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Full Length Research Paper

A prospective clinical study of myocarditis in cases of paraphenylenediamine (hair dye) poisoning in Northern India

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Myocarditis is unheard of and unreported albeit dangerous complication of ingestion of hair dyes containing paraphenylenediamine. Hence, a prospective study was planned to assess the myocardial damage with regard to clinical profile and outcome with different treatment approaches in patients with oral ingestion of hair dye so that a treatment protocol could be established for this under recognized complication. This study comprised 1595 cases admitted in the Department of Medicine, Maharani Laxmi Bai Medical College, Jhansi, Uttar Pradesh, India, from July 2004 to Jan 2011. Out of 1595 cases, 1060 cases were of indigenous stone hair dye poisoning and 535 cases were of other branded hair dyes (powdered form containing less amount of paraphenylenediamine). Diagnosis of myocarditis was made solely on the basis of clinical signs and symptoms suggestive of myocardial damage, electro-cardiographic changes, elevated cardiac biomarkers and abnormalities on transthoracic echocardiography. The cases were thoroughly studied for cardiac complications. Myocarditis was reported in 15% of the total cases, with mortality rate of 29%. Occurrence of myocarditis was directly related to the amount of hair dye ingested. Out of patients developing myocarditis, 9% developed life threatening ventricular tachycardia or ventricular fibrillation. Therefore, it was concluded that hair dye (paraphenylenediamine) is highly toxic. In patients who consumed more than 10 g of paraphenyl-enediamine, myocarditis is a dangerous complication. Judicious management includes continuous cardiac monitoring to prevent sudden cardiac death.

Key words: Arrhythmias, cardioversion, hair dye ingestion, myocarditis, paraphenylenediamine poisoning, syncope, sudden death.

INTRODUCTION

Hair dye is available in several forms, but the most common and cheapest form is the Stone Hair Dye, which is available in 20 g pack (Jain et al., 2011). Other branded hair dyes like 'Godrej', 'Kesh kala', 'Colour mate' etc. are available in powder or liquid forms. Paraphenylenediamine is used in hair dye formulations, photographic developers, tyre cord industry, accelerating vulcanization, and also used with "Henna" for dyeing hands and feet of women. The concentration of paraphenylenediamine (active substance) varies from 70-90% in indigenous stone hair dye to 2-10% in branded dyes, which are used for dying the hair. The stone hair dye is extremely cheap and freely available, making it an attractive option for suicidal intent. It has been previously reported that contact with paraphenylenediamine causes skin irritation, dermatitis, arthritis, asthma, conjunctivitis,

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Abbreviations: PPD, Paraphenylenediamine; **TTE,** trans thoracic echocardiography; **VT/VF,** ventricular tachycardia/ventricular fibrillation; **ICCU,** intensive coronary care unit; **ECG,** electrocardiography; **LVEF,** left ventricular ejection fraction; **ICCU,** intensive coronary care unit; **IVCD,** intra ventricular conduction defect; **CPK-MB,** creatine phosphokinase isoenzyme-MB fraction; **IV,** intravenous.

chemosis, lacrimation, exophthalmos and even permanent blindness. Systemic toxicity occurs either by percutaneous absorption or oral ingestion.

The chemical used in hair dye is a derivative of para nitro-aniline called paraphenylenediamine (PPD). It is brownish to black coloured solid, partially soluble in water and easily soluble in hydrogen peroxide (H_2O_2). Paraphenylenediamine is a good hydrogen donor and is metabolized by electron oxidation to an active radical (benzoquinone diamine) by cytochrome P450 peroxidase. This is further oxidized to a trimer known as Brandowaski's base, a compound reported to cause anaphylaxis as well as being strongly mutagenic. Oral ingestion of paraphenylenediamine causes mainly two types of acute presentations leading to immediate death within 1 or 2 h. The first manifestation is angioneurotic edema, presenting as rapid development of severe edema of the face, neck, pharynx, tongue and larynx, with respiratory distress sometimes requiring emergency tracheostomy. The second one is acute myocardial damage in the form of fulminant myocarditis, leading to fatal arrhythmias, cardiac arrest and death, if not managed properly and timely. Acute renal failure was seen as the late cause of death in acute hair dye poisoning cases. Tubular obstruction by myoglobin casts is regarded as the principal mechanism for producing acute renal failure. By the second or third day, patient develops oliguria. Vomiting, gastritis, hypertension, hypotension, vertigo, tremors, seizures, nasal regurgitation and delayed presentation of myocarditis, have also been reported.

