crediblemeds.org).

Ischemic Changes (ST/T Wave Abnormalities or Other Changes)

In the 569 without known CAD, hypertensive heart disease, or on digoxin therapy, possible ischemic changes were present in 27 (4.7%). T wave inversion was the most common (3.5%), followed by ST depression (1.8%), the presence of Q waves (0.5%), and poor R wave progression (0.4%).

Multiple Unexplained ECG Abnormalities

25 subjects (4.2%) had multiple unexplained ECG abnormalities, including those potentially co-associated, such as QT prolongation and bundle branch block, AV nodal dysfunction, or ischemic changes.

TABLE 1 *ECG Abnormalities in Those Without Risk Factors in Early Stage HD*

ECG abnormality	Age ranges separated by disease stage											
	All age ranges, n (%)			20-39 years, n (%)			40-59 years, n (%)			≥60 years, n (%)		
	Total (n = 590)	Stage 1 (n = 271)	Stage 2 (n = 319)	Total (n = 105)	Stage 1 (n = 53)	Stage 2 (n = 52)	Total (n = 346)	Stage 1 (n = 151)	Stage 2 (n = 195)	Total (n = 139)	Stage 1 (n = 67)	Stage 2 (n = 72)
Unexplained abnormal ECGs	231 (39.2)	105 (38.7)	126 (39.5)	29 (27.6)	11 (20.8)	18 (34.6)	136 (39.3)	64 (42.4)	72 (36.9)	66 (47.5)	30 (44.8)	36 (50.0)
Unexplained abnormal ECGs (not including bradycardia with HR ≥50)	139 (23.6)	61 (22.5)	78 (24.5)	16 (15.2)	5 (9.4)	11 (21.2)	79 (22.8)	36 (23.8)	43 (22.1)	44 (31.7)	20 (29.9)	24 (33.3)
Brady-arrhythmia: expressed as % of pool without individual risk factors[a]	**(n = 502)**	**(n = 233)**	**(n = 269)**	**(n = 97)**	**(n = 48)**	**(n = 49)**	**(n = 303)**	**(n = 137)**	**(n = 166)**	**(n = 101)**	**(n = 48)**	**(n = 53)**
Bradycardia (HR<60)	142 (28.3)	68 (25.1)	74 (29.2)	20 (20.6)	10 (20.8)	10 (20.4)	84 (27.7)	40 (29.2)	44 (26.5)	38 (37.6)	18 (37.5)	20 (37.7)
Marked bradycardia (HR<50)	29 (5.8)	16 (6.7)	13 (4.8)	6 (6.2)	4 (8.3)	2 (4.1)	17 (5.6)	8 (5.8)	10 (6.0)	6 (5.9)	4 (8.3)	2 (3.8)
Ectopy: expressed as % of pool with or without individual risk factors[b]	**(n = 553)**	**(n = 254)**	**(n = 299)**	**(n = 101)**	**(n = 51)**	**(n = 50)**	**(n = 331)**	**(n = 147)**	**(n = 184)**	**(n = 121)**	**(n = 56)**	**(n = 65)**
Ectopy (atrial and ventricular)	22 (4.0)	10 (3.9)	12 (4.0)	3 (3.0)	0 (0)	3 (6.0)	8 (2.4)	3 (3.1)	5 (2.7)	11 (9.1)	7 (12.5)	4 (6.2)
PVCs	11 (2.0)	7 (2.8)	4 (1.3)	1 (1.0)	0 (0)	1 (2.0)	4 (1.2)	2 (1.4)	2 (1.1)	6 (5.0)	5 (8.9)	1 (1.5)
Bigeminy	1 (0.2)	1 (0.4)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.3)	1 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)
Conduction abnormalities												
AV block: expressed as % of pool without individual risk factors[c]	**(n = 543)**	**(n = 250)**	**(n = 293)**	**(n = 103)**	**(n = 51)**	**(n = 52)**	**(n = 327)**	**(n = 147)**	**(n = 180)**	**(n = 113)**	**(n = 52)**	**(n = 61)**
All AV block	23 (4.2)	12 (4.8)	11 (3.8)	0 (0)	0 (0)	0 (0)	12 (3.7)	7 (4.8)	5 (2.8)	11 (9.7)	5 (9.6)	6 (9.8)
1st degree AV block	22 (4.1)	12 (4.8)	10 (3.1)	0 (0)	0 (0)	0 (0)	11 (3.4)	7 (4.8)	4 (2.1)	11 (9.7)	5 (9.6)	6 (9.8)
Mobitz 2 Wenckebach	1 (0.2)	0 (0)	1 (0.3)	0 (0)	0 (0)	0 (0)	1 (0.3)	0 (0)	1 (0.6)	0 (0)	0 (0)	0 (0)
Infra-Hisian block: expressed as % of pool without individual risk factors[d]	**(n = 555)**	**(n = 261)**	**(n = 294)**	**(n = 103)**	**(n = 53)**	**(n = 50)**	**(n = 330)**	**(n = 150)**	**(n = 180)**	**(n = 122)**	**(n = 58)**	**(n = 64)**
Prolonged QRS (≥110ms)	27 (4.9)	9 (3.4)	18 (6.1)	1 (1.0)	0 (0)	1 (2.0)	17 (5.2)	7 (4.7)	10 (5.6)	9 (7.4)	2 (3.4)	7 (10.9)
IVCD	19 (3.4)	7 (2.7)	12 (4.1)	0 (0)	0 (0)	0 (0)	15 (4.5)	5 (3.3)	10 (5.6)	4 (3.3)	2 (3.4)	2 (3.1)
RBBB	7 (1.3)	2 (0.8)	5 (1.7)	1 (1.0)	0 (0)	1 (2.0)	2 (0.6)	2 (1.3)	0 (0)	4 (3.3)	0 (0)	4 (6.3)
LBBB	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other: Wolff-Parkinson-White	1 (0.2)	0 (0)	1 (0.3)	1 (1.0)	0 (0)	1 (2.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

