Cardiac Rhythm Abnormalities - An Underestimated Cardiovascular Risk in Adult Patients With Mucopolysaccharidoses

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Highlights

• Cardiac conduction abnormalities in adult patients with Mucopolysaccharidosis (MPS) are common.
•It is mandatory to screen for them to identify abnormal rhythms and treat them.
• There is a need for using loop recorders and pacemakers in adults with MPS.
• There is an increasing role of wearable technology in monitoring heart rhythm in MPS patients.

Abstract:

Patients with Mucopolysaccharidosis (MPS) have an increased risk of cardiovascular complications, conduction tissue abnormalities and arrhythmia; all rare but underestimated. It has been reported that conduction system defects are progressive in this group of patients and may result in sudden cardiac death. The aim of this study is to review our current practice and suggest best practice guidelines regarding the frequency of cardiac rhythm monitoring in this patient group.

Seventy-seven adult MPS patients who attended metabolic clinics between 2013 and 2019 were included in this retrospective observational study. Patients were affected with different MPS types: MPS I (n=33), MPS II (n=16), MPS IV (n=19), VI (n=8) and VII (n=1). The

assessments included: 12-lead electrocardiogram (ECG), 24-hour ECG (Holter monitor), loop recorder/pacemaker interrogation assessment.

Data from 12-lead ECG (available from 69 patients) showed a variety of abnormalities: T wave inversion in a single lead III (n=19), left ventricular hypertrophy (n=14), early repolarization (n=14), right axis deviation (RAD, n=11), partial RBBB (n=9), right bundle branch block (RBBB) (n=1) and first degree AV block (n=1). ECG changes of bundle branch block, RAD (left posterior fascicular block) could represent conduction tissue abnormality and equally could be related to the underlying lung tissue abnormality which is present in most of the patients with MPS. T wave abnormality in a single lead is usually insignificant in healthy individuals; however in MPS patients it could be as a result of chest shape.

Among the 34 patients for who 24-hour ECG was available, sinus tachycardia was the most common rhythm noted (n= 9), followed by sinus bradycardia (n=4), atrial fibrillation (AF) (n=1) and atrio-ventricular nodal re-entry tachycardia (AVNRT) (n=1). Permanent pacemaker was inserted in two patients. AF was observed in one patient with MPS II.

In conclusion, we postulate that regular cardiac monitoring is required to warrant early detection of underlying conduction tissue abnormalities. In addition, 12-lead ECG is the first line investigation that, if abnormal, should be followed up by 24-hour Holter monitoring. These findings warrant further research studies.

Key words: Mucopolysaccharidosis, arrhythmia, echocardiogram, electrocardiogram

Abbreviations:

AVNRT- atrio-ventricular node re-entry

AV- atrio-ventricular

AF- atrial fibrillation

CMR- cardiac magnetic resonance

ECG- electrocardiogram

ECHO- echocardiogram

HSCT- haematopoietic stem cell transplantation

MPS-Mucopolysaccharidosis

LVH-left ventricular hypertrophy

PVC- premature ventricular contractions

VT- ventricular tachycardia

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1. Introduction:

Mucopolysaccharidoses (MPS) are a heterogeneous group of disorders (type I, II, III, IV, VI and VII) that results in the absence or deficiency of lysosomal enzymes, leading to an inappropriate storage of material (glycosaminoglycans) and disruption of cell metabolism in various tissues of the body such as bones, heart valves, arteries and nervous system [1]. Cardiovascular abnormalities occur in up to 80% of cases, resulting in cerebral infarction [2] or acute ischaemic attacks [3]. Cardiac disease emerges silently and contributes significantly to early mortality, often suddenly. Cardiac valve infiltration with resulting severe stenosis and/or regurgitation are common and may require valve replacement (more severe for left-sided than for right-sided valves [4]. Conduction abnormalities, coronary artery and other vascular involvement are rarer complications [4]. It is believed that the infiltration of the cardiac conduction system by large vacuolated cells or in heart valves and arteries contributes to the increased cardiovascular risk as was shown at autopsy [5, 6].

Traditional biomarkers of cardiovascular disease e.g. lipid profile, did not prove to be useful in evaluating the risk of cardiovascular disease in patients with MPS [7] and significantly increased carotid intima media thickness and carotid stiffness have been shown to be more useful in documenting extensive vascular pathology in MPS (I, II, III and VI) [8].