Myocarditis due to hair dye poisoning

Myocarditis is a fatal and commonly neglected complication of paraphenylenediamine poisoning, due to lack of awareness about this complication in medical community and paucity of data in medical literature. Oral ingestion of paraphenylenediamine in doses more than 10 g, especially unbranded stone hair dyes, results in extensive myocardial damage leading to decrease in blood pressure, fatal life threatening arrhythmias in the form of ventricular tachycardia or ventricular fibrillation and sudden death. The clinical features are fatigue, dyspnea on exertion or at rest, chest pain, palpitations, presyncope (feeling of giddiness, faintness) and syncope with non-specific electrocardiographic changes in the form of sinus tachycardia, bundle branch blocks, intra ventricular conduction defect (IVCD), atrial and ventricular premature complexes, atrial fibrillation, ventricular tachyarrhythmia, ST segment elevation or depression and T wave inversion. Cardiac biomarkers suggestive of myocardial necrosis like troponin T/I (more than 0.1 ng/ml) and creatine phosphokinase isoenzyme-MB fraction (CPK-MB) are elevated in most of the cases. Transthoracic echocardiography reveals wall motion abnormality and decreased left ventricular systolic function (LVEF ≤ 35%), which subsequently improves on follow up. Cardiac dilation in the absence of regional coronary artery disease and evidence of rapid recovery of ventricular function occurs during follow up in some cases.

Lethal dose

The lethal dose of paraphenylenediamine is not well known, although estimates vary from 7 g and above. However, it is known that the toxic effects of paraphenylenediamine are dose related. Lethal dose also depends upon individual susceptibility; deaths are reported even at the dose of 2 g. A dose more than 10 g is highly cardiotoxic and leads to myocardial damage in the form of myocarditis in majority of the cases.

Management plan

Supportive management is life saving if instituted early as even a little delay is disastrous, and may lead to death. Diagnosis is easy to make as clinical features are quite distinctive; orofacial edema, chocolate brown urine and history of paraphenylenediamine intake (Figures 1 to 4). Till date, there is no definite guideline for management, so we formulated our own line of management. After a rapid clinical examination, special attention was given to the vital parameters. Since the immediate cause of death is hypoxia and fatal arrhythmias, airway patency is maintained by Guedel's airway and emergency tracheostomy. Endotracheal intubation is not possible in majority of the cases because of massive angioedema. Circulatory volume and blood pressure are maintained by giving appropriate fluid therapy. The treatment is based on the following principles:

1. Since no antidote is available against paraphenylenediamine, management is basically supportive.
2. Gastric lavage is done with activated charcoal and tap water, which is highly effective if done within 4 h of ingestion.
3. Oxygen is administered for hypoxic cases proven by arterial blood gas analysis or in patients who have massive angioedema.
4. Emergency tracheostomy is life saving when patient is in severe distress and endotracheal intubation is not possible because of marked orofacial swelling.
5. Continuous cardiac monitoring in intensive coronary care unit is required in cases with suspected myocarditis.
6. Vasopressors (intravenous dopamine and/or noradrenaline) are used if hypotension persists despite adequate fluid therapy.
7. Intravenous amiodarone is administered intravenously

