REVIEW

Cardiac disease and Rett syndrome

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Rett syndrome (RS) is a neurodevelopmental disease,[1] affecting approximately 1 in 10 000–15 000 females.[2] Clinical severity of RS may vary with increasing age, following a four stage model.[3]

Mutations in the methyl-CpG-binding protein 2 gene (MECP2) are present in the majority of cases of RS, but a proportion of atypical cases may result from mutations in CDKL5, particularly the early onset seizure variant.[4] MECP2 was originally thought to be a global transcriptional repressor, but recent evidence suggests that it may have a role in regulating neuronal activity dependent expression of specific genes such as brain derived neurotrophic factor (BDNF) which is important in synapse development and neuronal plasticity.[4] MECP2 absence or reduction in neurones of Rett children may account for the failure of structural maturation in the brain and for the alterations in neurotransmitters, required for the regulation of normal brain development.[5] Neurometabolic alterations include reduced levels of dopamine, serotonin, noradrenaline, choline acetyltransferase, nerve growth factor (NGF), endorphines, substance P, glutamate, and other aminoacids and their receptor levels in the brain.[3]

Rett patients may survive into middle and old age, but their life expectancy is reduced and the incidence of sudden death (SD) is greater than that of the general population. The mortality rate in RS is 1.2% for year; of these deaths, 48% occur in debilitated people, 13% are from natural causes, 13% occur in those with prior severe seizures, and 26% were SD.[6] In comparison, the incidence of SD in the general population, between 1 and 22 years of age, is 1.3 per 100 000 patient-years.[7] Possible causes of SD in RS include brain stem autonomic failure (respiratory failure, apnoea, cardiac arrhythmias);[8] the possibility that cardiac electrical instability might be the underlying pathogenetic mechanism has prompted efforts to determine the cardiac alterations in RS.

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ANATOMICAL FINDINGS

Measurement of organ weights, as recorded in 44 postmortem examination studies, suggests that the heart grows normally until 8 years of age; thereafter the weight is less than the normal range, but it continues to increase, reaching a plateau between 16 and 20 years of age.[9]

Kearney and colleagues[10] examined the cardiac conduction system from postmortem hearts of six RS patients (aged 7–27 years), five of which had suffered from SD. Histological examination showed a significant dispersion of conduction system fibres within the central fibrous body (archipelagos), with focal premature connections to the crest of the ventricular septum (Mahaim fibres). The ''archipelagos'' of the conduction system in RS resemble the immature configuration of the conduction system in the newborn and young infant, suggesting a possible development arrest in this region of the heart.

In a recent study,[11] 32 girls with Rett syndrome were evaluated by echocardiography: all had normal cardiac structures, dimensions, and function, suggesting that in RS there are no cardiomyopathies or cardiac valve alterations.

ELECTROCARDIOGRAPHIC FINDINGS

In recent years, many studies have shown the presence of risk factors for life threatening cardiac arrhythmias in RS; in particular, a prolongation of QT corrected interval (QTc)—that is, the QT interval divided by the square root of the preceding RR interval (normal values <440 msec).[12]

Cardiac arrhythmias

Sekul and colleagues[13] evaluated a total of 61 standard 12-lead electrocardiograms (ECGs) in 34 individuals with RS aged 2–22 years: sinus tachycardia was observed in 6% of patients (2/34), but no other cardiac arrhythmias were observed.

Madan and colleagues[14] described a case of severe sinus bradycardia in a 2 year old girl with RS, suggesting that this cardiovascular manifestation may provide an explanation for SD in these patients.

Ellaway and colleagues[15] investigated the presence of cardiac tachyarrhythmias in 24 hour Holter ECG monitoring in a cohort of 34 Rett girls, and found no significant arrhythmias.

Guideri and Acampa[16] studied 214 Rett girls with a 10 minute 12-lead ECG. In one patient an asymptomatic grade 2 sinoatrial block was observed, and in another patient a ventricular tachycardia was documented before death.

Panossian and Duro[17] described a case of atrioventricular dissociation with third degree atrioventricular block in a 6 month old girl with Rett syndrome.

Ventricular repolarisation

Sekul and colleagues[13] were the first to show alterations of ventricular repolarisation in RS, observing a prolongation of QTc interval (>0.45 sec) in 14/34 Rett girls (table 1), significantly more prolonged across clinical stages.