Cardiac conduction abnormalities have been reported in about half of the patients with MPS VI and 7% of those with MPS II [9, 10], with some requiring permanent pacemaker insertion [11, 12]. Sudden and unexpected death due to heart block has been reported in isolated case reports of adults with MPS II, III and VI [13, 14].

Cardiac involvement in MPS III is less commonly reported compared with other types of MPS [15]. The main storage products of MPS III is heparan sulfate, which has been reported to potentially be an essential constituent of life-long cardiac conduction system plasticity and that its storage results in atrioventricular block [14]. Lin et al [15] estimated that approximately 45% of ECGs showed sinus arrhythmia, sinus bradycardia and sinus

tachycardia although the clinical significance was minor [15]. A recent study by Nijmeijer [16] showed that 15.6% of their patients with MPS III had a first-degree atrioventricular block on a routine 12-lead electrocardiogram (ECG).

The age of onset of conduction abnormalities is uncertain and it remains unclear whether all MPS patients are likely to develop them in their lifetime. Therefore, frequent cardiac rhythm monitoring is crucial in this group of patients. As ECG has been previously reported to be an unreliable tool for detecting cardiac rhythm abnormalities in MPS [17], we use 24-hour ECG in our clinical practice.

The aim of our study is to review cardiac rhythm abnormalities and changes in conduction in adult patients with MPS disorders and to suggest guidelines on the frequency of cardiac rhythm monitoring.

2. Materials and Methods:

2.1. *Patients*

Seventy seven adult patients; 49 males (median age 27, range18-55) and 28 females (median age 27.5, range 18-65) with confirmed biochemical and genetic diagnosis of MPS in childhood (MPS I= 33, MPS II= 16, MPS IV= 19, MPS VI= 8, and MPS VII= 1) were included in the study. Patients with MPS III were excluded from the analysis as none of them had cardiac investigations. Patients had been treated with either Haematopoietic Stem Cell Transplantation (HSCT) in childhood; MPS I (n=15) and MPS VI (n=1), Enzyme Replacement Therapy (ERT) (n=42) or had received no treatment (n=19). Among our cohort, 5 patients were already treated with antiarrhythmic (beta-blocker at a small dose e.g. bisoprolol 1.25mg to 2.5 mg once a day).

2.2. *Study design*

This is a descriptive retrospective observational analysis of ECG and cardiac rhythm monitoring performed over a period of 6 years (2013-2019).

2.3. *Investigations*

These included annual 12-lead ECG as well as Holter monitoring (24-hour ECG= 22; 48-hour ECG= 2; 72-hour=0; 5 days= 5; 7 days=2) and implantable loop recorders (n=2) (Figure 1).

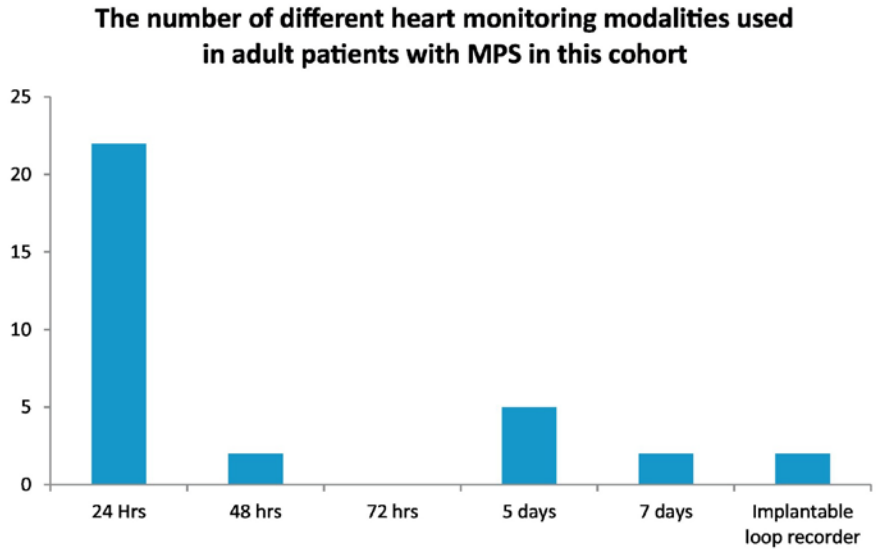

Fig. 1. The number of different heart monitoring modalities used in adult patients with different MPS types.