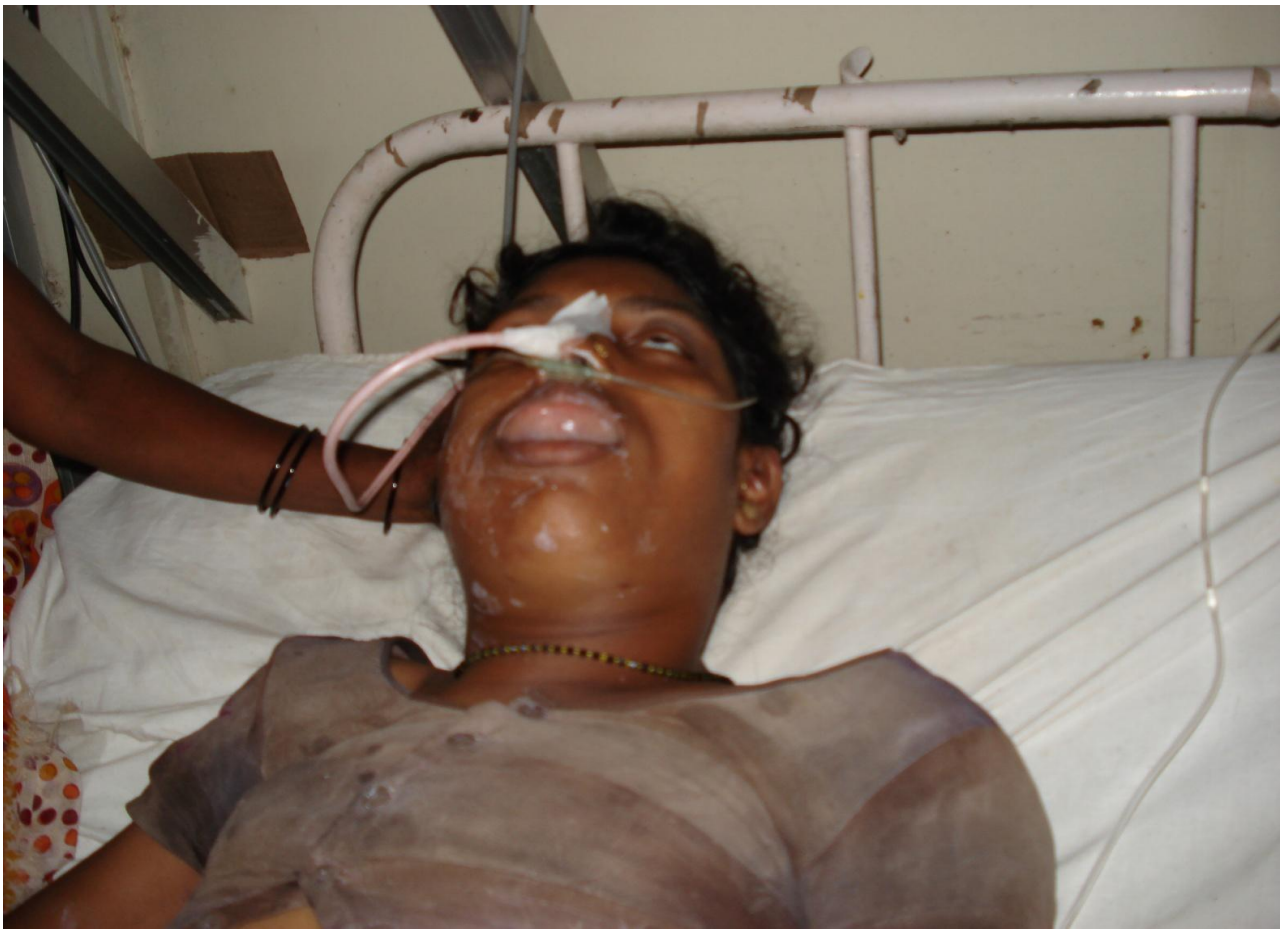

Figure 1. A 26 years old girl presenting with facial edema after hair dye ingestion (courtesy- Department of Medicine, MLB Medical College, Jhansi, India).

at initial doses of 15 mg/min for 10 min, followed by 1 mg/min for 6 h and then 0.5 mg/min for the remaining 18 h and for the next several days as necessary and defibrillation for ventricular tachyarrhythmia with hemodynamic compromise.

8. Intravenous hydrocortisone 200 mg as start dose and then 100 mg every 6 h is used till angioneurotic edema subside. In the last 2 years, we have been using intravenous methyl prednisolone 1 g/day as intravenous (IV) infusion for 5 days which has shown promising results, leading to decreased morbidity and mortality as evidenced by early subsidence of angioneurotic edema and decrease incidence of myocarditis. Although no randomized control trial has been done, but it was noticed in a pilot study that it hastens recovery, decreases hospital stay and reduces different complications including myocarditis.

9. Sodium bicarbonate is administered to prevent precipitation of myoglobin in kidney (average dosage is 1 ampule containing 22.5 meq. in 500 ml normal saline every 8 h) along with loop diuretics (furosemide or torsemide) to maintain adequate urine volume.

10. Chlorpheniramine maleate 1 ampule IV every 8 h is administered till orofacial edema subsided (average 3 to 5 days).

11. Calcium gluconate is given to counteract hypocalcaemia (10% calcium gluconate 10 ml every 8 h till hypocalcaemia subsides).

12. Dialysis- hemodialysis or peritoneal dialyses are used in cases with renal shut down and resistant hyperkalemia.

MATERIALS AND METHODS

Prospectively collected data of 1958 cases that ingested hair dye with suicidal intention was studied. The study comprised of 1595 cases, 67 cases were brought dead in emergency, who had history and features suggestive of hair dye poisoning. Eighty-three cases died within first 5 h of admission after gastric lavage, drugs and intravenous fluid therapy. These cases were excluded from the study because the aim of the study was to assess the incidence of myocarditis, its clinical profile and outcome with different treatment approaches in patients with ingestion of hair dye with suicidal intention. Out of the 1808 remaining cases, 167 cases of dye ingestion did not have any feature of toxicity and were discharged

Figure 2. Urine samples collected in plastic bottles showing cola coloured urine suggestive of myoglobinuria after hair dye ingestion (courtesy- Department of Medicine, MLB Medical College, Jhansi, India).

or absconded in the first 12 h. Forty-one cases of hair dye ingestion who had relatively mild disease, did not opt for investigations and were treated with Intravenous fluids and Intravenous antihistaminics, were also excluded from this study. In addition, 3 cases of known cardiac and 2 cases of known renal diseases were excluded from the study. Finally, the study comprised of 1595 cases that were thoroughly investigated and treated (Table 1).

