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BJMP March 2016 Volume 9 Number 1

Research Articles

- Isolated Arthroscopic Lateral Patella Retinaculum Release for Anterior Knee Pain – Is it worth it? 5
Sultan N Qasim, Kimberly Lammin and Phillip Edge
- Psychiatric Morbidity in Children and Adolescent Survivors of a Snowstorm Disaster in South Kashmir, India. 8
Abhishek Chowhan, Mushtaq A Margoob, Imtiyaz Mansoor and Arti Sakral

Review Articles

- A review of NICE guidelines on the management of Borderline Personality Disorder 16
Syed Ali and Christopher Findlay
- A comprehensive review on the pregnancy dermatoses. 23
Mohammad Adil, Tasleem Arif and Syed Suhail Amin
- Optimising stroke prevention in patients with atrial fibrillation in primary care 31
Yassir Javaid

Case Reports/Series

- Multiple ring enhancing lesions in brain: Neurocysticercosis or Tuberculoma? An extremely unusual / uncommon radiological presentation of a common disease: central nervous system tuberculosis 39
Manjunath M N, Bhakyalakshmi, Lakshmi, Chaitanya and Sharanya
- Lymphoplasmacyte rich meningioma-a rare morphological variant of meningioma 42
Manveen Kaur, Varsha Dalal, Karam Chand Sharma, Avninder Singh
- Correspondence - Another case report of a unusual reaction to IV Pethidine 45
Premila Hirubalan and Pierre Christian Ip-Yam
- Colonic Metastasis from a Breast Carcinoma, an Unusual Colonoscopic Finding 47
Wadah Ali, Zakir K Mohamed and D Thekkinkattil
-

Isolated Arthroscopic Lateral Patella Retinaculum Release for Anterior Knee Pain – Is it worth it?

Sultan N Qasim, Kimberly Lammin and Phillip Edge

Abstract

Introduction: ‘Anterior Knee Pain’ is a common presentation in all age groups and aetiology is not fully understood. Arthroscopic Lateral Patellar Retinaculum Release has been a commonly performed procedure to treat anterior knee pain with variable results.

Methods: We performed a retrospective review of all the patients who underwent isolated arthroscopic lateral patellar retinaculum release under a single surgeon between July 2007 and July 2010. Exclusion criteria included significant patellar instability, severe mal alignment, and additional procedures including meniscal repair/excision or medial patella plication. Primary outcome measure was improvement in post procedure Oxford Knee Score. 40 cases in 36 patients were included. The mean age was 58.7 years with male to female ratio of 1:1.5. The mean follow up duration was 20.43 months +/- 10.64.

Results: There was significant improvement in OKS, in particular ability to kneel and climb stairs, associated with a high degree of arthritis in patellofemoral articulation and post-operative physiotherapy. However, OKS components lost this significance with tibiofemoral articulation wear of Outerbridge grade 3 or higher. The procedure had a high mean satisfaction score of 8.2 (range 4 to 10) and 32 of 36 patients would have the procedure again if need be.

Conclusions: Isolated Patella Retinaculum release can be effective for anterior knee pain without significant instability or mal-alignment. It particularly improves patients’ ability to kneel and climb stairs giving a high satisfaction score - grade of wear of patellofemoral cartilage being most important factor. Post-operative physiotherapy further augments the good results. However it has no significant value in the presence of advanced tibiofemoral degeneration irrespective of state of patellofemoral articulation.

Keywords: Anterior Knee Pain, Arthroscopic, Patella, Lateral Release

Abbreviations: OKS - Oxford Knee Score

Introduction

Anterior knee pain or patellofemoral pain is a common clinical presentation especially in females. It is a challenging clinical problem. The specific cause can be difficult to diagnose as the aetiology remains poorly understood and there are various pathologic entities that can result in pain in the anterior aspect of knee.

Multiple surgical options have been used to treat the condition. Lateral retinacular release is one of these options and has been used to treat anterior knee pain with variable results¹⁻⁵. The aim of this study was to assess isolated patella lateral retinaculum release as a treatment for anterior knee pain.

Materials and Methods

We performed a retrospective review of all the patients who underwent isolated arthroscopic lateral patella retinacular release under a single surgeon between July 2007 and July 2010. Exclusion criteria included significant patellar instability and severe mal-alignment on both radiological and clinical assessment and additional procedures including cartilage

debridement, meniscal tear repair/excision or patella stabilization.

Data was collected from case notes (demographics, pre-operative and intra-operative findings and any post-operative complications), archived radiographs and postal questionnaires including pre and post procedure Oxford Knee Score (OKS), as well as patient satisfaction. Patient satisfaction questions included a grading of satisfaction of 1 (completely dissatisfied) - 10 (completely satisfied) and whether patient would reconsider the procedure if given the choice again.

Independent factors assessed were age, sex, tight lateral retinaculum, osteoarthritic x-ray changes of all compartments, intraoperative findings of grade of arthritis and lateral subluxation and postoperative physiotherapy. The primary outcome assessed was patient reported outcome measures, including the improvement in post procedure OKS and patient satisfaction scores. SPSS Version 20 was used for analysis.

Preoperative and Postoperative OKS – total and components - were compared using Wilcoxon Signed Rank Test. The Mann Whitney U test was used for nominal data and Kruskal-Wallis

test was used for continuous data for total OKS. Individual OKS components compared were ability to kneel and ability to climb stairs - more representative of patellofemoral joint.

Results

59 patients were identified with male to female ratio of 1:1.5. The mean age was 58.7 (range 25 to 77). 40 patients (67%) returned completed forms. Four patients had further surgery; three total knee replacement and one subsequent arthroscopic procedure for meniscal tears. These patients were excluded from the study. Four patients had bilateral procedures. Therefore after the exclusions for further surgery and those who failed to return completed forms 36 patients were included, on whom 40 procedures had been performed. Changes of osteoarthritis - graded according to Kellgren and Lawrence system - on the medial and lateral facets of the patella were noted on preoperative Merchant views (Table 1) and the tibiofemoral compartment as well.

Table 1 – Pre-Operative Radiographic grades of Patellofemoral change

Grade	Medial Facet		Lateral Facet	
	Frequency	%	Frequency	%
0	2	5	1	2.5
1	6	15	4	10
2	15	37.5	13	32.5
3	16	40	15	37.5
4	1	2.5	7	17.5
Total	40	100	40	100

All patients had undergone standardized preoperative physiotherapy regimen with no significant benefit. Two had, had intra-articular hyaluronic acid injection with no benefit.

All procedures were performed by a single surgeon (PE) and intraoperative findings of cartilage Outerbridge grade were noted in all compartments. Closed lateral retinacular release was performed with Smiley’s knife from just below lower end up to the upper border of patella.

Mean follow up duration was 20.43 months +/- 10.64. Patients were divided into three groups of follow up durations. 6-12 months had 6, 12-18months had 18 and >18months had 16 cases. The best results were in 12-18 month follow up but no statistically significant difference was found between different groups. There was no significant difference in age and gender distribution amongst different durations of follow up. Also there was no significant difference in age, gender and different durations of follow up between responders and non-responders of the questionnaire. There were no reported postoperative complications.

24(60%) underwent post-operative physiotherapy. The mean OKS improved from 23.05 (range11-40) to 35.30 (range14-48) [p value <0.0001]. Individual components of OKS, particularly ability to climb stairs and ability to kneel, also showed statistically significant improvements (Figure 1, Figure 2).

Fig 1 – OKS – ability to climb stairs

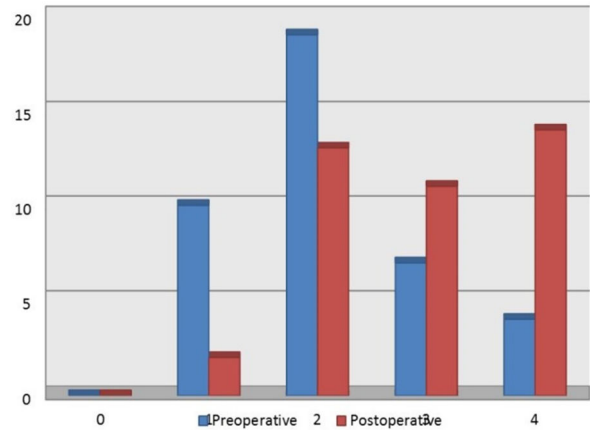
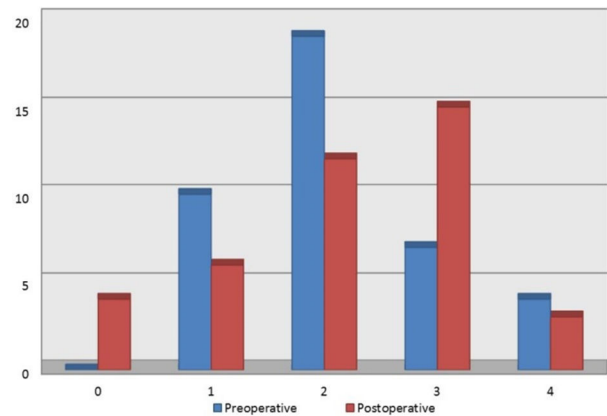


Fig 2 – OKS – ability to kneel



Univariate analysis showed improvement of total OKS and OKS for ability to kneel were significantly associated with higher grade of radiographic lateral patellofemoral joint wear (p value 0.025 and 0.042 respectively) and postoperative physiotherapy (p value 0.018 and 0.003) and improvement in OKS for ability to climb stairs was significantly associated with higher grade cartilage wear, noted intraoperatively, for trochlea (p value 0.042) and patella (p value 0.022).

However the OKS components lost this significance if there was Outerbridge Grade 3 or more wear in tibiofemoral articulation.

The procedure had a high mean satisfaction score of 8.2 (range 4 to 10), and 32 of 36 patients would have the procedure again if needed.

Discussion

Anterior Knee pain or patella pain syndrome is a very common clinical problem faced by orthopaedic surgeons. However the aetiology remains poorly understood. Mori et al identified evidence of degenerative neuropathy in 29 out of 35

histologically examined specimens of resected lateral retinaculum; thus suggesting it may originate in the lateral retinaculum. Lateral Retinacular release would denervate this tissue producing symptomatic relief. Ostermeier et al⁷ measured patellofemoral contact pressures and kinematics using fresh-frozen cadaver specimens both before and after lateral release. They concluded that release could decrease pressure on the lateral patella facet in flexion but did not stabilize the patella or medialise patella tracking. This possibly explains our finding of improvement with lateral patellofemoral joint wear.

Arthroscopic lateral release remains a controversial topic because of lack of well-designed randomised studies. Fulkerson and Shea⁸ suggested that knees showing lateral patellar tilt without subluxation were more likely to benefit from a lateral release in the absence of grade III or grade IV changes in the articular cartilage. Korkala et al⁹ showed that a lateral release tended to improve symptoms in patients with grade II to grade IV chondromalacia. Our findings concur that greater the patellofemoral articulation cartilage wear the more significant the improvement.