TABLE 1 *(Continued)*

ECG abnormality	Age ranges separated by disease stage											
	All age ranges, n (%)			20-39 years, n (%)			40-59 years, n (%)			≥60 years, n (%)		
	Total (n = 590)	Stage 1 (n = 271)	Stage 2 (n = 319)	Total (n = 105)	Stage 1 (n = 53)	Stage 2 (n = 52)	Total (n = 346)	Stage 1 (n = 151)	Stage 2 (n = 195)	Total (n = 139)	Stage 1 (n = 67)	Stage 2 (n = 72)
QT prolongation: expressed as % of pool without individual risk factors[e]	**(n = 294)**	**(n = 160)**	**(n = 134)**	**(n = 57)**	**(n = 31)**	**(n = 26)**	**(n = 171)**	**(n = 90)**	**(n = 81)**	**(n = 66)**	**(n = 39)**	**(n = 27)**
QT prolongation	11 (3.7)	4 (2.5)	7 (5.2)	2 (3.5)	0 (0)	2 (7.7)	7 (4.1)	3 (3.3)	4 (4.9)	2 (3.0)	1 (2.6)	1 (3.7)
Cardiac axis abnormalities and fascicular block: expressed as % of pool without individual risk factors[f]	**(n = 541)**	**(n = 249)**	**(n = 292)**	**(n = 105)**	**(n = 52)**	**(n = 50)**	**(n = 322)**	**(n = 141)**	**(n = 181)**	**(n = 117)**	**(n = 56)**	**(n = 61)**
Left axis deviation	20 (3.7)	8 (3.2)	12 (4.1)	0 (0)	0 (0)	0 (0)	8 (2.5)	3 (2.1)	5 (2.8)	12 (10.3)	5 (8.9)	7 (11.5)
Left anterior fascicular block	15 (2.8)	6 (2.4)	9 (3.1)	0 (0)	0 (0)	0 (0)	6 (1.9)	3 (2.1)	3 (1.7)	9 (7.7)	3 (5.4)	6 (9.8)
Unexplained Ischemic changes (ST, T other changes): expressed as % of pool without individual risk factors[g]	**(n = 569)**	**(n = 262)**	**(n = 307)**	**(n = 104)**	**(n = 53)**	**(n = 51)**	**(n = 341)**	**(n = 151)**	**(n = 190)**	**(n = 124)**	**(n = 58)**	**(n = 66)**
Total ischemic changes	27 (4.7)	14 (5.3)	13 (4.2)	3 (2.9)	1 (1.9)	2 (3.9)	17 (5.0)	9 (6.0)	8 (4.2)	7 (5.6)	4 (6.9)	3 (4.5)
Q waves	3 (0.5)	2 (0.8)	1 (0.3)	0 (0)	0 (0)	0 (0)	2 (0.6)	1 (0.7)	1 (0.5)	1 (0.8)	0 (0)	1 (1.5)
ST changes	10 (1.8)	4 (1.5)	7 (2.3)	2 (1.9)	0 (0)	2 (3.9)	6 (1.8)	3 (2.0)	3 (1.6)	2 (1.6)	1 (1.7)	1 (1.5)
T wave changes (T wave inversion)	19 (3.5)	11 (4.2)	9 (2.9)	3 (2.9)	1 (1.9)	2 (3.9)	13 (3.8)	8 (5.3)	5 (2.6)	4 (3.2)	2 (3.4)	2 (3.0)
Poor R wave progression	2 (0.4)	1 (0.4)	1 (0.3)	0 (0)	0 (0)	0 (0)	1 (0.3)	0 (0)	1 (0.5)	1 (0.8)	1 (1.7)	0 (0)
Left ventricular hypertrophy: expressed as % of pool without individual risk factors[h]	465	212	253	94	45	49	287	126	161	84	41	43
LVH	2 (0.4)	0 (0)	2 (0.8)	1 (1.1)	0 (0)	1 (2.0)	1 (0.3)	0 (0)	1 (0.6)	0 (0)	0 (0)	0 (0)