In all the cases, electrocardiography (Figure 5) was done within an hour of admission owing to symptoms suggestive of myocarditis (Figure 6), and then cardiac monitoring was done in Intensive coronary care unit (ICCU). The reason for ingesting dye was mainly suicidal (97.84%), while the other was accidental. The exact dose taken by each patient was not known. The data was analysed from the following points: (i) demographic profile; (ii) clinical profile; (iii) mortality pattern; (iv) outcome with different management strategies given in the hospital.

RESULTS

Out of the prospectively collected data of 1958 cases who ingested hair dye, a total of 1595 cases were studied after exclusion as mentioned above (Table 1). In all, 1214 patients were female, while 381 were male (Table 2). The reason for ingesting drug was suicidal in 1560 cases (97.84%), while the remaining were accidental 29 cases (1.86%) and homicidal 6 (0.29%) (Table 4). Symptoms were directly related to the dose of paraphenylenediamine ingested, type of hair dye (serious complications were mainly seen in stone hair dye, an indigenous brand), intention of ingestion (suicidal intention was associated with far worse prognosis) and the time lapsed after swallowing (far worse complications if dye was kept for more time in oral cavity before ingestion). Two types of presentation were seen: One in which neck swelling occurred predominantly and others in which myocarditis developed. It seems that cases who after putting the dye in the mouth thought whether to ingest or not, developed prominent edema of throat, tongue, lower jaw, eye lids, conjunctiva and neck, may be due to prolonged time of contact with oral-pharyngeal mucosa. While the cases that immediately swallowed sufficient quantity of dye developed myocarditis and renal failure later on (Table 3). Chest pain, palpitations and presyncope (the feeling of dizziness and fainting) or syncope were other common manifestations. These cases were at high risk of developing cardiac complications.

In present study, 240 cases were having strong suspicion of myocarditis on the basis of clinical features and electrocardiographic changes (Table 5). The clinical features were fatigue, dyspnea on exertion or rest, chest pain, palpitations, presyncope or syncope. Electrocardiographic changes seen were sinus tachycardia, T wave inversion, ST segment elevation or