The cardiac rhythm monitoring reports and all relevant ECG rhythm data were examined for all the patients by a consultant cardiologist. We used Sokolow-Lyon criteria to report left ventricular hypertrophy (LVH) documented on the 12-leads ECG. LVH is considered to be present when either of the following is available: the sum of S wave in 1 and R wave in V5 or V6 >= 35 mm or R wave in a VL >= 11 mm with concurrent left anterior fascicular block. Sinus tachycardia refers to heart rate >=100 bpm, and sinus bradycardia=< 60 bpm and considered to be present when there is more than one episode reported on the ECGs monitor, above 10 seconds and mainly day time. Atrio-ventricular nodal re-entrant tachycardia (AVNRT) was defined as any episode of more than 5 beats.

2.4. *Statistical analysis*

Descriptive statistics including means and standard deviations of all electrographic parameters were computed.

3. Results

3.1. *MPS I*

12-lead ECG data were available for 28 MPS I cases and showed sinus rhythm in all, LVH (10/28), high take of ST segment-elevation (early repolarization) (7/28), partial right bundle branch block (RBBB), i.e. QRS <0.12, 4/28 right axis deviation (3/28) and T wave inversion in a single lead (lead III) (7/28) (Figure 2).

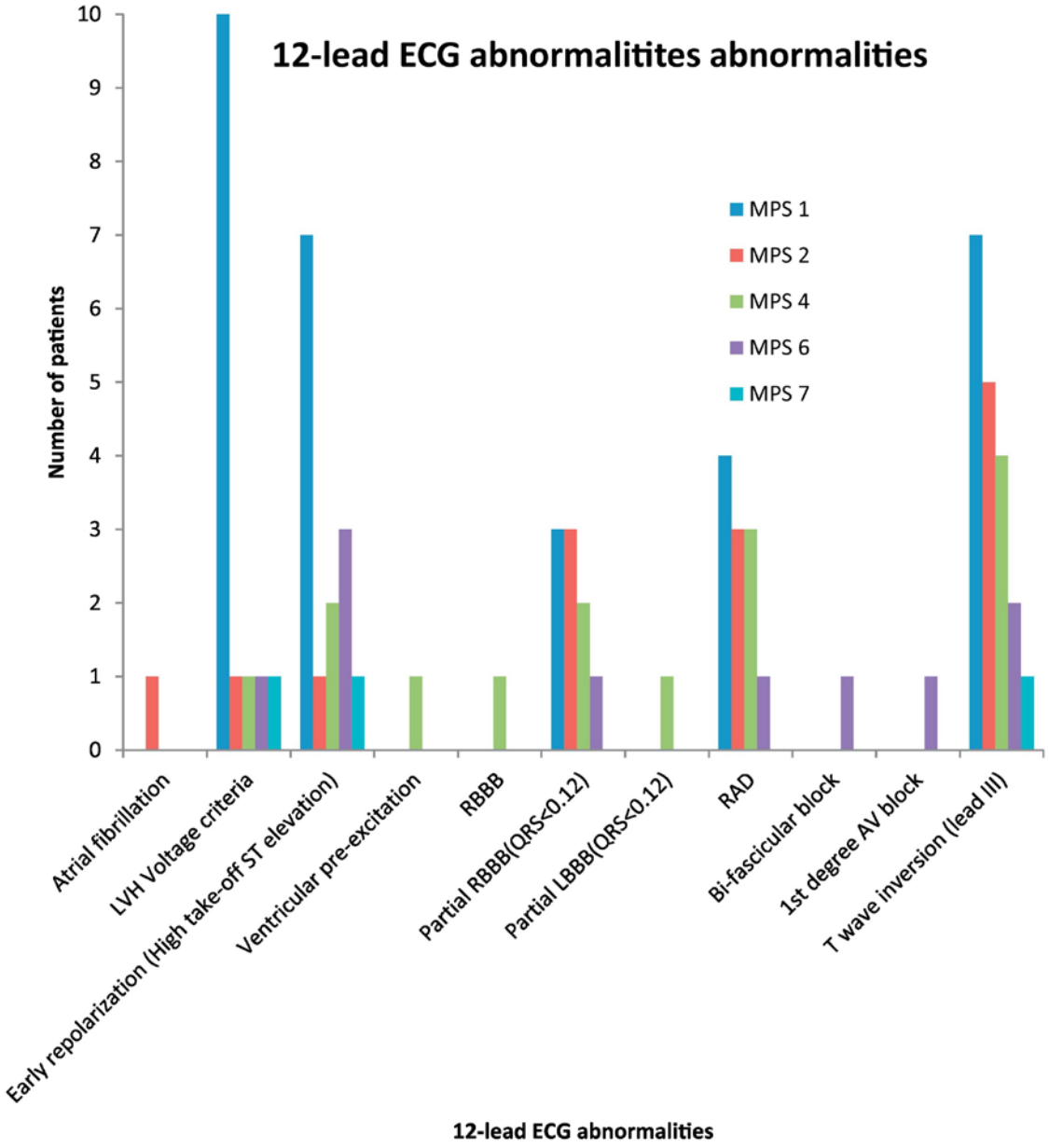

Fig. 2. 12-lead ECG abnormalities in 5 MPS types (I, II, IV, VI and VII). Data from 12- Lead ECG of 69 adult MPS patients attending metabolic clinics at Salford Royal NHS Foundation Trust (2013–2019). Atrial flutter, LBBB, LAD, tri-fascicular block, 2nd degree AV (Mobitz 1), 2nd degree AV (Mobitz 2), 3rd degree AV block or paced rhythm were not documented on 12-lead ECG in any of five MPS types.

24-hour ECG data were available for 14 MPS I cases and showed: 5/14 with sinus tachycardia (Figure 4), 1/14 with AVNRT, 2/13 with sinus bradycardia, 1/14 with second degree AV block (Mobitz II). In 2/14 infrequent extra systolic beats were described and classified as premature ventricular complex and as supraventricular ectopic beat. None had atrial fibrillation (AF) or flutter (Figure 3). Second degree AV block requires treatment with a permanent pacemaker and AVNRT may require antiarrhythmic therapy, the other findings are not of clinical significance.