Lodhi et al¹⁰ performed a prospective study of elderly patients with patellofemoral osteoarthritis and pain which conservative management had failed to improve and concluded that the procedure improves function and provides significant pain relief successfully deferring need for arthroplasty; therefore they recommended the procedure in middle aged to elderly patients with symptomatic patellofemoral osteoarthritis.

Twaddle and Parkinson¹¹ suggested lateral release to be an effective, reliable and durable procedure in 'carefully selected patients' through their retrospective study.

Our study has deficiencies regarding single surgeon series and retrospective review. However it reflects some of the findings from previous studies suggesting that it is an effective procedure to improve symptoms associated with cartilage changes in patellofemoral articulation without significant tibiofemoral joint osteoarthritis. Further well designed randomized controlled trials are needed to give a more definitive answer.

Conclusion

Isolated lateral patella retinacular release can be effective for anterior knee pain in carefully selected patients, (without significant instability or mal-alignment, with high patellofemoral but low tibiofemoral wear), who have failed conservative management. It particularly improves patients' ability to kneel and climb stairs, giving a high satisfaction score. The grade of wear of patellofemoral cartilage is the most

significant factor in determining this, with post-operative physiotherapy further augmenting the good results.

Competing Interests

None declared

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Psychiatric Morbidity in Children and Adolescent Survivors of a Snowstorm Disaster in South Kashmir, India

Abhishek Chowhan, Mushtaq A Margoob, Imtiyaz Mansoor and Arti Sakral

Abstract

Objective: To determine the long term psychiatric morbidity in children and adolescents in a snowstorm affected area in South Kashmir, India.

Methods: It is a cross sectional study done in a disaster affected population of children and adolescents in South Kashmir 5 years after the disaster. Mini International Neuropsychiatric interview for children and adolescents (MINI-KID) was applied for evaluation of symptoms and diagnosis on a randomly selected group of 100 children and adolescents. A semi-structured proforma was prepared for socio-demographic profile. Kuppusswamy's Socioeconomic Status Scale, 2007 was used for determining socio-economic status. Oslo-3 Social Support Scale (OSS-3) was used to calculate social support.

Results: Of the 100 children and adolescents studied (41.32% of the affected population of children and adolescents) 41 were noted to have at least one psychiatric diagnosis (patients). PTSD (14%) was the commonest diagnosis followed by GAD (5%), MDD (4%) and separation anxiety disorder (4%). Psychiatric morbidity was found to be more prevalent in Pre-Adolescents, Females, Primary schoolers, joint families, upper & lower socio economic classes, only-children and in those with poor social support.

Conclusion: Prevalence of psychiatric disorders remain high in children and adolescents long after the disaster has happened.

Keywords: Psychiatric Morbidity Children and Adolescents Disaster

Introduction

India ranks second in world not only in terms of its population but also in disaster proneness.¹ Disasters, whether they are natural or man-made, result in a wide range of mental and physical health consequences.² International public agenda has taken notice of protection and care of children in natural and man-made disasters. This, in large part, is due to observations that those affected and overlooked often include children and adolescents.³ There is continuous controversy about the impact of disasters on victims including children^{4, 5} and some investigations deny that serious psychological effects occur.^{6, 7, 8} However further research has found that the criterion used in these studies were extremely narrow and inadequate and hence more systematic, clinically relevant investigations are required.⁹ For children and adolescents, response to disaster and terrorism involve a complex interplay of pre-existing psychological vulnerabilities, stressors and nature of support in the aftermath. Previous research has shown that direct exposure to different types of mass traumatic events is associated with an increase in post-traumatic stress symptoms,^{10, 11, 12, 13} anxiety, and depression,^{11, 14} which are frequently comorbid with post-traumatic stress reactions among youth.¹⁵ To the best of our knowledge, studies on long term psychological effects of disasters on younger age groups from South Asian countries are only a handful even though the frequency and the extent of natural disasters in this part of the world are considerable. As

trauma during childhood and adolescents can etch an indelible signature in the individual's development and may lead to future disorder,¹⁶ it underscores the need for such studies.

A snowstorm followed by an avalanche took over a small mountainous village "Waltengu Nard" in South Kashmir, India on 19th Feb. 2005, about a month after the devastating Indian Ocean Tsunami. Of the total population, 24.77% (n=164) had perished.¹⁷ As reported, the total population of children and adolescents prior to disaster was 242, of whom 52 died (21.49%).¹⁷ The present study is a discreet one which aims to determine long term psychiatric morbidity among the surviving children and adolescents of this disaster affected region five years after the snowstorm disaster. This is based on the notion that psychiatric disturbances can be present in children and adolescents years after a disaster has occurred.^{18, 19, 20} The socio-demographic variables of the patients are also studied. The results may support the need to apply wide area epidemiological approaches to mental health assessment after any large scale disaster.

Material and Methods

The study was designed as a survey of children attending school. Children from ages 6 years to 17 years from the high school near Waltengu Nard were taken up for the study. Only those children who were present in the area during the disaster were included in the study. Those with presence of any

psychiatric disorder prior to the time of disaster, mental retardation, organic brain disorder, serious physical disability prior to disease (e.g. blindness, polio, amputated limbs etc.) or severe medical condition (e.g. congenital or rheumatic heart disease, tuberculosis, malignancy etc.) were excluded from the study. Within the school, an alphabetically ordered list was prepared including all classes of school with children aged 6-17 years 11 months. Every 3rd student on this list was chosen and subjected to inclusion and exclusion criteria until a sample size of 100 children was complete. Informed consent was obtained both from the child and one of his/her caregivers or parents.

Selected children were subjected to the Mini International Neuropsychiatric interview for children and adolescents (MINI-KID) for evaluation of symptoms and diagnosis which is a DSM-IV based diagnostic interview with high reliability and validity.^{21, 22} A semi structured proforma was prepared for socio-demographic profile. Kuppuswamy's Socioeconomic Status Scale, 2007 was used for determining socio-economic status.²³ Oslo-3 Social Support Scale (OSS-3) was used to calculate social support.²⁴

Interviews were conducted following formal training in instituting MINI-KID by trained psychiatrists of the Department of Psychiatry GMC Srinagar. The data was then subjected to appropriate statistical methods. A p-value less than 0.05 was taken as significant.

Results

Of the 100 children and adolescents studied (41.32% of the affected population of children and adolescents) 41 were noted to have at least one psychiatric diagnosis (patients). The socio-demographic profile of these patients is represented in Table 1. Age and sex distribution of diagnoses is presented in Table 2 and Table 3 respectively.

A total of 54 diagnoses were observed in these 41 patients (Figure 1), with comorbidities present in 12 patients (29.27%). 11 of these 12 patients were experiencing two psychiatric disorders present concurrently and 1 was enduring three concurrent psychiatric diagnoses. Post-Traumatic Stress Disorder (PTSD) was the commonest comorbidity seen in 6 patients. This comes to 42.86% of total PTSD cases. This was followed by Major Depressive Disorder (MDD), Generalized Anxiety Disorder (GAD), Suicidality, Social Phobia, Panic Disorder, Agoraphobia and Separation Anxiety Disorder (SAD) in 2 each. Attention Deficit/Hyperactivity Disorder (ADHD), Conduct Disorder (CD), Specific Phobia (dark), Substance Abuse and Dysthymia were comorbid in one patient each. Studies have consistently shown presence of psychiatric comorbidities post-disaster.^{48, 49} Of the total 54 diagnoses, the commonest were Anxiety disorders (except PTSD), PTSD and affective disorders (includes MDD, dysthymia and mania) comprising 37.04% (N=20), 25.93% (N=14) and 14.81% (N=8) of total diagnosis respectively.

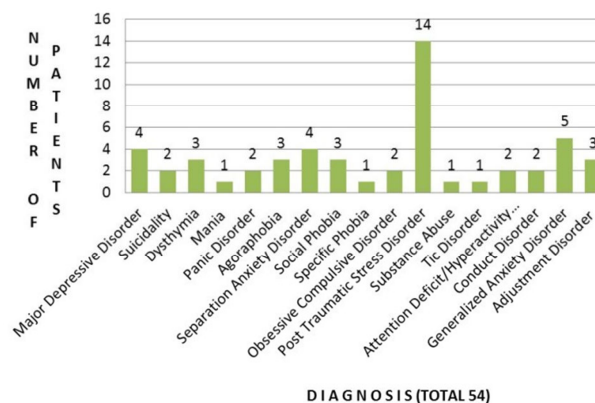


Figure 1: Diagnostic profile of the patients

Discussion

When children and their families are involved in natural or man-made disasters they may be exposed to diverse stressors which may impact mental health of the survivors, including children.²⁵ Studies have suggested that reliance on parental reports of children's distress may not be valid as parents typically under-report symptoms compared with child and adolescent self-report in mental health surveys.²⁶ Thus in our study the psychiatric interview of each child was done individually without getting leads from their parents. In the early "heroic" and "honeymoon" phases of disaster relief there is much energy, optimism, and altruism. As fatigue sets in over the time and frustrations and disillusionment accumulate, more stress symptoms may appear.²⁷ Accordingly, the study was carried out five years after disaster to catch this delayed response to disaster in the form of psychiatric morbidity.

Consequences of the extensive amount of stress on our sample population due to the snowstorm resulted in a high prevalence of psychiatric disorders in our sample which was apparently not due to any other psychological stress during this period. Despite the fact that the study was done five years after the disaster, the research generated high psychiatric morbidity. Many young survivors reported restlessness and fear with the return of the season in which snowstorm occurred. All these kept the memories of the disaster and the losses fresh in their mind thus not allowing the wounds to heal. Some said that they couldn't keep their minds off the snowstorm during the weeks approaching the anniversary. This was much like the so called anniversary reactions.²⁸ Even children and adolescents, who have rebuilt their homes or found new dwellings to rent, frequently feel a sense of loss at the anniversary. Though the area was provided with adequate relief in terms of better infrastructure, education, employment and financial help in years post disaster to make their life without psychological distress, but, perhaps four such anniversary reactions and the fact that they are still living in the same geographical area and climate conditions have not allowed them to settle down in a routine since the psychological distress. Of the total sample of 100 patients, 41 % (N=41) reported at least one diagnosis. This is almost similar to a study by Kar and Bastia after a natural