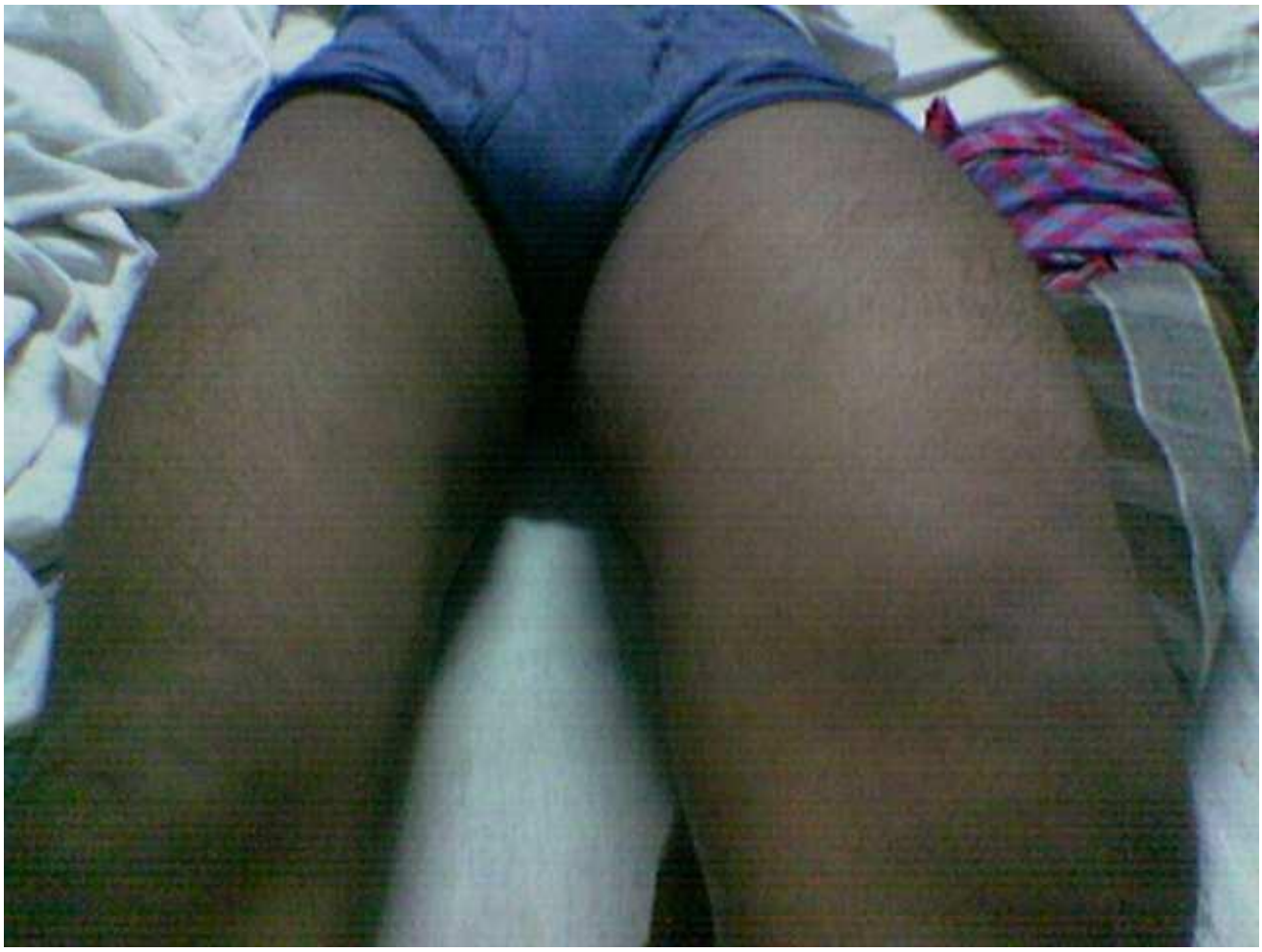

Figure 3. A young male showing calf muscles edema after hair dye ingestion (Courtesy- Department of Medicine, MLB Medical College, Jhansi, India).

depression, bundle branch blocks, atrial and ventricular premature complexes, atrial fibrillation, while 22 cases developed ventricular tachyarrhythmia during therapy. Troponin T was positive (more than 0.1 ng/ml was taken to be positive) in 138 cases with positive electrocardiographic changes. Transthoracic Echocardiography (TTE) was done in all 240 cases; the findings were regional wall motion abnormality and decreased left ventricular ejections fraction (LVEF≤35%) in 138 cases on day 2 to 5, which subsequently improved on follow up in patients who survived. Cardiac dilatation in the absence of regional coronary artery disease and evidence of rapid recovery of ventricular function during follow up in 110 cases out of 240 cases was observed (Table 6).

Patients with suspicion of myocarditis as per electrocardiographic changes and clinical features had high mortality (69 out of 240 expired) of 29%. Of 22 (9%) patients that developed ventricular tachyarrhythmia had further bad prognosis and 14 cases expired out of 22 (64%) despite standard medical management (Table 7). Patients who were hemodynamically unstable (that is-who presented with shock; systolic BP < 90 mm Hg) had mortality rate of around 45% and were kept on vasopressor support. Cardiovascular compromise because of ventricular tachycardia was promptly treated with DC cardio version followed by IV amiodarone drip. A pilot study done in the department revealed that 5 days duration of methyl prednisolone injection therapy produced optimum results and decreased incidence of myocarditis in hair dye poisoning. The duration of steroid was guided primarily by oro-facial edema, swallowing difficulty and change in colour of urine. The overall mortality decreased significantly from 27.77 to 14.02% (Table 8).

DISCUSSION

The present study showed that hair dye poisoning

Figure 4. Changing pattern of urine colour after hair dye ingestion as time passes. Bottles from right to left shows collected urine samples on day 1, 2, 3 and 4, respectively (courtesy- Department of Medicine, MLB Medical College, Jhansi, India).

Table 1. Design of the study.

S/N	Description of cases	Number of cases
1	Cases excluded	363
A	Brought dead	67
B	Died within 5 hours	83
C	Mild/no symptoms	167
D	Not willing to part	41
E	Known cardiac /renal disease	5
2	Cases included in study after PPD ingestion	1595
Total		1958

A total of 1958 cases were chosen, out of which 363 cases were excluded on different grounds and the final study comprised 1595 cases of hair dye (PPD) ingestion.

(paraphenylenediamine) is more common among females (76%) and younger age group around 15 to 25 years (50.21%); the maximum number of cases (97.84%) were of suicidal intent and overall mortality rate was 22.48%. Myocarditis is a fatal complication of ingestion of hair dye (paraphenylenediamine) and was reported in 15% of total cases and directly related to amount of paraphenylenediamine ingested. In patients developing myocarditis, 9% developed life threatening ventricular tachycardia or ventricular fibrillation and 64% of those