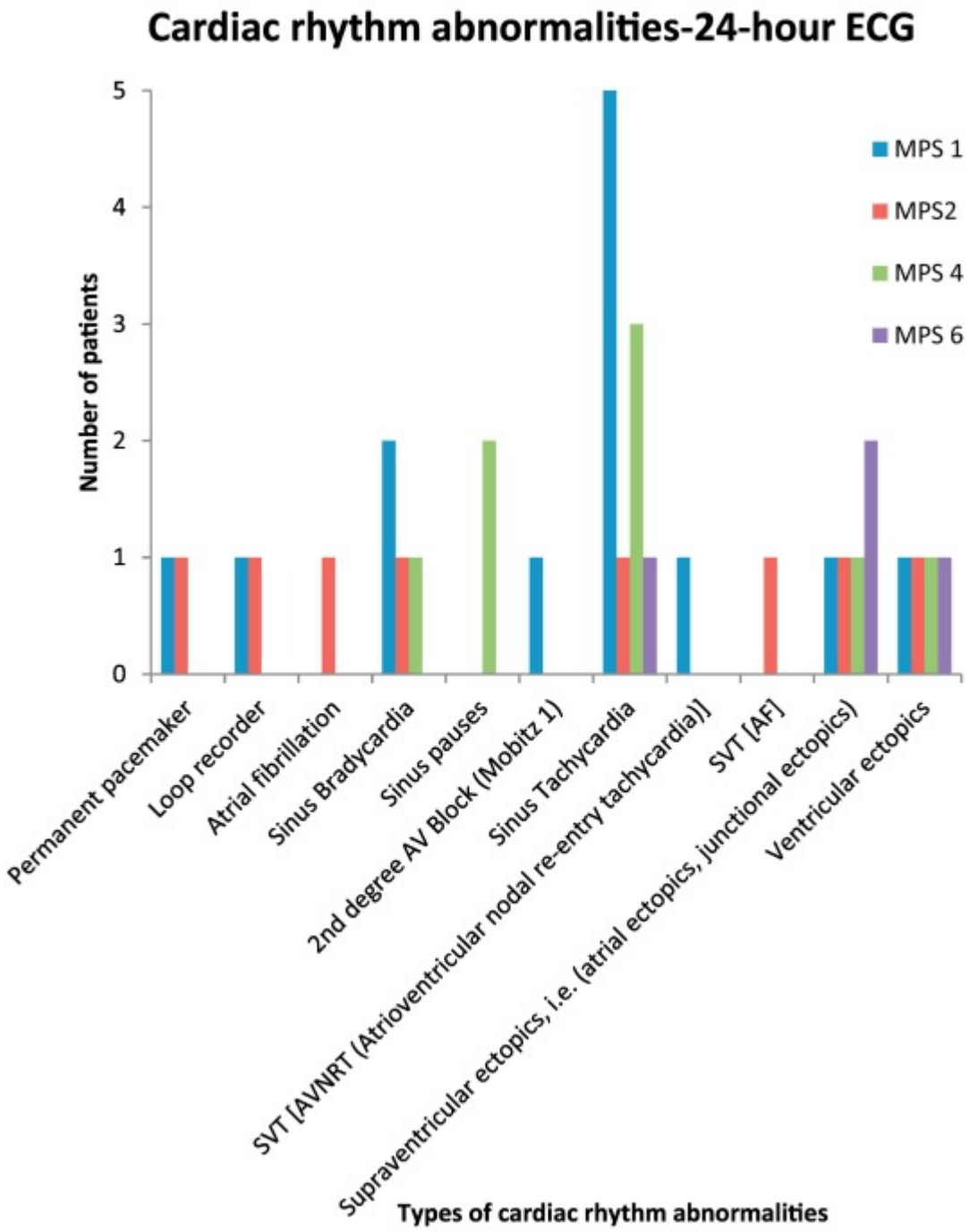

Fig. 3. Cardiac rhythm abnormalities in 4 MPS types (I, II, IV and VI). Data from 24-hour ECG of 33 adult MPS patients attending metabolic clinics at Salford Royal NHS Foundation Trust (2013–2019). The use of loop recorders and pacemakers in adult MPS patients attending metabolic clinics at Salford. Atrial flutter, 1st degree AV block, 2nd degree AV