Table 1: Sociodemographic Profile

Variable	Sample Size (100)		Patients (41)		Chi square	p-value
	N	%	N	% (of category sample)		
<u>Age</u>						
Pre-Adolescence (6-10)	31	31	19	61.29	2.36	0.1245
Early Adolescence (11-13)	30	30	12	40	0.01	0.9203
Middle Adolescence (14-16)	26	26	6	23.07	1.54	0.2146
Late Adolescence (17+)	13	13	4	30.77	0.06	0.8065
<u>Sex</u>						
Males	47	47	16	34.04		
Females	53	53	25	47.17	0.46	0.4976
<u>Educational Status</u>						
Primary School (1 st To 5 th Standard)	49	49	25	51.02	1.23	0.2674
Middle School (6 th To 8 th Std.)	43	43	13	30.23	1.11	0.2921
High School (9 th & 10 th Std.)	8	8	3	37.5	0.04	0.8415
<u>Family Type</u>						
Nuclear	22	22	6	27.27	0.58	0.4463
Extended Nuclear	24	24	9	37.5	0.00	1
Joint	54	54	26	48.15	0.7	0.4028
<u>Socio-Economic Status</u>						
Upper	0	0	0	0	-	-
Upper Middle	0	0	0	0	-	-
Lower Middle	4	4	1	25	0	1
Upper Lower	55	55	27	49.09	1	3.173
Lower	41	41	13	31.71	0.71	0.3994
<u>Social Support</u>						
Good/Fair	31	31	5	16.13		
Poor	69	69	36	52.17	4.46	0.0347
<u>Birth Order</u>						
Eldest	14	14	10	71.43	1.55	0.2131
Middle	51	51	13	25.49	3.62	0.0571
Youngest	26	26	12	46.15	0.04	0.8415
Only Child	9	9	6	66.67	0.47	0.493
<u>Income Source Of Family</u>						
Farming/Cattle	81	81	34	41.97	0	1
Semi-Government Job	15	15	6	40	0.04	0.8415
Government Job	4	4	1	25	0	1

Table 2: Age Wise Distribution of Diagnosis

	Diagnosis	Age groups							
		Pre-adolescence (6-10 yrs) (n=31)		Early adolescence (11-13 yrs) (n=30)		Middle adolescence (14-16 yrs) (n=26)		Late adolescence (17+ yrs) (n=13)	
			%		%		%		%
1	Major Depressive Disorder (MDD) (4)	1	3.23	1	3.33	2	7.69	-	-
2	Suicidality (2)	-	-	-	-	2	7.69	-	-
3	Dysthymia (3)	-	-	2	6.66	1	3.84	-	-
4	Mania (1)	-	-	-	-	-	-	1	16.66
5	Panic Disorder (2)	1	3.23	1	3.33	-	-	-	-
6	Agoraphobia (3)	1	3.23	2	6.66	-	-	-	-
7	Separation Anxiety Disorder (SAD) (4)	4	12.9	-	-	-	-	-	-
8	Social Phobia (3)	2	6.45	-	-	1	3.84	-	-
9	Specific Phobia (1)	1	3.23	-	-	-	-	-	-
10	Obsessive Compulsive Disorder (OCD) (2)	1	3.23	1	3.33	-	-	-	-
11	Post Traumatic Stress Disorder (PTSD) (14)	7	22.58	3	10	2	7.69	2	33.33
12	Alcoholism (0)	-	-	-	-	-	-	-	-
13	Substance Abuse (1)	-	-	-	-	-	-	1	16.66
14	Tic Disorder (1)	1	3.23	-	-	-	-	-	-
15	Attention Deficit/Hyperactivity Disorder (ADHD) (2)	2	6.45	-	-	-	-	-	-
16	Conduct Disorder (CD) (2)	1	3.23	1	3.33	-	-	-	-

17	Oppositional Defiant Disorder (ODD) (0)	-	-	-	-	-	-	-	-
18	Psychotic Disorders (0)	-	-	-	-	-	-	-	-
19	Anorexia Nervosa (0)	-	-	-	-	-	-	-	-
20	Bulimia Nervosa (0)	-	-	-	-	-	-	-	-
21	Generalized Anxiety Disorder (GAD) (5)	-	-	2	6.66	2	7.69	1	16.66
22	Adjustment Disorder (3)	2	6.45	1	3.33	-	-	-	-
23	Pervasive Development Disorder (PDD) (1)	1	3.23	-	-	-	-	-	-
	Total (number of diagnosis) (54)	24		14		10		6	
	Total number of patients (41)	19		12		6		4	

Table 3: Sex Wise Distribution of Diagnosis

	Diagnosis	Sex			
		Males (n=47)		Females (n=53)	
			%		%
1	Major Depressive Disorder (4)	1	2.12	3	5.66
2	Suicidality (2)	1	2.12	1	1.89
3	Dysthymia (3)	1	2.12	2	3.77
4	Mania (1)	1	2.12	-	-
5	Panic Disorder (2)	-	-	2	3.77
6	Agoraphobia (3)	1	2.12	2	3.77
7	Separation Anxiety Disorder (4)	1	2.12	3	5.66
8	Social Phobia (3)	1	2.12	2	-
9	Specific Phobia (1)	-	-	1	1.89
10	Obsessive Compulsive Disorder (2)	1	2.12	1	1.89
11	Post Traumatic Stress Disorder (14)	5	10.64	9	16.98
12	Alcoholism (0)	-	-	-	-
13	Substance Abuse (1)	1	2.12	-	-
14	Tic Disorder (1)	1	2.12	-	-
15	Attention Deficit/Hyperactivity Disorder (2)	1	2.12	1	1.89
16	Conduct Disorder (2)	2	4.25	-	-
17	Oppositional Defiant Disorder (0)	-	-	-	-
18	Psychotic Disorders (0)	-	-	-	-
19	Anorexia Nervosa (0)	-	-	-	-
20	Bulimia Nervosa (0)	-	-	-	-
21	Generalized Anxiety Disorder (5)	1	2.12	4	7.55
22	Adjustment Disorder (3)	1	2.12	2	3.77
23	Pervasive Development Disorder (1)	1	2.12	-	-
	Total (Number of Diagnosis) (54)	21		33	
	Total number of patients (41)	16		25	

disaster in Orissa (cyclone) who found 37.9 % of adolescents with any diagnosis.²⁹ Similarly Margoob et al found that 34.39 % had a psychiatric disorder at the end of one year, after disaster.¹⁷ Other studies yielded results in the range of 12% to 70% in terms of total psychiatric morbidity.^{26, 30-33}

PTSD was the commonest individual diagnosis in our study with 14% (N=14) of the total population. Studies have shown PTSD prevalence after disaster from as high as 72 %³⁴ to as low as 8 %.³⁵ However, these were done immediately or within a few months after the disaster and the longitudinal pattern was not studied. A study conducted by Margoob et al reported a prevalence of 18.51 % in a sample of survivors one year after the same snowstorm on which this present study is based.¹⁷ Similarly, Bockszczanin et al 2.5 years after a flood in Poland reported 18 % of children to be suffering from PTSD.³⁶ Thus our results of 14 % patients suffering from PTSD are also similar to the trend as we are studying them after a period of five years following the disaster. Diagnosis of PTSD

in our study was more common among the pre-adolescent age group, 22.58 % (N=7) and adolescents 33.33% (N=2). Similar findings were reported by Hoven et al who found a prevalence of 20.1 % in this age group.³⁰ Also PTSD was more frequent in females in our study. It was observed in 16.98 % females (N=9) as compared to 10.64 % for males. Hoven et al also found high prevalence in girls (13.3 % vs. 7.4 %).³⁰

Anxiety Disorders (excluding PTSD) formed the most common collective diagnostic category in our sample. Anxiety disorders were present in 20 % (N=20) of our sample population which formed about 37.04 % of total diagnosis. These included cases of GAD 5% (N=5), SAD 4% (N=4), Social Phobia 3% (N=3), Agoraphobia 3% (N=3), Panic Disorder 2% (N=2), OCD 2% (N=2) and Specific Phobia 1% (N=1). Similarly Norris et al found anxiety in various forms in 32% of their sample of disaster victims.²⁵ Similar findings were also reported by Reijneveld et al.³⁷ Hoven et al in an important study after 9/11 found prevalence of various anxiety disorders to the magnitude

of 28.6%.³⁰ Our study correlated very closely to the above mentioned study. GAD was the commonest anxiety disorder among the above group. A prevalence of 5% (N=5) was found in the study sample. This prevalence was almost half of the earlier studies in children and adolescents after a disaster by Kar and Bastia²⁹ where it was 12% and by Hoven et al.³⁰ where it came out to be 10.3 %. However these studies were conducted within a few months after the disaster and hence came out with a higher prevalence of GAD than ours. It was more common in girls in contrast to boys (7.55 % vs. 2.12%) similar to study by Hoven et al.³⁰ SAD was also seen to predominate in anxiety disorders with 4 % (N=4) of the sample receiving the diagnosis. Some studies like one by Hoven et al found it to be prevalent in 12.3 % of their sample 6 months after 9/11.³⁰ However other studies have found SAD to be comparatively less frequent post disaster in children and adolescents.³⁴ Thus our findings are modest and lie somewhere between the above two studies. Also ours was a long term study hence SAD figures are a bit low. SAD in our study was more prevalent in girls than boys (5.66% vs. 2.12%). Moreover, it was exclusively seen in ages below 10 years. The above findings are in tune with the study by Hoven et al.³⁰ Panic disorder showed a low prevalence in our study and was found in only 2 % (N=2) patients. In both of these patients it was found to be comorbid, with MDD in one and with Agoraphobia in another. Studies immediately post disaster found the prevalence to be around 10.8 % (Math et al)³² and 8.7% (Hoven et al).³⁰ However in the survivors of the same area, in which our study is based, an earlier study one year after the disaster found 3.08 % prevalence of panic disorder which is very similar to our study.¹⁷ It was more prevalent in females and is well correlated to a study by Hoven et al.³⁰ Agoraphobia was present in 3 % (N=3) patients. It was comorbid in two patients with panic disorder and with PTSD, and an individual diagnosis in one. Hoven et al have found high rates of Agoraphobia post disaster i.e., about 14.8%.³⁰ But again this study was done only 6 months after 9/11 hence more morbidity. Female preponderance of the diagnosis was established (3.77 % vs. 2.12 %) as with earlier studies.³⁰ Obsessive traits are known to increase subsequent to disaster in the surviving population.³⁸ Similarly 2 % of cases satisfying the criteria for OCD were seen in our study. The commonest obsessions were recurrent intrusive and annoying themes related to the disaster and ruminations about whether it could have been prevented, followed by worries related to harm befalling themselves, family members, or fear of harming others due to losing control over aggressive impulses. Other obsessive themes were related to scenes of trauma and commonly blood. Obsessions regarding extreme fears of contamination were also present.