Abbreviations: AV, atrioventricular); CAD, coronary artery disease; HR, heart rate; IVCD, intraventricular conduction delay; LVH, left ventricular hypertrophy; PVCs, premature ventricular contractions; RBBB, right bundle branch block; TdP, torsades de pointes.
[a]Bradyarrhythmias unexplained by SA nodal blocking drugs, hypothyroidism, CAD, or hypertensive heart disease (defined as LVH/CAD/CHF).
[b]Ectopy unexplained by CAD, hyperthyroidism or stimulants.
[c]AV block unexplained by CAD or AV nodal blocking drugs.
[d]Infra-Hisian block unexplained by QRS prolonging drugs or CAD.
[e]QT prolongation unexplained by QT prolonging drugs with a known or possible risk of TdP or cardiac disease.
[f]Cardiac axis abnormalities and fascicular block unexplained by CAD, hypertensive heart disease or obstructive sleep apnea.
[g]Ischemic changes unexplained by CAD, digoxin therapy or hypertensive heart disease.
[h]Left ventricular hypertrophy unexplained by hypertension.

DISCUSSION

Our study suggests that significant ECG abnormalities, primarily involving rate (bradycardia) and cardiac conduction (QRS prolongation, AV, and QT prolongation) appear to occur in HD, with a greater prevalence associated with advancing age and advancing disease severity, and not associated with known secondary causes. This suggests that a diagnosis of HD alone provides an independent and significant cardiac risk factor. While one of the strengths of our retrospective study is the large sample size of a rare neurodegenerative disorder, one potential limitation is that our cohort did not include healthy controls. However, the rates of ECG abnormalities appear to be significantly greater than what has been reported in the literature and suggests that these findings may have great potential clinical relevance.

The prevalence of conduction abnormalities in early HD, in the absence of known CAD or the use of mediations known to affect cardiac conduction, suggests possible compromise of the cardiac bundles and AV node, which could lower the threshold for arrhythmia or sudden cardiac death and cause and/or aggravate cardiac failure.[5] In particular, the rates of QRS-prolongation, including infra-Hisian block (prolonged QRS 4.7% vs. 1.30%; IVCD 3.4% vs. 0.60%)[6] and RBBB (1.3% vs. 0.90%),[7] were higher in HD than normative population values. In the general population, IVCD can both increase cardiac mortality (RR 2.53) and all-cause mortality (RR 2.01), with a 3-fold increased risk of sudden arrhythmic death.[6] RBBB, usually associated with structural heart disease, is associated with increased risk of myocardial infarction and increased all-cause mortality.[7] Bradycardia was observed in almost one-third of our population and marked bradycardia, with heart rates in the low 40s in approximately 6% of our cohort—higher than reported values in the general population.[8] Studies have reported decreased cardiovagal activity in mid-stage disease, suggesting an imbalance between sympathetic and parasympathetic cardiac innervation.[9] Significant bradycardia can also exacerbate angina, or worsen heart failure which may complicate late stages of disease.[1]

It is important to note that serotonin-uptake inhibitors and neuroleptics (not uncommonly given to treat common behavioral and psychiatric symptoms in HD), as well as tetrabenazine, might also increase the risk of QT-prolongation and predispose HD patients to torsades-de-pointes and potentially fatal arrhythmias.[4,10] Our study suggests that careful monitoring of use of these medications in the HD population is warranted.

Conclusions

These results provide evidence of significant electrocardiographic abnormalities in early stage HD, which could increase the risk of symptomatic cardiac disease or lower the threshold for other cardiac risks to become symptomatic. Our results provide a definitive rationale for future controlled studies of cardiac pathology in HD.

Author Roles

1. Research Project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript Preparation: A. Writing the First Draft, B. Review and Critique.

C.D.S.: 1B, 1C, 2A, 2B, 2C, 3A, 3B
H.D.R.: 1A, 1B, 1C, 2C, 3A, 3B
J.H.: 2C, 3B
G.S.: 2C, 3B
S.M.H.: 1A, 2C, 3A, 3B

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Supporting Information

Additional Supporting Information may be found in the online version of this article.

Table S1. Prevalence of unexplained ECG abnormalities in HD grouped by gender and compared with reference data in non-HD healthy populations

Table S2. Prescription rates of medications that may affect QTc in the cohort