block (Mobitz 2), 3rd degree AV block, SVT (AVRT), SVT (Atrial flutter) and ventricular tachycardia were not documented on 24-hour ECG in patients with 4 MPS types.

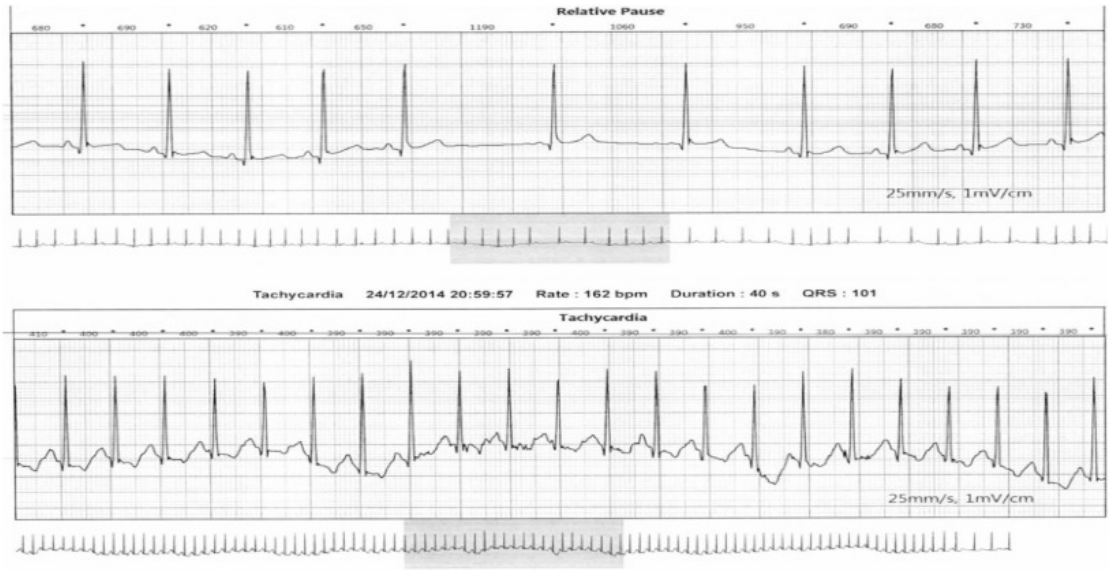

Fig. 4. 24-hour ECG in an MPS I patient: an episode of atrial tachycardia (bottom trace) with heart rate of 158 beats/min (SVT). The top trace shows baseline rhythm in the same patient.