Abbreviations: HRV, heart rate variability; RS, Rett syndrome; SD, sudden death

They also showed non-specific T wave changes in 18/34 Rett girls and other ECG abnormalities such as a right ventricular conduction delay (7/34), and a counterclockwise loop in the frontal plane (2/34).

Johnsrude and colleagues[18] evaluated routine ECGs in 25 RS females, confirming a prolongation of QTc interval (table 1).

Guideri and colleagues[19] showed in 74 Rett children a prolongation of QTc interval without any progression across the clinical stages (table 1); in Rett girls with preserved speech, QTc prolongation was only observed in 20% of patients, but QTc interval was significantly longer than in the control group (0.42 ± 0.03 *v* 0.40 ± 0.01 sec).

Ellaway and colleagues[15] showed, in a cohort of 34 Rett girls, QTc values ranging from 0.38 to 0.53 sec (mean value 0.44 sec), identifying a prolonged QTc interval in 9/34 patients (table 1) without T or U wave abnormalities.

Recently, in RS, alterations of ventricular repolarisation were evaluated by means of magnetocardiographic mapping,[20] showing in nine Rett girls an abnormal magnetic field gradient orientation, more altered with clinical stage and a prolongation of JT peak, JT end, QT end, T peak-end intervals, and QT dispersion.[20]

Pathogenesis of QTc prolongation is still unknown; but it is well known that cardiac autonomic dysfunction may influence QTc interval duration, in particular sympathetic imbalance may increase QTc interval.[21] However, Johnsrude *et al* showed that Rett children with QTc >0.45 sec and those with QTc <0.45 had similar heart rate variability (HRV) parameters[18] (HRV represents the variation of both instantaneous heart rate and RR intervals and is considered a marker of cardiac autonomic nervous system activity[22]). Similarly, our group did not observe any correlation between sympathetic hyperactivity and QTc prolongation.[19]

Recently, we observed low NGF plasma levels in RS patients with prolonged QTc and higher QTc dispersion suggesting a role for neurotrophic factors in the alterations of ventricular repolarisation; low NGF plasma levels may cause an abnormal heart innervation pattern and an increased in QTc interval through a delayed pattern of both nexal and desmosomal junction formation and by the dispersion in the action potential duration[23] (fig 1).

In particular, desmosome alteration may cause the destabilisation of myocardial cell adhesion complexes, inhibiting preservation of normal numbers of gap junctions resulting in heterogeneous conduction and significantly contributing to arrhythmogenesis.[24]

Cardiac autonomic nervous system

There is clinical and experimental evidence that in RS, the autonomic nervous system is abnormal at various levels.[25] Julu and colleagues[26] measured the autonomic reactions to hyperventilation in RS to understand the interactions between medullary autonomic and cardiorespiratory neurones, suggesting that medullary cardioinhibition is immature in RS; in particular, measuring the cardiac response to the baroreflex, he observed a reduced cardiac vagal tone, leading to sympathovagal imbalance with higher risk of cardiac arrhythmias and possibly SD.

It is well known that cardiac dysautonomia has a role in the pathogenesis of lethal ventricular arrhythmias: sympathetic stimulation lowers the ventricular fibrillation threshold, whereas vagal stimulation antagonises sympathetic activity and decreases the ventricular fibrillation threshold.[27]

Johnsrude and colleagues[18] studied HRV parameters from 24 hour ECG ambulatory monitoring in 25 females with RS (aged 3–27 years). Diminished HRV was shown in RS with respect to the mean and standard deviation of normal RR for all 5 minute segments, root mean square successive differences, difference percentage between normal RR >50 msec, and high frequency spectral component power.

Guideri and colleagues[19 28] studied the cardiac autonomic nervous system by means of HRV, and found that: (1) the total power spectrum of HRV was significantly lower in children with RS and this alteration progresses with age and with clinical stages; (2) the sympathovagal balance expressed by the ratio LF/HF (low frequency/high frequency) was significantly higher in RS, reflecting the prevalence of sympathetic activity; and (3) the girls with preserved speech variant show a slight increase of sympathetic tone but a normal values of total power of HRV (fig 2).