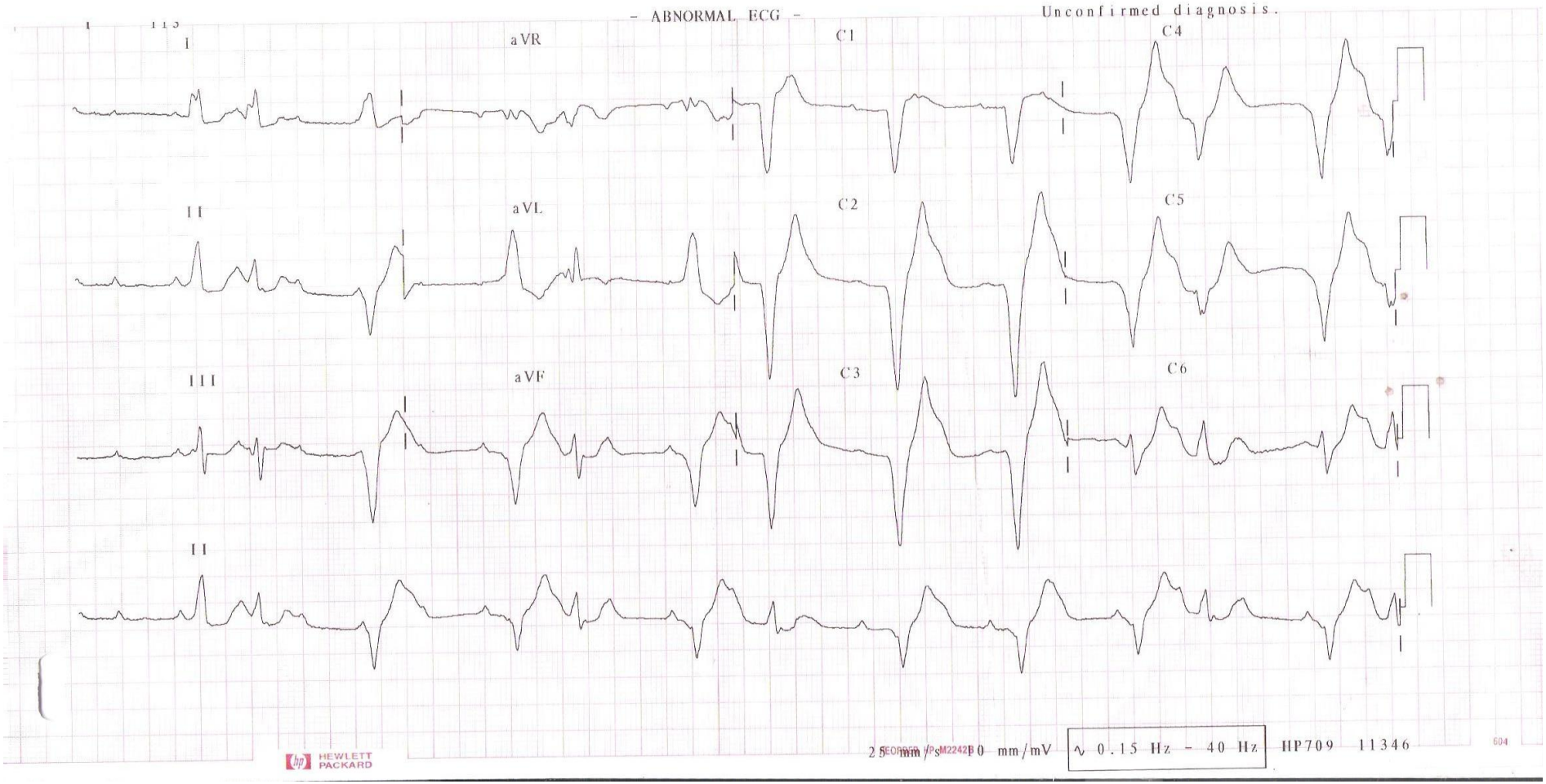

Figure 5. ECG of a patient showing non specific changes with frequent premature ventricular complexes suggestive of myocarditis after hair dye ingestion (courtesy- Department of Medicine, MLB Medical College, Jhansi, India).

cases died during treatment. Shalaby (2010) in a retrospective study of over 7 years (2001-2007) on 25 cases with acute paraphenylenediamine intoxication admitted to the poison control centre, Ain Shams University Hospitals, Cairo, Egypt, reported that 16% of the patients died due to ventricular arrhythmia. In the present study, the incidence of ventricular arrhythmias was seen around 9% over a period of 6 years (March 2004 to January 2011).