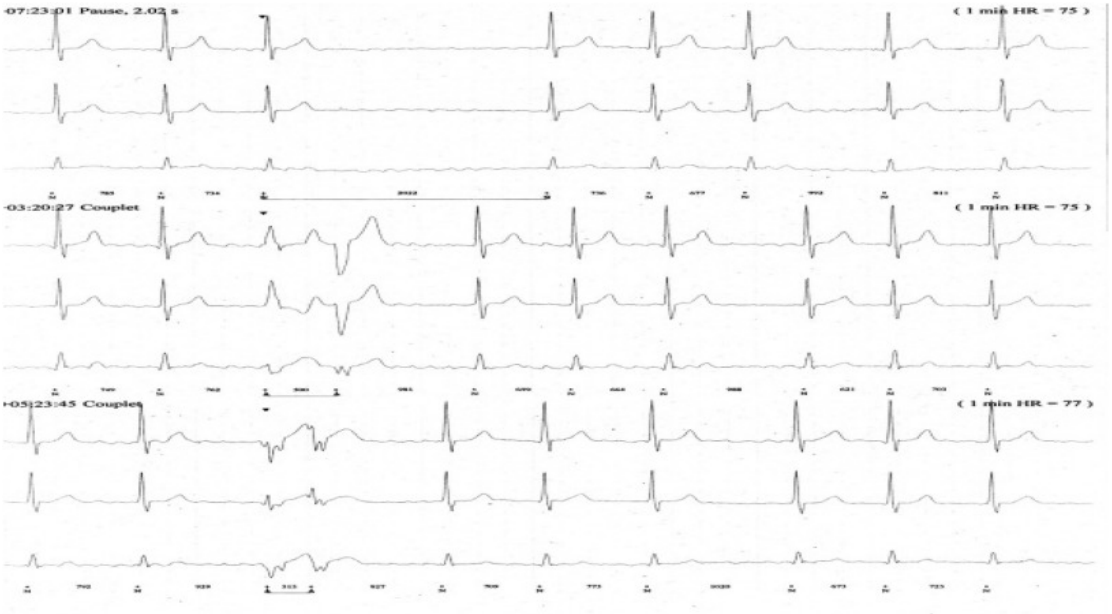

Fig. 5. 24-hour ECG in an MPS II patient – showing atrial fibrillation and asymptomatic pauses (2.03 s).

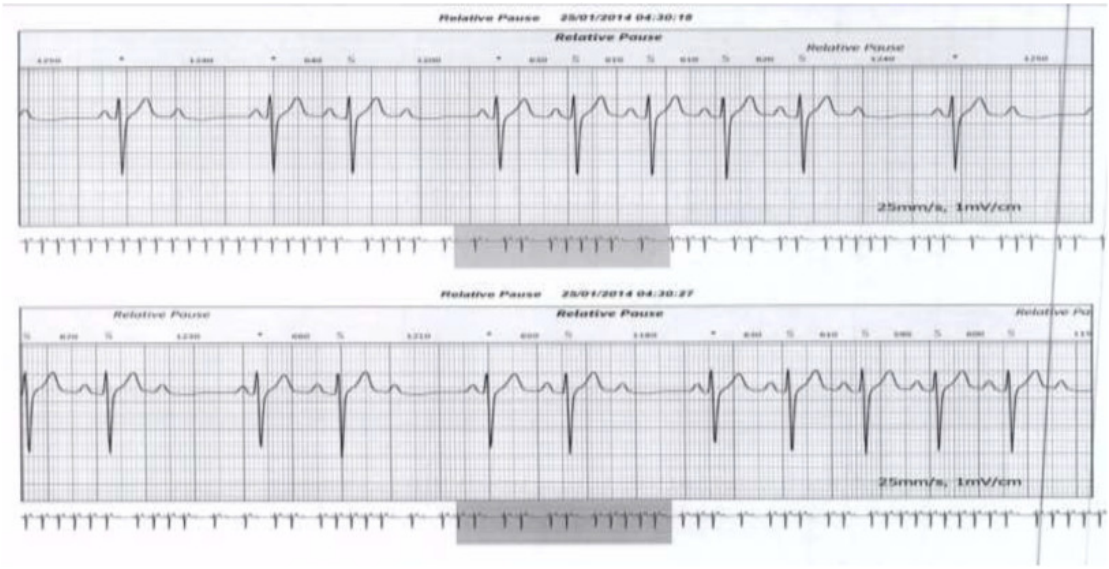

Fig. 6. 24-hour ECG in an MPS II patient; showing intermittent Mobitz 2, second degree AV block.

One male patient treated with ERT had a pacemaker inserted at the age of 32 due to P-wave asystole lasting 8 seconds on 24-hour ECG.

One patient had a loop recorder inserted in the age of 38. Analysis of the download showed no arrhythmias in general or at the time of symptoms.