The affective disorders have been studied less often than PTSD after disaster. Depression is known to occur with increased frequency subsequent to disaster.²⁵ MDD was present in 4 % (N=4) of the total sample population. Studies conducted immediately after disasters have found higher prevalence. Math et al,³² Kar & Bastia²⁹ and Catani et al³³ found the prevalence of

13.5 %, 17.6 % and 19.6 % in their studies respectively. A study at three months and at one year after disaster on the adults in the same population as our study found the prevalence of MDD as 29.6 % and 14.28 % respectively.¹⁷ This decreasing trend is substantiated by the findings of our study and is in line with it. MDD was more common in females (5.66 % vs. 2.12%) which is similar to the study of Hoven et al.³⁰ Our findings of increased prevalence of MDD in middle adolescents (7.69 %) as compared to other age groups is also comparable to Hoven et al.³⁰ Of the Dysthymia cases, 3 % (N=3) were observed in our studies. Increased prevalence of dysthymia has not been reported post disaster in earlier studies. Our findings could be a part of large affective diaspora with dysthymia resulting from diminished self-esteem and a sense of helplessness subsequent to disaster. In addition to the time period for depression these patients were given the diagnosis of dysthymia because the depressed mood in them was more apparent subjectively than objectively. Finally these patients could have been on a natural course of dysthymia which usually begins in childhood. Combined dysthymia and MDD accounted for 7 % (N=7) of patients which if taken as a collective depression category, the results are slightly more comparable with the above studies. One patient had Mania (past). This patient had a positive family history of Bipolar Affective Disorder. This could be an incidental finding even though psychological stress is known to precipitate mania.³⁹ Also the prevalence is 1 % in our study which is even less than the prevalence in general population thus it could be an artifact.⁴⁰ Studies have consistently found increased prevalence of adjustment disorder after disaster.⁴¹ In our study prevalence of adjustment disorder was 3% (N=3, anxiety 2, depression 1). In a study by Math et al 3 months after tsunami it was 13.5%.³² A lower prevalence in our study was again due to the long term nature of study. The role of trauma, stress, and negative life events as risk factors for suicidal ideation and behavior has long been recognized.⁴² A longitudinal investigation looking at the trends in suicidality and mental illness in the aftermath of Hurricane Katrina found significant increases in suicidal ideation and plans in the year after the disaster as a result of unresolved hurricane related stresses.⁴³ The suicidality in our population sample was found to be 2% (N=2) of sample. These results were in tune with that of Kessler et al, although it was immediately after hurricane Katrina and hence a higher prevalence of 6.4%.⁴³

Many symptoms of PTSD overlap with the symptoms of ADHD and CD.⁴⁴ In our study, each of the disorders were present in 2 % of the sample. In one patient, they were comorbid with each other (ADHD with CD). In a study by Hoven et al 6 months after 9/11, the prevalence of CD was found to be as high as 12.8 %.³⁰ This could be because of immediate post disaster nature of the study. Also because of the symptom overlap more weight was given to the PTSD diagnosis.

Three patients had a diagnosis of Substance Abuse, Tic Disorder and PDD, 1 % each. Though substance abuse is known to increase subsequent to disaster in adolescents,³⁰ no evidence was found for relation of tic disorder or PDD to the post-disaster psychiatric stress. The cause of a low prevalence of substance abuse in our sample was because of the fact that the area is inhabited by Muslim population and hence alcohol is not religiously sanctioned, and, harder substances are either not available or they can't be afforded. The only substance which is available is marijuana or cannabis. However, most used it only recreationally and the criterion for abuse was not met. Even the sole patient of substance abuse was also taking cannabis. Also, it is a well known phenomenon that drug dependent subjects do not reveal the true information and deny any history of abuse at first contact with the investigating team.⁴⁵ Tic disorder and PDD are regarded as biological disorders and their relation to trauma is only incidental.^{46, 47}

Studies have consistently shown presence of psychiatric comorbidities post disaster.^{48, 49} The same was observed in our study where 29.27 % of total patients had comorbid psychiatric diagnosis. Similar results were found by Kar and Bastia who found comorbidities in 39% of adolescents.²⁹ PTSD is the most common comorbid disorder observed during the period post disaster^{48, 49} and the same was observed in our study with PTSD comorbid in 14.63 % (N=6) of cases. However when all the anxiety disorders were combined except PTSD, they were found to exceed the comorbidity of PTSD and they were comorbid in 21.95 % (N=9) patients. There is expanding literature regarding comorbidity of anxiety and depression in children and adolescents.^{50, 51, 52} Similar comorbidity of an anxiety disorder (including PTSD) and depressive disorder (including Dysthymia) were seen in 7.32 % (N=3) of patients in our study. These results show that psychiatric diagnoses are frequently comorbid after the disaster and there is a need to be vigilant about them for a holistic psychiatric assessment, treatment and rehabilitation of the survivors.

Sociodemographic Profile: In our sample the prevalence of psychiatric morbidity was at maximum in pre-adolescents (6-10 years age group) and it was 61.29 % of the sample of pre-adolescents. This is consistent with the research that has suggested that younger children possess fewer strategies for coping with both the immediate disaster impact and its aftermath, and thus may suffer more severe emotional and psychological problems.⁵³ Second commonest group was of 11-13 years with 40 % morbidity in them which was consistent with an earlier study which also found significant morbidity in this age group.⁵⁴ The age characteristics of the total population also closely matched the above findings. More females than males were found to exhibit psychiatric morbidity in our study (47.17 % vs. 34.04 %). Though these findings were in tune with those of Hoven et al, their findings were a little lower than ours (34.7 % vs. 21.8 %).³⁰ Some studies have found that girls express more anxiety-depressive disorders³⁰ and PTSD symptoms^{55, 56} and boys seen to exhibit more behavioral

problems.⁵⁷ Similarly in our study rates of anxiety disorders, depressive disorders and PTSD were higher in girls and conduct disorder was exclusively found in boys.

Our study suggested that children up to 5th standard were (51.02 %) more susceptible than those in higher classes. This was in accordance with an earlier study by Kar et al.⁵⁴ These findings are also in accordance with the findings of a study by Hoven et al. which found maximum morbidity (34.1 %) in preschoolers.³⁰ Thus it could be said that higher educational status was protective, in addition to increasing age. Psychiatric morbidity was highest in children who were from joint family systems (48.15%). This was followed by children from extended nuclear (37.5%) and nuclear (27.27%) families. This pattern is consistent with an earlier study by Margoob et al.⁵⁸ This could be because of the fact that in the sample of joint families there was loss of more family members in the tragedy. There were no cases of upper and upper-middle socio-economic class and lower-middle class was significantly less in our sample. This was because of the demographics per se and was not a sampling error. Consequently, higher morbidity was seen in the upper-lower socio-economic class (49.09%) followed by the lower class (31.71%). All the above findings are in accordance with an earlier study by Margoob et al.⁵⁸

Psychiatric morbidity was not found to be influenced by the source of family income. Same was observed by Kar and Bastia in their study.²⁹ The majority of the patients had poor social support (52.17%, p=0.03). These findings are substantiated by earlier studies.⁵⁹ Loss of a parent was strongly associated with lower social support and high psychiatric morbidity. This was also reported by earlier studies.^{31, 60} Our study reported higher psychiatric morbidity in first-born children (71.43%). This could be due to increased burden of family matters on an eldest child subsequent to a disaster especially when head of family or mother has perished in such a catastrophe. This was in accordance with earlier studies on birth order and psychiatric morbidity.⁶¹ However in our study only child also documented significant morbidity which is in contrast to earlier studies.⁶¹ This could be due to the fact that an only child had significantly less social support due to fewer siblings and death in the family due to disaster considerably compounding the problem. Also, often the youngest born is more pampered and hence more likely to feel emotionally insecure when attention is shifted from him in the aftermath of a disaster.

There was an unavoidable limitation in the study; the disaster-affected population was not compared with a normal or control population. The difficulty we faced was finding a control population as the area has a racially, geographically and culturally distinct population of Gujjars and all of them were affected. So no appropriate control group could be found. However if we compare it with most of the studies done in populations from the north India, the prevalence in our study is largely greater than those found in those studies.⁶²

Conclusion

This research portrays and scrutinizes the experience of children and adolescents in the aftermath of a snowstorm disaster and supports the idea that children are susceptible to morbid psychological experiences long after the traumatic event has occurred. With that said, we want to stress the decisive role of support agents for children. These agents include the adults and peers who help children and youth recuperate in the long term. Provision of an outreach psychosocial and clinical service long after the disaster when no one is around to help after the initial knee jerk response of relief agencies is also stressed.

Competing Interests

None declared

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A review of NICE guidelines on the management of Borderline Personality Disorder

Syed Ali and Christopher Findlay

Abstract

Aims and objectives: This report aims to review the current guidelines regarding the management of Borderline Personality Disorder and explore the literature according to the research recommendations. The psychological/psychosocial and pharmacological aspects will be the focus of this review.

Methods: A summary of the NICE guidance was made and each recommended psychotherapy (i.e. mentalization-based therapy, dialectical behaviour therapy, cognitive analytic therapy, cognitive behavioural therapy, schema-focused therapy and transference focussed therapy) and pharmacological options were dissected and analysed using the literature.

Results: All of the psychotherapies showed promising results when applied to borderline personality disorder. Two were seen as superior due to there being more evidence to support their use. In terms of psychotropics, despite the NICE guidance negating their use, the literature found evidence that some second-generation antipsychotics and mood stabilisers could improve symptoms in the short term. Those pharmacological agents that carry the strongest evidence base should be considered if off-label use is deemed appropriate.

Conclusion: Specialist psychological treatments such as dialectical behaviour therapy and mentalization based therapy substantiate the use of psychotherapy in borderline personality disorder. By crystallising the important aspects of the array of psychotherapies available, a more comprehensive approach could be developed. By understanding the disorder in terms of psychological and biological aberrations, it will enable a more specific dual approach to its management in the future.

Keywords: Borderline Personality Disorder, Emotionally unstable personality disorder, Personality disorder.

Abbreviations: BPD - Borderline Personality Disorder, DSM-5 - The Diagnostic and Statistical Manual of Mental Disorder, ICD-10 - The International Classification of Diseases, NICE - The National Institute for Health and Care Excellence, DBT - Dialectical Behaviour Therapy, MBT - Mentalization Based Treatment, CAT - Cognitive Analytic Therapy, NHS - National Health Service (UK), CBT - Cognitive behavioural therapy, TFT - Transference focussed therapy, NHMRC – The National Health and Medical Research Council of Australia.

INTRODUCTION

During my placement in Psychiatry at the Brooker Centre, Runcorn, UK, I have come into contact with a wide array of psychiatric disorders, none more so than borderline personality disorder (BPD). It is undoubtedly one of the most prevalent problems in the area which the Brooker Centre serves. I can recall an example of a patient with BPD who had been quite unwell for a prolonged period of time and had struggled with affective instability. This patient had been quite successfully treated with Lithium therapy, has exhibited stability and is happy on the current treatment. There is a pattern of pharmacological treatment in BPD patients despite the fact that guidelines suggest otherwise...

Personality disorders are defined as 'an enduring pattern of inner experience and behaviour that deviates markedly from the expectations of the individual's culture, is pervasive and inflexible, has an onset in adulthood, is stable over time, and leads to distress or impairment'. Personality disorders are

representative of long-term functioning and are not considered in terms of episodes of illness¹.

The Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), groups the various personality disorders into three clusters based on their descriptive similarities.