Zeggwagh et al. (2003) also reported a case of myocarditis and left ventricular thrombus induced by paraphenylenediamine poisoning in an 18-year old woman who was admitted with asphyxia and rhabdomyolysis, Electrocardiography showed

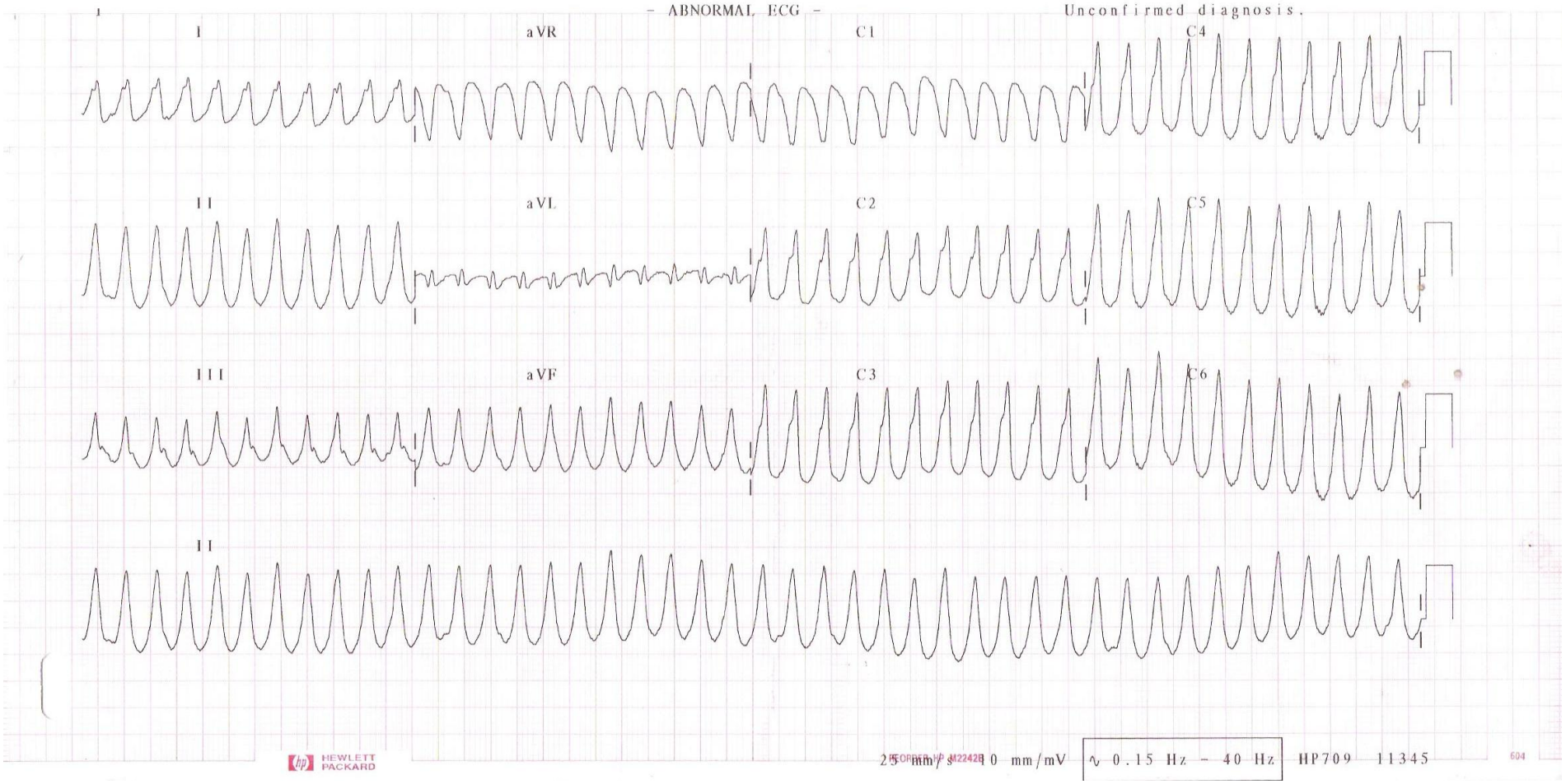

Figure 6. ECG of a patient showing ventricular tachycardia suggestive of myocarditis after hair dye ingestion (courtesy- Department of Medicine, MLB Medical College, Jhansi, India).

ventricular extrasystoles and negative T waves and transthoracic echocardiography showed significant left and right ventricular hypokinesia. In the present study, myocarditis was reported in 15% of total cases of acute paraphenylenediamine poisoning based on clinical and investigational profile. Regional wall motion abnormality and decreased left ventricular ejections fraction (LVEF≤35%) was reported in 130 (54%) cases out of 240 cases of suspected myocarditis on the 2nd to the 5th day, which subsequently improved on follow up. Cardiac dilatation in the absence of regional coronary artery disease and evidence of rapid recovery of ventricular function during follow up in 110 cases out of 240 cases (46%) was observed. In the present study, cardiac biomarkers of injury (CPK-MB and troponin T/I) were raised in 57.5% of

Table 2. Distribution of cases according to age group and sex.

S/N	Age group(years)	Male	Female	Total number	Percentage
1	15-25	152	649	801	50.21
2	26-35	130	505	635	40
3	36-45	79	32	111	10.88
4	>45	20	28	48	4.71
	Total	381	1214	1595	100

Majority of the cases belong to young age group and were females.