These results suggested that loss of physiological HRV associated with an increase of adrenergic tone and QTc prolongation may represent the electrophysiological basis of cardiac instability and SD (fig 1).

The pathogenesis of cardiac dysautonomia in RS is not well known; Julu and Witt-Engerström observed that baseline brain stem functions (breathing rhythm, cardiac sensitivity to baroreflex, and cardiac vagal tone, which are maintained by complex integrative inhibition) are affected in RS, with heterogeneous clinical phenotypes,[29] suggesting an insufficient reciprocal innervation and a leak of integrative inhibition within the cardiorespiratory neurones of the brain stem.

Neurotransmitters may also have a role in the pathogenesis of cardiac dysautonomia (fig 1): in RS, substance P is deficient in the central nervous system, contributing to the impairment of autonomic nervous system resulting in cardiac dysautonomia.[30]

Furthermore, Guideri and colleagues[31] observed that serotonin plasma levels are low in RS and correlated positively with sympathovagal balance (LF/HF ratio), suggesting a link between cardiac dysautonomia and serotoninergic dysfunction. Central serotoninergic pathways innervate autonomic areas involved in cardiovascular regulation;[32] in particular, an increase in central nervous system serotoninergic neurotransmission reduces the susceptibility to ventricular fibrillation, because the increase in central serotonin produces a decrease in sympathetic nerve traffic to the heart.[32] Therefore, it seems likely that the brain's control of sympathetic output is closely linked with central serotoninergic mechanisms (high serotonin/low sympathetic out-

Table 1 Summary of studies investigating QTc interval prolongation in Rett syndrome

First author	QTc interval (msec)				Pts with ↑ QTc (%)
	Total	Stage II	Stage III	Stage IV	
Sekul[13] (n = 34)	430 ± 20	420 ± 20	440 ± 30	440 ± 20	41%
Johnsrude[18] (n = 25)	441 ± 32				9%
Guideri[28] (n = 54)	441 ± 20	435 ± 20	445 ± 20	439 ± 20	48%
Ellaway[15] (n = 34)	438 ± 4	410 ± 42	441 ± 27	437 ± 8	30%
Guideri[19] (n = 74)	440 ± 20	440 ± 20	438 ± 20	439 ± 20	55%

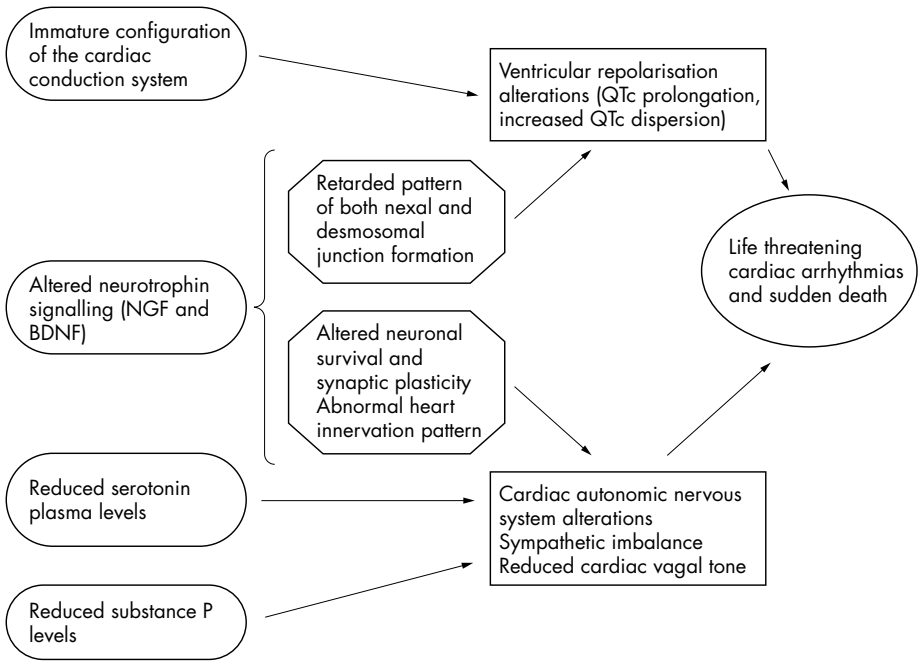

Figure 1 *Hypothesis of pathogenetic mechanisms explaining sudden death in Rett syndrome.* The immature configuration of conduction system fibres may cause an alteration of ventricular repolarisation, also determined by a retarded pattern of both nexal and desmosomal junction formation, related to low NGF plasma levels. Furthermore, the altered neurotrophin signalling, serotoninergic dysfunction, and deficiency of substance P may contribute to impairment of the autonomic nervous system, resulting in cardiac dysautonomia with sympathetic imbalance. Finally, alterations of ventricular repolarisation and cardiac dysautonomia may favour the onset of life threatening ventricular arrhythmias with higher risk of sudden death.