Cluster A includes the Paranoid, Schizoid, and Schizotypal personality disorders which are categorised as 'odd/eccentric';

Cluster B includes the Antisocial, Borderline, Histrionic, and Narcissistic personality disorders which are categorised as 'dramatic/emotional/erratic';

Cluster C includes the Avoidant, Dependent, and Obsessive-compulsive personality disorders which are categorised as 'anxious/fearful'².

The International Classification of Diseases, 10th edition (ICD-10), specifies the condition of emotionally unstable personality disorder which has two subtypes: The impulsive type and the borderline type. The borderline type in essence overlaps with the DSM-5 definition³.

It has proven difficult to provide robust clinical recommendations with regards to the treatment of personality disorder. This is, in part, due to the fact that study populations are diverse but also compounded by the use of different assessment criteria. Furthermore, it is important to consider that personality disorders often present with a great deal of psychiatric comorbidity. Of the personality disorders, particular attention has been paid to borderline personality disorder (BPD) as the symptom clusters which it involves have been shown to improve considerably with treatment⁴.

Figure 1: Diagnostic Criteria for Borderline Personality Disorder according to DSM-5²:

A pervasive pattern of instability of interpersonal relationships, self-image, and affects, and marked impulsivity, beginning by early adulthood and present in a variety of contexts, as indicated by five (or more) of the following:

1. Frantic efforts to avoid real or imagined abandonment. (Note: Do not include suicidal or self-mutilating behaviour covered in Criterion 5.)
2. A pattern of unstable and intense interpersonal relationships characterised by alternating between extremes of idealization and devaluation.
3. Identity disturbance: markedly and persistently unstable self-image or sense of self.
4. Impulsivity in at least two areas that are potentially self-damaging (e.g. spending, sex, substance abuse, reckless driving, binge eating). (Note: Do not include suicidal or self-mutilating behaviour covered in Criterion 5.)
5. Recurrent suicidal behaviour, gestures, or threats, or self-mutilating behaviour.
6. Affective instability due to a marked reactivity of mood (e.g. intense episodic dysphoria, irritability, or anxiety usually lasting a few hours and only rarely more than a few days).
7. Chronic feelings of emptiness.
8. Inappropriate, intense anger or difficulty controlling anger (e.g. frequent displays of temper, constant anger, recurrent physical fights).
9. Transient, stress-related paranoid ideation or severe dissociative symptoms.

Borderline personality disorder is characterised by a pervasive instability in mood, interpersonal relationships, self-image and behaviour. The condition was first recognised in the United States by Adolf Stern in 1938. He described that these are a group of patients who neither fit into psychotic or psychoneurotic group, which gave rise to the term 'borderline'. BPD is often diagnostically comorbid with depression and anxiety, eating disorders (notably bulimia), post-traumatic stress disorder, substance misuse and bipolar affective disorder. Furthermore, psychotic disorders have also been found to overlap. Due to this extent of comorbidity it is rare to see a patient who has a pure BPD⁵.

The pharmacological treatments of BPD are tailored according to the symptom clusters that present. These include impulsivity, affective instability, transient stress-related psychotic symptoms and suicidal & self-injurious behaviours^{5,6}.

Recommended Psychological and Pharmacological treatment, 2009 National Institute for Health and Clinical Excellence (NICE) guidelines on Borderline Personality Disorder^{5,7}:

Psychological

NICE guidelines state that when offering psychology for BPD or for the individual symptoms of the disorder, brief psychological interventions (i.e. less than a 3 month period) should not be used. It states that the frequency of psychotherapy sessions should be adapted to the patient's needs and 'context of living' and suggests that twice-weekly session may be considered. The guidelines also specify that for women with BPD for whom recurrent self-harm is a priority, a comprehensive dialectical behaviour therapy programme should be considered. NICE recommends that when psychological treatment is provided in BPD, the effects should be monitored using a broad range of outcomes. These should include personal functioning, drug and alcohol use, self-harm, depression and the symptoms of BPD.

Pharmacological

The NICE guidance states that drug treatment should not be used specifically for BPD or for the individual symptoms or behaviour associated with the disorder (e.g. repeated self-harm, marked emotional instability, risk taking behaviour and transient psychotic symptoms). It goes on to suggest that antipsychotics should not be used for the medium- and long term treatment of BPD. However, with regards to the management of comorbidities, it specifies that drug treatment may be considered and that in each case, the NICE guidelines for each comorbid condition must be referred to. Antidepressants, mood stabilisers and antipsychotics are commonly used in clinical practice. The guidelines mention that short-term use of sedative medication may be considered in a crisis. 'Short-term' denotes treatment lasting no longer than one week.

With regards to drug treatment during a period of crisis, NICE recommends that there should be a consensus among prescribers and other involved professionals about the proposed drug treatment and also that a primary prescriber should be identified. There should be an appreciation of the likely risks of prescribing, including alcohol and illicit drug use. NICE emphasises that the psychological role of prescribing (both from the patient's and prescriber's perspective) should be taken into account, and the impact that such prescribing decisions may have on the therapeutic relationship and overall care plan. NICE recommends that a single drug be used and that polypharmacy is to be avoided as much as possible.

In a crisis NICE recommends prescribing 'a drug that has a low side-effect profile, low addictive properties, minimum potential

for misuse and relative safety in overdose.’ The minimum effective dose is favourable, prescribing fewer tablets more frequently if there is a significant risk of overdose and also agreeing with patient on the symptoms that are being targeted. NICE suggests that following a crisis, a plan should be made to stop drug treatment that was started during a crisis. If this is not possible, a regular review of the effectiveness, side effects, misuse and dependency of the drug is advised. BPD patients can often have concomitant insomnia and for this, NICE details basic advice regarding sleep hygiene and forwards on to the guidance on the use of zaleplon, zolpidem and zopiclone for the short-term pharmacological management of insomnia.

AIMS AND OBJECTIVES

This report will review the current guidelines specifically regarding the management of borderline personality disorder and explore the literature according to the research recommendations that are set by NICE. The report is to focus on the two aspects of the management of BPD – The psychological/psychosocial aspect and the pharmacological aspect.

CURRENT NICE GUIDELINES ON PSYCHOLOGICAL AND PHARMACOLOGICAL TREATMENT OF BPD ⁷:

Psychology

Mentalisation-based therapy and dialectical behavioural therapy are proposed in the setting of a ‘well structured, high quality community based service’ e.g. a day hospital setting or a community mental health team. NICE suggests that these techniques should be compared with ‘high-quality community care delivered by general mental health service without the psychological intervention for people with BPD’ in order to measure efficacy. For outpatients, *cognitive analytic therapy, cognitive behavioural therapy, schema-focussed therapy* and *transference focussed therapy* are suggested and are catered to those with less severe BPD (i.e. fewer comorbidities, higher level of social functioning, greater ability to depend on self-management methods). Randomised controlled trials reporting medium term outcomes (e.g. quality of life, psychosocial functioning, employment outcomes and BPD symptomatology) of a minimum of 18 months are recommended

Pharmacology

Mood stabilisers are proposed as it is detailed that emotional instability is a key feature in BPD. In particular, topiramate and lamotrigine are mentioned as they have been shown to produce encouraging results in small-scale studies. A randomised placebo-controlled trial with medium to long-term follow up is recommended.

ANALYSIS

Psychology: Dialectical Behaviour Therapy (DBT)

Dialectics can be defined as the art of investigating the relative truth of opinions, principles, and guidelines ⁸. Dialectical in

DBT refers to a means of arriving at the truth by examination of the argument i.e. the ‘thesis’ and ‘antithesis’ and resolving the two into a rational synthesis. DBT was introduced in 1991 by Marsha Linehan (a psychology researcher) and colleagues tailored as a treatment for BPD. In this, patients are supported in understanding their own emotional experiences and are taught new skills for dealing with their stresses. A combination of individual and group sessions are used. More adaptive responses and effective problem-solving techniques are integrated to improve functioning and quality of life as well as improving morbidity and mortality ^{9,10}.

A study published in 2015 by M. Linehan et al detailed a randomized clinical trial that set out to compare

- 1) Standard DBT (DBT group skills training + DBT individual therapy) with
- 2) A treatment that evaluated DBT group skills training with manual case management (i.e. with the removal of DBT individual therapy) and
- 3) A treatment that removed DBT skills training by providing only DBT individual therapy with an activities group and prohibited individual therapists from teaching DBT skills.

All 3 versions of the treatment were found to be comparably effective at reducing suicide attempts, suicidal ideation, medical severity of intentional self-harm, use of crisis services owing to suicidality and improving reasons for living ¹¹.

Psychology: Mentalization based therapy

Mentalization is ‘the process by which we make sense of each other and ourselves, implicitly and explicitly, in terms of subjective states and mental processes.’ It is a social construct suggesting that we are attentive to the mental states of those we are with, physically or psychologically ¹². Mentalization based treatment is a psychosocial treatment for BPD in which therapists monitor attachment and mentalizing capacity, and use interventions that aim to reinstate or maintain the capacity of patients to mentalize ¹³.

A longitudinal study, published in 2008, involving an eight-year follow-up of patients treated for BPD evaluated the effect of mentalization-based treatment (MBT) with partial hospitalization compared with treatment as usual. Five years after discharge from MBT, the MBT group exhibited clinical and statistical superiority to treatment as usual measured on suicidality, diagnostic status, service use, medication use, global function and vocational status ¹⁴. A more recent review article, published in 2015, emphasises the consideration of disruptions in three closely related domains in individuals with BPD. These are ‘in attachment relationships, in different polarities of mentalizing, and in the quality of epistemic vigilance and trust’. It is suggested that this approach allows seemingly paradoxical features of BPD patients appear more coherent. It is supposed that this approach provides a clear focus for the therapist enabling them to monitor the therapeutic process in terms of

imminent mentalizing impairments and epistemic mistrust due to activation of the attachment system.

The article goes on to assert that the effectiveness of MBT in BPD may be elucidated due to the fact that it 'enables the therapist to maintain and foster a mentalizing stance, even—and perhaps particularly—under high arousal conditions that are so characteristic of work with these patients' ¹⁵.

Psychology: Cognitive analytic therapy (CAT)

CAT is a brief focal therapy that is informed by cognitive therapy, psychodynamic psychotherapy and elements of cognitive psychology. It was originally developed by Anthony Ryle tailored towards the needs of the NHS ¹⁶. It is based on a collaborative therapeutic position which sets out to create narrative and diagrammatic reformulations with patients concerning their difficulties. The theory centres on descriptions of sequences of linked external, mental and behavioural events. At first, the emphasis was on how such procedural sequences prevented revision of dysfunctional ways of living. More recently, this has been extended to understanding the origins of reciprocal role procedures in early life and their repetition in current relationships and self-management ¹⁷.

One study detailed a randomised controlled trial which aimed to investigate the effectiveness of time-limited CAT for participants with personality disorder. The study found that participants receiving CAT exhibited reduced symptoms and showed considerable improvement compared with the control group who showed signs of deterioration during the treatment period. They concluded that CAT is superior to treatment as usual in improving outcomes associated with personality disorder ¹⁸.