Table 3. Distribution of cases according to clinical features after ingestion of hair dye.

S/N	Symptoms/signs	Number of cases	Percentage
1	Severe edema of face and neck	1180	74
2	Dysphagia	1148	72
3	Chocolate brown colour urine	861	54
4	Pain/rigidity of limb	765	48
5	Respiratory difficulty	366	23
6	Sinus Tachycardia	350	22
7	Presyncope /syncope	287	18
8	Palpitation	255	16
9	Chest pain	265	15.65
10	Hypotension	239	15
11	Oliguria	143	9
12	Ventricular tachycardia/fibrillation	22	9
13	Rise in blood pressure	127	8
14	Nasal twang of voice	95	6
15	Anuria	80	5
16	Convulsion	47	3
17	Nasal regurgitation	40	2.5

Table 4. Reasons for ingestion of hair dye (PPD) as shown in this study.

S/N	Reason	Number of cases	Percentage
1	Suicidal	1560	97.84
2	Accidental	29	1.86
3	Homicidal	6	0.29

Majority of cases took it for suicidal intention.

Table 5. Myocardial damage in cases of hair dye ingestion.

S/N	Clinical history suggestive of myocardial damage	Number of cases	Percentage
1	Present	240	15
2	Absent	1355	85

Myocardial damage was present in 15% of cases after hair dye ingestion.

cases. Jatav et al. (2008) in a case report of hair dye poisoning also reported myocardial damage suggested by clinical and electrocardiographic changes which succumbed to cardio respiratory arrest on the fifth day of

Table 6. Different form of myocardial damage in cases after hair dye ingestion.

S/N	Form of cardiac complication	Number of cases	Percentage (n/240 × 100)
1	Elevated cardiac biomarkers	138	57.5
2	Decreased left ventricular ejection fraction (LVEF <35%)	130	54
3	Cardiac dilation	110	46
4	Death due to cardiac causes	69	29
5	Ventricular tachycardia/ ventricular fibrillation	22	9

Ventricular arrhythmias occurred in 9% of the cases, and culminate into sudden death if not treated properly and timely.

Table 7. Incidence of death due to cardiac causes.

S/N	Cardiac cause of death	Total number of cases	Mortality	Percentage of mortality
1	Myocarditis	240	69	29
2	Sudden death (VT/VF)	22	14	64

Myocarditis was responsible for 29% mortality in cases of hair dye ingestion.

Table 8. Decrement in mortality after use of i/v methyl prednisolone.

IV Corticosteroid	Duration of treatment (days)	No. of patients	Disappearance of edema (days)	No. of death	Mortality (%)
Hydrocortisone (300 mg/day)	7	300	8 ± 2	83/300	27.77
Methyl prednisolone (1 g/day)	5	720	4 ± 1	101/720	14.02

In 300 patients treated with iv hydro cortisone, 83 cases (22.48%) died after consuming hair dye poison. Whereas after use of iv methyl prednisolone in 720 cases, only 101 cases (14.02%) died.

presentation.

In addition, Brahmi et al. (2006) reported a case of myocarditis with myocardial infarction included by paraphenylenediamine, which was confirmed by angiography that showed septo-apical hypokinesia due to spasm of anterior interventricular coronary artery. In our study, angiography was not done because of unavailability of onsite catheterization laboratory. But reduced left ventricular function was present in 54% of total cases. In the present study, which is the largest ever series of myocarditis due to acute paraphenylenediamine poisoning, clinical manifestations of acute myocarditis were seen in 15% of total cases, which ranged from asymptomatic to fatal. Electrocardiographic changes such as multiple ventricular and supra ventricular extrasystoles, ST-T wave changes, bundle branch blocks, ventricular tachyarrhythmias were commonly seen. Positive troponin-T and decreased left ventricular ejection fraction (<35%) and regional wall motion abnormality in large number of cases that is 54 to 57.5%, with subsequent improvement in left ventricular ejection fraction further supports the diagnosis of myocarditis.

Conclusion

Myocarditis in hair dye poisoning has been previously reported, but not very frequently. Low recognition of paraphenylenediamine poisoning in the medical community may be responsible for this. The present study, which is the largest ever case series on hair dye poisoning, strongly concluded that myocarditis is a fatal complication due to ingestion of high dose (>10 g) of hair dye (paraphenylenediamine). If not timely treated, it results in sudden death. So we must be vigilant regarding cardiac manifestations in every case of paraphenylenediamine poisoning. Immediate ban on the sale of local unauthorized stone hair dye in whole of the Northern India and nearby areas should be implemented soon. Prohibition of paraphenylenediamine importation and its sale in combination with other dyes along with the regulation of its industrial use is urgent so that paraphenylenediamine should be used for “dyeing and not for dying”.

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