3.2. MPS II

12-lead ECG data were available for 17 MPS II cases and showed; sinus rhythm in most (16/17), AF (1/17), LVH (1/17), early repolarization (1/17), partial RBBB (3/17), right axis deviation (3/17) and T wave inversion in a single lead (lead III) (5/17) (Figure 2).

24-hour ECG data were available for 6 MPS II cases and showed; sinus tachycardia in one (1/6), sinus bradycardia in one (1/6), and AF in one (1/6) (Figure 5). One patient (1/6) had a permanent pacemaker inserted at the age of 27, the indication being intermittent 2:1 AV Mobitz II block (Figure 6). Subsequent pacemaker assessments showed pacing 1% of the time. In two cases (2/6) extra systolic beats, classified as premature ventricular complexes and supraventricular ectopic beat were confirmed. Both were not frequent (Figure 3) and included 25 VEs per 24 hours and 115 premature ventricular contractions (PVC) per 24 hours. Apart from AF, and AV block, the other types of arrhythmia mentioned above are of no clinical significance if asymptomatic.

One 24-year old MPS II patient had a loop recorder inserted after an episode of collapse. This enabled long-term rhythm monitoring in this patient. The underlying rhythm was sinus rhythm; the patient had symptomatic episodes of sinus tachycardia with ventricular rate 133 bmp (lightheadedness) and asymptomatic nocturnal sinus bradycardia with ventricular rate of 44 beat/minute.

3.3. MPS IV

12-lead ECG data were available for 16 MPS IV cases and showed; sinus rhythm in all cases, LVH (1/16), early repolarization (2/16), RBBB (1/16), partial RBBB (2/16), right axis deviation (3/16), T wave inversion lead III only (4/16) (Figure 2).

24-hour ECG data were available for 10 MPS IV cases and showed sinus tachycardia (3/10), sinus bradycardia (1/10), sinus pauses <3 sec (2/10). None of MPS IV cases had AF or atrial flutter (Figure 3). Sinus pauses of <3 sec when asymptomatic are of doubtful clinical significance.

3.4. *MPS VI*

12-lead ECG data were available for 7 MPS VI cases and showed; sinus rhythm in all MPS VI cases, LVH in one of them (1/7), early repolarization (3/7), partial RBBB (1/7), right axis deviation (1/7), bifascicular block (1/7) and T wave inversion in lead III only (2/7) (Figure 2).

24-hour ECG data were available for 4 MPS VI cases and showed; sinus tachycardia (1/4) and extra systolic beats (3/4), two of which classified as premature ventricular contraction and one as supraventricular ectopic (VE) beat. None of MPS VI patients had AF, atrial flutter or any other form of tachyarrhythmia or bradarrhythmia (Figure 3).

3.5. *MPS VII*

12-lead ECG data were available for 1 MPS VII case and showed; sinus rhythm with LVH and an early repolarization and T wave inversion lead III (1/1) (Figure 2). Holter monitoring data for this patient is not available.

In total 12-lead ECG data was available for 69 MPS patients and 24-hour ECG data was available for 33 patients.

4. Discussion

This is the first study to describe cardiac conduction defects and the incidence of pacemaker use in adult MPS patients. Based on the findings from our MPS cohort, the most significant findings were of cases of 2nd degree AV block and P wave asystole, which require permanent pacemaker implant in order to prevent syncope or sudden cardiac death. One patient had AVNRT which may require antiarrhythmic therapy. Other findings were benign and comparable with non-MPS patients We would recommend that all MPS patients should have annual 12-lead ECG and Holter monitoring The frequency of cardiac monitoring should otherwise be dictated by the frequency of patient symptoms (eg lightheadedness, syncope, palpitations) and may include more prolonged Holter monitoring, external loop recorders or implantable loop recorder.

In our clinical practice we use Sokolow-Lyon criteria to assess the ECG voltage. However, false positive results are common in young or people of low BMI and false negatives in obese patients, those with RBBB and those with chronic obstructive lung disease [18, 19].

The Romhilt-Estes score uses more QRS parameters than voltage alone including left axis deviation, duration of QRS, ST-T segment changes and P wave [20]. We did not prefer this score as many adult MPS patients have high ST-T segment changes (high take off ST elevation/ early repolarization), partial RBBB and right axis deviation. Cardiac imaging, i.e echocardiography or cardiac magnetic resonance (CMR), is required to diagnose LVH definitively which was beyond our aims of this project.