Psychology: Cognitive behavioural therapy (CBT) and Schema-focussed therapy

CBT is a time-limited, problem focussed psychotherapy that has been applied to a wide range of psychiatric disorders. The development of this technique was born out of the observation that patients referred for psychotherapy often would hold ingrained, negatively skewed assumptions of themselves, their future and their environment. The therapy is based on the notion that disorder is caused not by life events, but by the view the patient adopts of events. The therapy focusses on current problems and helps to develop new skills to provide symptom relief and sustain recovery ^{9,19}.

Initially CBT was predominantly insight-orientated, using introspection to bring about change. Beck et al began to integrate a range of behavioural techniques to improve the impact on dysfunctional controlling belief systems (schemas). The goal of treatment is not to replace the dysfunctional schemas; it aims to modify beliefs and develop new ones allowing the patient to cope more effectively in challenging situations ^{20,21}.

A 2013 review article that set to explore schema-focussed therapy concluded that schema-therapy is based on a 'cohesive theoretical model' and that there seems to be sufficient evidence supporting its validity. Regarding effectiveness, it goes on to indicate that one should be encouraged by the results of studies, however it points out that due to the small number of 'methodologically-good efficacy studies' it is difficult to be certain. The article claims that when evaluated against other psychotherapeutic treatments, specifically DBT and MBT, schema-therapy requires more investigation ²². A pilot study (2013) set out to monitor the effects of group schema-based CBT on global symptomatic distress in young adults with personality disorders or features of personality disorder. Their findings provide preliminary evidence that schema-based CBT might be an effective treatment ²³.

Furthermore, there is a multicentre randomized controlled trial being conducted with the aim of investigating schema-focussed therapy versus treatment as usual in BPD, which has a closing date of 1st February 2016 ²⁴.

Psychology: Transference focussed therapy (TFT)

The classic use of the term transference originates in psychoanalysis and comprises "the redirection of feelings and desires and especially of those unconsciously retained from childhood toward a new object" ²⁵. Transference-focussed psychotherapy is an evidence-based manualised treatment using a psychodynamic approach with a focus on object relations theory ²⁶. TFT aims to 'facilitate the reactivation, under controlled circumstances, of the dissociated internalised object relations in the transference relationship to observe the nature of the patient's split polarised internal representations, and then, through a multistep interpretive process, work to integrate them into a fuller, richer, and more nuanced identity' ²⁷.

Yeomans et al produced an article in 2013 consisting of vignettes to illustrate the techniques used in TFT with the view to evaluate its use in treating BPD. Their findings supported the validity of TFT in treating BPD patients who specifically had difficulty with relationships.

They distilled TFT down to three important components ²⁸:

- 1) The treatment contracting/setting the frame
- 2) Managing one's affective response
- 3) The interpretative process

Pharmacology

A Cochrane intervention review assessing the effects of drug treatments in BPD, included twenty-eight randomised control trials, published in the period 1979-2009 (20 of 28 trials dating from 2000 or later), involving a total of 1742 participants ²⁹.

The authors arrived at the conclusion that pharmacotherapy in BPD 'is not based on good evidence from trials'. The review found that there is support for the use of Second-generation antipsychotics (in improving cognitive-perceptual symptoms

and affective dysregulation); Mood stabilisers (in diminishing affective-dysregulation and impulsive-aggressive symptoms); and Omega-3 fatty acids.

Figure 2: The pharmacological agents that were tested included the following:

First-generation antipsychotics:

Flupenthixol decanoate

Haloperidol

Thiothixene

Second-generation antipsychotics:

Aripiprazole

Olanzapine

Ziprasidone

Mood stabilisers:

Carbamazepine

Valproate semisodium

Lamotrigine

Topiramate

Antidepressants:

Amitriptyline

Fluoxetine

Fluvoxamine

Phenelzine sulfate

Mianserin

Dietary supplementation:

Omega-3 fatty acid

However, these claims were made based on single study effects and therefore require replication. No drug was found to significantly affect the symptom clusters, specific to BPD, including avoidance of abandonment, chronic feelings of emptiness, identity disturbance, and dissociation.

One noteworthy finding was that Olanzapine was associated with an increase in self-harming behaviour. Furthermore, the review states that 'special attention' is needed in BPD when prescribing tricyclic antidepressants (due to toxic effects in overdose) and hypnotics & sedatives (due to there being potential for misuse or dependence). Another problem that was highlighted was that in comorbid eating disorders the use of Olanzapine can contribute to weight gain and Topiramate can produce weight loss.

The review goes on to elucidate that there is not any evidence from randomised controlled trials that any drug reduces the severity of BPD and that it consists of 'distinct pathology facets'. They recommend that the pharmacotherapy of BPD should be targeted at 'defined symptoms' and that polypharmacy is not supported by the latest evidence and should be avoided as much as possible.

The authors end by reaffirming that the evidence is not robust and that the studies may not satisfactorily reflect certain characteristics of the clinical environment. They propose that further research is needed in order to produce reliable

recommendations. They detail the complications that arise from the 'polythetic nature' of BPD i.e. each patient is likely to experience different aspects of the disorder. There lacks a consensus among researchers about a common battery of outcome variables and measures. They comment that there is a fragmentary view on drug effects and that it is unknown as to how the alteration of one symptom affects another.

Comorbidity

Comorbidity is a foremost concern in the interpretation of data concerning personality disorders³⁰. A majority of individuals diagnosed with one personality disorder often meet criteria for at least one other personality disorder³⁰. A large proportion of patients with personality disorder have one axis I³¹ disorder comorbidly, mostly depression, anxiety and alcohol and substance use disorders³². [Axis I is a reference to the multi-axial classification system used in the Diagnostic and Statistical Manual of Mental Disorders that was removed in the latest version, DSM-5²

It is important to consider therefore that, an improvement in the symptom clusters in personality disorders might be an improvement in comorbid axis I disorder symptoms. It is reported that the rates of depression are very high in BPD³³ and that the response to antidepressants in depressed individuals with comorbid personality disorders appears lower than in those without comorbid personality disorder³².

The most recent guidance on the treatment of BPD from the National Health and Medical Research Council of Australia (NHMRC), which reviewed the literature and integrated a series of meta-analyses, details that pharmacotherapy does appear to be effective in altering the nature and course of BPD and that evidence does not warrant the use of pharmacotherapy as a sole or first-line treatment for BPD³⁴.

DISCUSSION

All of the aforementioned psychotherapy techniques are shown to produce promising results when applied to the treatment of BPD, with some standing out, such as DBT and MBT, due to the presence of a relatively robust evidence base. With such a wide variety of different approaches that all show some propensity for successful treatment of BPD it is clear that these approaches must be taken more seriously in clinical practice. These treatments have been shown to considerably improve symptomatic outcomes however there is a shortcoming in that they have failed to significantly improve social functioning. Each of the therapies follow distinct theories, however, when each treatment modality is applied to BPD, similar effects are seen. This is intriguing and should be explored further.

An analysis of these therapies revealed some common features which are now suggested as core requirements for all effective psychotherapeutic treatments:

An update to the aforementioned Cochrane review²⁹ was published in 2013. The update focussed on the psychotherapies that are available for the treatment of BPD and included a total

of 1804 participants spread over 28 studies. The psychotherapies discussed were divided into 'comprehensive' if they substantially involved an individual psychotherapy element or as 'non-comprehensive' if they did not. The comprehensive therapies included dialectical behaviour therapy, mentalization-based therapy (delivered in either a partial hospitalisation or outpatient setting), transference-focussed therapy, cognitive behavioural therapy, dynamic deconstructive psychotherapy, interpersonal psychotherapy and interpersonal therapy for BPD. These were assessed against a control condition and also with some direct comparisons against each other. Non-comprehensive psychotherapies included DBT-group skills training, emotion regulation group therapy, schema-focussed group therapy, systems training for emotional predictability and problem solving for borderline personality disorder (STEPPS), STEPPS plus individual therapy, manual assisted cognitive treatment, and psychoeducation³⁷.

Figure 3: Five common characteristics of evidence-based treatments for BPD^{35,36}.

1. Structured (manual directed) approaches to prototypic BPD problems
2. Patients are encouraged to assume control of themselves (i.e. sense of self-agency)
3. Therapists help connections of feelings to events and actions
4. Therapists are active, responsive, and validating
5. Therapists discuss cases with others, (including personal reactions)

The authors concluded that both comprehensive and non-comprehensive therapies indicated beneficial effects for the core pathology of BPD and associated general psychopathology. The authors identified that dialectical behaviour therapy had been studied the most comprehensively followed by mentalization-based therapy, transference-focussed therapy, schema-focussed therapy and STEPPS. However, the authors do state that none of the treatments presented a very robust evidence base and that there are concerns over the quality of individual studies³⁷.

In terms of pharmacotherapy, the NICE and NHMRC guidelines agree with the 2006 Cochrane interventional review among others^{38, 39} that there is some evidence that some second-generation antipsychotics (aripiprazole and olanzapine) and some mood stabilisers (topiramate, lamotrigine and valproate) could improve BPD symptoms in the short term. However, for some of these agents, it is necessary to balance risks against benefits as they have considerable long-term risks (e.g. with antipsychotics, extrapyramidal side effects such as tardive dyskinesia can persist even after withdrawal of the drug⁴⁰). Such risks are not a problem in psychological treatments and it is probable that this influences guidelines. In practice, off-label use of psychotropics is widespread, despite the fact that the NICE guidance negates their use. It is arguable that clinicians should preferentially use pharmacological

treatments that have the strongest evidence base (i.e. antipsychotics and mood stabilisers) and refrain from using agents with the least evidence (i.e. antidepressants and benzodiazepines).

CONCLUSION

Specialist treatments, in particular DBT and MBT substantiate the use of psychotherapy in BPD and these findings support the validity of the NICE guidance. However, the array of such treatments must be amalgamated with the view to provide a comprehensive, multi-faceted treatment approach. Each treatment must be broken down in order to outline the components that are particularly useful in BPD with the view to understand the condition in greater depth and to provide more focussed therapies.

The 2013 Cochrane review³⁷ highlights that further psychotherapies are available and have been shown to successfully treat BPD core pathology, however, as it is clearly stated the evidence base lacks robustness and there is a need for further studies that can replicate results. The therapies that have been included in this Cochrane review that have not been covered in the guidelines (e.g. STEPPS) may prove to be superior to those put forward by NICE, and I recommend that these be explored thoroughly when the guidelines are due for update.

While the NICE guidance emphasises that the use of psychotropics is reasonable in the management of comorbidities, it worth noting that to understand BPD, it is necessary to explore both the underlying aberrant psychological processes and biological processes that manifest in the disorder. This will enable the use of more specific pharmacological therapies in targeting the symptoms of BPD in the future.