put; low serotonin/high sympathetic output).[32] Recently Paterson and colleagues[33] observed an altered serotonin innervation and/or uptake in the dorsal motor nucleus of the vagus (preganglionic parasympathetic outflow), suggesting a potential implication for clinical autonomic dysfunction; this alteration may be caused by an overexpression of BDNF that may potentially cause a general disruption of serotoninergic neuronal development and a specific abnormality in serotoninergic synapse formation.

An alteration of NGF levels may also contribute to an altered sympathovagal balance, because NGF also functions as a modulator of synaptic transmission between sympathetic neurones and cardiac myocytes[34] (fig 1).

TREATMENT OF CARDIAC ALTERATIONS

In RS, alterations of ventricular repolarisation and cardiac dysautonomia may contribute to life threatening cardiac arrhythmias and probably to the high incidence of SD. QTc prolongation and sympathetic hyperactivity in RS may be reduced by the use of β blockers; however, this does not represent a strong recommendation as in the inherited forms of long QT syndrome in where QT intervals reach much longer values (>500 msec). Furthermore, prokinetic agents (such as cisapride), antipsychotics (such as thioridazine), tricyclic antidepressants (such as imipramine), antiarrhythmics (such as quinidine, sotolol, amiodarone), and antibiotics (such as erythromycin, ketoconazole) should therefore be avoided because of the possibility of precipitating QT abnormalities.

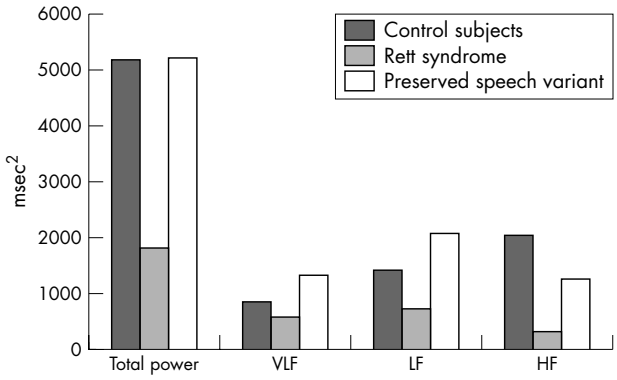

Figure 2 Heart rate variability parameters in control subjects, and those with Rett syndrome and in preserved speech variant.[19] VLF, very low frequency; LF, low frequency; HF, high frequency.

Julu and Witt-Engerström[29] suggested that the pharmacological manipulation of brain stem neurotransmitters may offer a means of clinical intervention: L-glutamate is required for baroreceptor input; serotonin receptor type 5-HT4, angiotensin II, and enkephalin are all modulators of cardiac sensitivity to baroreflex at the nucleus of tractus solitarius; γ-aminobutyric acid is used also to modulate cardiac sensitivity to baroreflex and cardiac vagal tone by supramedullary centres. Treatment with serotonin analogues or serotonin reuptake inhibitors may be useful in improving serotoninergic neurotransmission as well as sympathovagal imbalance. A case report of a Rett girl treated with a serotoninergic type 2A agonist (buspirone) showed a dramatic improvement in breathing pattern, but no data were reported on cardiac alterations.[35]

Recently Guideri and colleagues[36] observed a potential pharmacological role for acetyl-L-carnitine, which, by exerting neurotrophic properties, may improve cardiac dysautonomia in RS; in particular, acetyl-L-carnitine produces a significant increase of HRV total power and a slight reduction of sympathetic overactivity.

However, large trials looking at mortality or occurrence of arrhythmias should be carried out in order to determine the role for this type of drug in protecting these patients from the risk of lethal arrhythmias and SD.

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