A number of benign ECG findings were noted: T wave inversion was a common ECG finding in our adult MPS patients (27.5%, 19/69). Whereas T wave inversion in one lead is not a significant finding in general healthy population, in our cohort it could be related to the chest shape and body habitus typical of many adult MPS patients. Partial RBBB and right axis deviation (RAD, posterior fascicular block) are likely to be due to concomitant lung pathology, which is present in most adult MPS patients. Sinus tachycardia (27%), AF (3%), sinus bradycardia (12%) with sinus pauses (6%) (Figure 2 and 3) were noted. Kampmann et al (2016) suggested that sinus tachycardia in MPS IVA patients is likely to be a physiological reflex to maintain cardiac output in a small-sized heart with impaired filling patterns rather than an arrhythmia, a result of a sinus node or autonomic dysfunction [21]. It was recommended that the reduction of heart rate using pharmacological agents should be considered with caution in these patients because of the possible reduction in cardiac output [21].

Given that there is an incidence of sudden cardiac death in patients with MPS [6] and that bradarrhythmia may be risk factors for increased mortality, regular clinical review and cardiac monitoring are required in order to reduce this risk. In our MPS cohort only 2 patients have had a pacemaker inserted so far (2.6%; 2/77); however one patient had unexpected asymptomatic Mobitz 2 heart block and the other patient had symptomatic P-wave asystole lasting 8 seconds on 24-hour ECG (Figure 6).

None of our patients have yet been found to have ventricular tachyarrhythmia.

Tachyarrhythmia observed in our MPS cohort (atrial tachycardia, atrial fibrillation, sinus tachycardia or symptomatic atrial/ventricular ectopics) have been managed with a beta-blocker [22, 23]. Symptoms were controlled by using beta-blockers. Treatment with a beta blocker requires an ongoing clinical assessment and Holter monitoring for possible bradarrhythmia [24]. Wearable technology (e.g. a FitBit device or Kardia Alive Cor) allows continuous observations for potentially life-threatening bradyarrhythmias among patients with all MPS types [25, 26, 27].

Among our 33 patients with MPS I, 15 underwent HSCT in childhood. Among our patients post HSCT, 46% had an abnormal ECG (Table 1 / Figure 2). Chemotherapy regimens including busulfan and cyclophosphamide at high doses [28] as well as reduced-intensity conditioning [29], have been shown to predispose patients to cardiac complications in adulthood. This particular group of MPS I patients requires regular monitoring of their heart rhythm, although it has been previously shown that overall long-term cardiopulmonary outcomes look promising [30].

Table 1. Cardiac rhythm in MPS I, II and IV respective of the therapy: HSCT, ERT or none.

	HSCT	ERT	No treatment
MPS I; n = 33	7/15	11/15	0/3
MPS II; n = 16	–	7/11	4/5
MPS IV; n = 19	–	10/12	4/7

For most MPS types enzyme replacement therapy is available, however the effect of this treatment on cardiac conduction has not been well described so far. Our findings are that irrespective of the ERT type, most MPS I, II and IV patients were found to have minor ECG abnormalities (Table 1). New emerging therapies i.e. gene therapy will also need to be evaluated in terms of efficacy in prevention of cardiac rhythm abnormalities.

4.1 Limitations of the study:

As a retrospective and uncontrolled study, there was no healthy control group to compare the electrocardiographic parameters with those of our patients. Not all of the patients in this cohort had follow-up electrocardiographic data. 12-lead ECG data was missing for 8/77 (10%) of patients. In 57.1% (44/77) of patients, no Holter monitoring was available. MPS III patients were excluded from the analysis due to severe learning difficulties and agitation, such that routine cardiac investigations are not practicable.

5. Conclusion:

Adult MPS patients have a significant incidence of bradyarrhythmia. Therefore regular cardiac rhythm monitoring and regular symptom review in cardio-metabolic clinics is recommended. Close cardiology surveillance aims to reduce mortality and morbidity among adult MPS who are at high risk of significant dysrhythmia. Routine monitoring with annual 12-lead ECG and 24-hour ECG is recommended in order to detect occult tachyarrhythmia and bradarrhythmia. Additional cardiac monitoring with external loop recorders or implantable loop recorders should be used to obtain symptom-ECG correlation because of the possibility of potentially life-threatening bradyarrhythmia or symptomatic tachyarrhythmia, which would require treatment with either permanent pacemaker implant or antiarrhythmic therapy respectively. It is likely that the use of implantable loop recorders in these patients will increase and further research is required in this field.

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