Competing Interests

None declared

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A comprehensive review on the pregnancy dermatoses

Mohammad Adil, Tasleem Arif and Syed Suhail Amin

Abstract

Pregnancy results in cutaneous changes in more than 90% of women. This is the result of the altered endocrine, metabolic and immunological state in the female. Many cutaneous changes are common and benign; these are referred to as the physiological changes of pregnancy. They may be of cosmetic concern to the patient and seldom require intervention. These changes are so well recognized that they act as contributory evidence of pregnancy. Many pre-existing dermatological conditions tend to change in pregnancy; some are aggravated while others may be relieved. Knowledge of these conditions is important to forewarn the patient and to prepare for upcoming complications. There are a group of dermatoses specific to pregnancy and there has been much confusion in the literature about their classification and nomenclature. Atopic Eruption of Pregnancy is the most common pregnancy specific dermatoses followed by Polymorphic Eruption of Pregnancy. These are benign conditions with no risk to the mother or baby. Pemphigoid Gestationis and Intrahepatic Cholestasis of Pregnancy carry fetal risk and require antepartal surveillance. This article discusses the current knowledge of the various cutaneous changes of pregnancy with emphasis on their clinical features, diagnosis, management and prognosis.

Keywords: Dermatoses, endocrine, physiological changes, pregnancy.

Abbreviations: Melanocyte Stimulating Hormone (MSH), Systemic Lupus Erythematosus (SLE), Pemphigoid Gestationis (PG), Herpes Gestationis (HG), Polymorphic Eruption of Pregnancy (PEP), Pruritic Urticarial Papules and Plaques of Pregnancy (PUPPP), Prurigo of Pregnancy (PP), Pruritic Folliculitis of Pregnancy (PF), Intrahepatic Cholestasis of Pregnancy (ICP), Atopic Eruption of Pregnancy (AEP), Bullous Pemphigoid Antigen 2 (BPAg2)

INTRODUCTION

The state of pregnancy results in a multitude of cutaneous changes in the female. These are a reflection of the profound alterations in the endocrine, metabolic and immunological profiles that occur during this period.¹ Skin manifestations occur due to the production of a number of proteins and steroid hormones by the fetoplacental unit and also by the maternal pituitary, thyroid and adrenals.² The placenta, a new endocrine organ in the woman, produces progesterone. Dehydroepiandrosterone is produced by the fetal adrenals from pregnenolone and this is aromatized to estradiol. At term, the level of progesterone is 7 times, estradiol is 130 times and prolactin level is 19 times of that present at 8 weeks of gestation.³ There occurs an overall preference for the Th2 cytokine profile, which helps in fetal protection from the immune system.⁴ This is due to the high levels of progesterone, which promotes Th2 cytokines like IL-4, IL-5 and IL-10 and has inhibitory effects on TNF alpha production. Oestrogen suppresses IL-2 production. The postpartum period is marked by withdrawal of hormones and consequent elevation of Th1 cytokine levels.⁴

Cutaneous changes develop in more than 90% of all pregnant females.⁵ These include common cutaneous changes that occur in most cases to severe diseases, some of which are seen exclusively in the pregnant and postpartum state. Cutaneous manifestations can be grouped into three broad categories:

physiological cutaneous changes related to pregnancy; diseases modified by pregnancy and specific dermatoses of pregnancy.⁶

PHYSIOLOGICAL CHANGES IN PREGNANCY

These changes are so common that they are not considered abnormal. Rather, they provide contributory evidence of a pregnant state. This however, does not mean they are cosmetically acceptable to all patients. The various physiological changes during pregnancy have been summarized in Table 1.

Pigmentation:

Hyperpigmentation is one of the most common and early signs of pregnancy, seen in more than 90% of patients.⁷ High levels of Melanocyte Stimulating Hormone (MSH), oestrogen and progesterone are believed to be responsible for hyperpigmentation. Progesterone augments the oestrogen mediated melanin output, the levels of which correlate with pigmentary changes.⁸

Generalized hyperpigmentation is seen which is more marked in the dark haired skin.⁶ Pigmented areas of the body, namely the genitalia, perineum, areolae and upper medial thighs, demonstrate more pronounced pigmentation. Linea nigra, a hyperpigmented line extending from the pubic symphysis to umbilicus and further up to the xiphisternum, replaces the linea alba.⁹ Chloasma, also termed as mask of pregnancy, is the well marginated brownish pigmentation of the face like melasma. It

is seen in 45-75% of pregnant women in western literature but in less than 10% cases in women with pigmented skin.^{5,10,11} Pigmentary demarcation lines appear on the limbs with borders of abrupt transition; freckles, naevi and scars tend to darken and enlarge.¹²

The pigmentation gradually fades after delivery, though the resolution of skin colour is usually incomplete. Chloasma tends to persist in 30% cases postpartum.¹³ Sun protection and reassurance is all that is needed. Topical formulations containing hydroquinone and tretinoin are avoided in pregnancy and can be added after delivery.

Table 1: Physiological changes in pregnancy

Pigmentation Generalized hyperpigmentation Pigmentation of inner thigh, genitalia, axilla Secondary areola Linea nigra Chloasma Prominence/ appearance of pigmentary demarcation lines Enlargement and darkening of freckles, naevi and scars
Connective tissue changes Striae distensae (Striae gravidarum) Molluscum fibrosum gravidarum
Vascular changes Oedema of distal extremities and hands Spider angiomas Palmar erythema Leg varicosities Rectal haemorrhoids Cutis marmorata Capillary haemangioma
Glandular changes Miliaria Dyshidrotic eczema Montgomery's tubercles Aggravation of acne
Oral mucosal changes Oedema and hyperaemia of gingivae Pregnancy epulis
Hair changes Hirsutism Hypertrichosis Delayed anagen release after delivery
Nail changes Brittle nail plate Onycholysis Beau's lines after delivery

Physiological connective tissue changes:

Gross distension of abdomen with adrenocortical activities are responsible for the red-blue depressed streaks seen on abdomen and breasts in 70-90% pregnancies, called striae distensae.^{5,14} These usually develop in the second trimester. Females with pre-existing striae on breasts and thighs are more likely to develop striae gravidarum¹⁵, seen in White women more than Asian and African-American.¹⁴ Preventive therapies

are controversial and postpartum treatment options include topical tretinoin, excimer laser or surgery.¹⁰

Soft tissue fibromas of pregnancy are called molluscum fibrosum gravidarum. They appear in the second trimester on the neck, face and beneath the breasts. These disappear after delivery.¹⁶

Physiological vascular changes:

Vascular growth factors released during pregnancy by the pituitary, adrenals and placenta are believed to be causative and this has been demonstrated in vitro as well.¹⁷ Non-pitting oedema of the face, hands and feet is present in around half of all females in the later part of pregnancy.¹³ This is probably due to sodium and fluid retention and pressure of the gravid uterus on the inferior vena cava. Spider naevi or spider angiomas are small raised lesions with a central pulsatile punctum and radiating telangiectatic vessels frequently present over the area drained by the superior vena cava. They are present in 67% of White women and 11% Black women during the second trimester.⁵ Palmar erythema is seen in two-thirds of White and one-third of Black women.⁸ Other vascular changes include varicosities of legs and anus (40%)¹³, cutis marmorata (0.7%)¹⁸ and capillary haemangioma (5%)⁹. These changes revert after the postpartum period.

Physiological glandular changes:

Eccrine gland activity is usually increased but the palms show decreased sweating. Thus, the incidence of miliaria and dishidrotic eczema is increased. There is inconclusive evidence to suggest that apocrine gland activity is decreased during pregnancy.¹⁹ Sebaceous activity increases in the third trimester leading to acne and enlargement of Montgomery's tubercles.¹⁴ One-third to half of all pregnant women develop these tubercles, which are modified sebaceous glands.^{5,8} However, sebum excretion has not been found to decrease in lactating females post-delivery.²⁰

Oral mucosal changes:

Oedema and hyperaemia of the gingivae in pregnancy is attributable to local irritation and nutritional deficiencies and is seen in around 80% women.⁵ Gingivitis not related to poor oral hygiene may occur. Granuloma gravidarum or pregnancy epulis might occur that regresses postpartum.

Hair changes:

Hair changes are seen in 3-12% of pregnant females.²¹ Hirsutism and hypertrichosis occurs due to oestrogen. This leads to an increase in the percentage of hair in anagen.² Approximately 2-3 months after delivery, loss of telogen hair occurs.²² This is termed as late anagen release as the hair follicles are no longer stimulated to stay in anagen phase by the maternal hormones. The hair recovery occurs in 3-12 months. A small number of females may experience episodic shedding of hair for long periods. This has been proposed to be due to the inability of some hair follicles to revert to

asynchronous shedding.²³ Rarely, male pattern baldness may occur in women.²

Nail changes:

Nail growth increases during pregnancy.⁶ Brittleness of the nail plate and distal onycholysis may be seen.¹⁹ Beau's lines may develop after delivery.¹² Reassurance is all that is needed for these benign nail problems.

DISEASES MODIFIED BY PREGNANCY

Many pre-existing dermatoses may be exacerbated or ameliorated by pregnancy. Certain tumours may also show remission or exacerbation. This is due to the shift in pregnancy to the Th2 state and a return to Th1 state in the postpartum period and also the discontinuation of some drugs due to their teratogenic potential.

Infections:

Depressed cell-mediated immunity makes the pregnant woman susceptible to more severe and frequent infections.²⁴

Candidiasis is quite common and was found to be the commonest cause of white discharge per vagina, being present in 22% pregnant females.⁵ Half of all neonates born to infected mothers are positive for *Candida* and some may show signs of infection.²⁵ *Pityrosporum folliculitis*, caused by *Pityrosporum ovale*, is more common in pregnancy.²⁵

Genital warts are the commonest sexually transmitted disease seen in 4.7% subjects, these increase in size during pregnancy.^{9,25} Prophylactic caesarian section to prevent laryngeal papillomas in the neonate is not recommended now.²⁶ Herpes simplex virus infection carries 50% risk of transmission to neonate in the primary episode and 5% risk in recurrent episode, caesarean section might be warranted to prevent such transmission.²⁶ Varicella zoster virus infection has been reported to cause pneumonia in 14% of mothers and death in 3%.²⁷ Bowenoid papulosis, caused by human papilloma virus appears first during pregnancy or may get aggravated.⁶

Pregnancy prepones the clinical manifestations in HIV infected females, possibly due to additive immune suppression. *Pneumocystis pneumonia* or listeriosis may prove to be fatal.²⁷ Kaposi's sarcoma may occur in these females.²⁷ 20-30% women present with leprosy for the first time in pregnancy and the postpartum period.²⁸ The disease tends to downgrade towards the lepromatous pole in pregnancy and upgrades during lactation.²⁹ Type 1 lepra reactions are more frequent in the first trimester and after delivery, whereas type 2 lepra reactions peak in third trimester.²⁹ Trichomoniasis is diagnosed in 60% of pregnant women.²⁵

Autoimmune diseases:

Systemic Lupus Erythematosus (SLE) is associated with a better prognosis than previously thought, if the disease is in remission and nephropathy and cardiomyopathy are not present.¹⁰ If the

disease is active, half of the patients' disease will get worse and there might be fatalities.¹⁴ SLE tends to be more severe if it first presents in pregnancy.¹⁴ Babies of such mothers are likely to develop neonatal lupus.

Patients with scleroderma are usually unaffected and some are improved in pregnancy. However, occasional reports of renal crisis, hypertension and pre-eclampsia are reported.³⁰ Course of dermatomyositis is usually unaltered but the disease may worsen in some patients.³¹

Pemphigus tends to be exacerbated or present for the first time in pregnancy.³² The clinical presentation in pregnancy is similar to that of the regular presentation. Differentiation from herpes gestationis is important.

Metabolic diseases:

Effect of pregnancy on porphyria cutanea tarda is not clear, though some females show biochemical and clinical deterioration.³³ Acrodermatitis enteropathica shows clinical worsening.³⁴

Connective tissue diseases:

Pregnancy can lead to bleeding, uterine lacerations and wound dehiscence in patients of Ehlers-Danlos syndrome. Pseudoxanthoma elasticum patients may suffer massive gastrointestinal bleeds.³⁵ Lichen sclerosis et atrophicus of the vulva usually improves in pregnancy and a normal delivery is mostly possible.

Disorders of glands:

Acne can aggravate during pregnancy. Hidradenitis suppurativa and Fox-Fordyce disease become better as a result of decreased apocrine gland activity.²⁷

Keratinization diseases:

The course of psoriasis remains unaltered in 40% females during pregnancy while it improves in a similar percentage of females and worsens in the remaining.³⁶ It is more likely to deteriorate in the postpartum period.³⁷ Psoriatic arthritis has been found to worsen or present for the first time in pregnancy.²

Generalized pustular psoriasis of Von Zambusch may rarely occur. Though most patients have a preceding or family history of psoriasis, some may develop the disease without ever having a preceding episode.³⁸ Peak incidence is seen in the last trimester and the disease tends to recur.³⁸ Multiple, discrete, sterile pustules at the margins of erythematous macules on the umbilicus, medial thigh, axillae, inframammary folds, gluteal creases and sides of neck are seen. These break to form erosions and crusts. Painful, circinate mucosal erosions may form. Prednisolone is used for management.¹² Von Zambusch pustular psoriasis of pregnancy was earlier termed 'Impetigo Herpetiformis' but the term is best avoided as it is impossible to differentiate it from the former, both clinically and

histologically.⁶ Erythrokeratoderma variabilis is reported to worsen during pregnancy.²⁷

Tumours:

A melanoma that develops during pregnancy carries worse prognosis but if pregnancy occurs after the tumour is resected, the prognosis is unaltered.³⁹ Metastasis in the fetus has been seen and a minimum period of two years following tumour resection is recommended.³² A female with neurofibromatosis may develop neurofibroma for the first time in pregnancy or older neurofibromas may grow in size. Rupture of major vessels may occur.⁶ Pregnancy may worsen mycosis fungoides and eosinophilic granuloma.⁶

Miscellaneous diseases:

Prognosis of atopic dermatitis is unpredictable in pregnancy, with reports of both improvement and worsening.²⁷ Predisposed patients may first develop atopic dermatitis during pregnancy.⁴⁰ Allergic contact dermatitis may improve in pregnancy.¹² Hand eczema may worsen in the puerperal period.⁶ Erythema multiforme may be precipitated by pregnancy.⁶ Autoimmune progesterone dermatitis has been described in pregnancy.¹² This disease is characterized by hypersensitivity to progesterone demonstrated by a positive intradermal skin test and cutaneous lesions resembling urticaria, eczema, erythema multiforme and dermatitis herpetiformis.⁴¹ The disease is associated with fetal mortality and recurs in subsequent pregnancies.¹²

PREGNANCY SPECIFIC DERMATOSES

These are a heterogeneous group of inflammatory skin diseases specific for pregnancy.⁴² Most of these conditions are benign and resolve spontaneously in the postpartum period but a few of these are associated with fetal complications.⁴² Almost all of them present with pruritus and a cutaneous eruption of varying severity.⁵

Classification:

The first attempt to classify these conditions was made by Holmes and Black in 1982-83 who classified them into: a) Pemphigoid Gestationis (PG) or Herpes Gestationis (HG), b) Polymorphic Eruption of Pregnancy (PEP) or Pruritic Urticarial Papules and Plaques of Pregnancy (PUPPP), c) Prurigo of Pregnancy (PP) and d) Pruritic Folliculitis of Pregnancy (PF).^{43,44} Shornick was of the view that all patients with PF also had papular dermatitis, so he included PF in the PP group. He included Intrahepatic Cholestasis of Pregnancy (ICP) in his classification for dermatoses where secondary skin lesions due to scratching are produced. He proposed that failure to consider ICP in the classification has led to confusion in terminology of pregnancy specific diseases. Thus, his classification included PG, PEP, PP and ICP.⁴⁵ Ambros-Rudolph et al carried out a retrospective review of 505 pregnant patients over a 10 year period and gave a more rationalised classification system in 2006. They clubbed PP, PF and eczema of pregnancy in one group called Atopic Eruption of Pregnancy

(AEP) due to their overlapping features and found this group to be the most common pruritic condition in pregnancy. Thus, they proposed four conditions: a) AEP, b) PEP, c) PG and d) ICP.⁴⁶ The various specific pregnancy dermatoses have been elaborated in Table 2.

Atopic eruption of Pregnancy (AEP): (Syn: Besnier's prurigo, prurigo gestationis, Nurse's early onset prurigo of pregnancy)

It is the most common pregnancy specific dermatoses that includes eczematous or papular lesions in females with personal or family history of atopy and elevated IgE - accounting for nearly half of all patients.⁴⁶ The disease tends to recur in subsequent pregnancies with 75% of all cases occurring before the start of the third trimester.⁴⁷ It carries no risk for the mother or baby however, infant may develop atopy later in life.⁴⁸ Treatment is symptomatic with antihistamines and corticosteroids.

E-type AEP: This group comprises of 67% of AEP patients and includes patients with eczematous features; previously referred to as Eczema of Pregnancy (EP). It was not until 1999 that a high prevalence of atopic eczema was noted in pregnancy.⁴⁹ 80% of pregnant women develop the first episode of atopic dermatitis during pregnancy.⁴⁶ This is attributed to the Th2 cytokine profile in pregnancy and a dominant humoral immunity.⁴ It is more common in primigravida, in single gestation, begins in early pregnancy and affects whole body including face, palms and soles.⁴⁶

P-type AEP: This group includes what was referred to previously as Prurigo of Pregnancy and Pruritic Folliculitis of Pregnancy. Prurigo of Pregnancy (PP) is seen in one out of 300 to 450 pregnancies and occurs predominantly in the second to third trimester.⁵⁰ Excoriated or crusted papules are seen over the extensors of extremities and abdomen and are associated with some eczematization. The eruption lasts up to 3 months after delivery and recurrences in subsequent pregnancies are common.⁵¹ PP is associated with ICP with the differentiating feature being the absence of a primary lesion in the latter.⁵⁰ Personal and family history of atopic dermatitis or raised IgE may be seen in PP.⁵² Serology is normal. There are no specific changes on histopathology and immunofluorescence results are found to be negative.⁵⁰ There appears to be no maternal or fetal risk.⁴⁵

Pruritic Folliculitis of Pregnancy (PF), first described by Zoberman and Farmer, is now believed to be as common as PG or PP, though only a few cases have been reported.⁵⁰ It begins in the latter two trimesters and affects roughly one in 3000 pregnancies.⁵¹ Pruritus is not a defining feature, despite what the name suggests.² Multiple, follicular papules and pustules occur on the shoulders, arms, chest, upper back and abdomen and are acneiform in nature.⁴² The lesions tend to resolve in a couple of months following delivery. Histopathological examination reveals non-specific features with sterile folliculitis

and immunofluorescence studies are negative.⁵⁰ No maternal or fetal risk is described except for low birth weight neonates in a single study.⁵² Pathogenesis of PF is unknown with no definite role of androgens or immunologic abnormalities.⁵³ There is no

evidence to suggest that it is a hormonally aggravated acne as proposed by some workers.⁵⁴

Table 2: Comparison of different pregnancy specific dermatoses in relation to clinical characteristics, prognosis, investigations and treatment.

	AEP	PEP	PG	ICP
Pruritus	+	+	+	+
Primary cutaneous involvement	+	+	+	-
Skin lesions	Eczematous or papular	Papules, vesicles and urticarial lesions	Vesiculo bullous lesion on urticarial base	Excoriations, papules secondary to scratching
Site of lesions	Trunk, extensors of limbs, rest of the body also involved	Abdominal involvement, in striae distensae, periumbilical sparing	Abdominal, particularly periumbilical involvement	Palms and soles followed by rest of the body
Time	First trimester	Third trimester, Post partum	Second and third trimester, post partum	Second and third trimester
Risk with primigravidae	-	+	-	-
Association with multiparity	-	+	-	+
Flare at delivery	-	-	+	-
Recurrence	+	-	+	+
Family history	+	+	-	+
Histopathology	Non-specific	Non-specific	Specific, sub epidermal vesicle	Non-specific
Immunofluorescence	-	-	Linear deposition of C3	-
Other lab findings	Ig E elevated	-	Indirect IMF +	Increased serum bile acids
Maternal risk	-	-	Progression to pemphigoid, thyroid dysfunction	Gallstones, Jaundice
Fetal risk	-	-	Prematurity, Small for age baby, neonatal blistering	Premature births, fetal distress, stillbirth
Treatment	Steroids, antihistaminics	Steroids, antihistaminics	Oral steroids, antihistaminics	Ursodeoxycholic acid

Polymorphic Eruption of Pregnancy (PEP): (Syn: Pruritic Urticarial Papules and Plaques of Pregnancy or PUPPP, Bourne's Toxaemic Rash of Pregnancy, Toxic Erythema of Pregnancy, Nurse's Late Prurigo of Pregnancy)

With a prevalence of a case in every 130-300 pregnancies, this disease is the second most common pregnancy specific dermatoses and was seen in 21.6% pregnancies reviewed by Ambros-Rudolph et al.⁴⁶ They found it began in late pregnancy in 83% cases and 15% in the postpartum period.⁴⁶ The disease occurs predominantly in primigravida and a familial predisposition is present.⁵⁵ Lesions are pleomorphic, usually urticarial but purpuric, vesicular, polycyclic and targetoid lesions may be present. The striae on the abdomen are the first to be involved and there is a characteristic periumbilical sparing.⁵⁶ The lesions seldom occur on the body above the breast and on hands and feet.¹² The lesions resolve with scaling and crusting in six weeks. The disease is more common in excessive weight gain during pregnancy and in multiple gestation.^{57,58} Histopathology is non-specific and shows spongiosis, occasional subepidermal split and eosinophilic infiltration. Serology and immunofluorescence is negative.⁵⁰ Treatment is symptomatic, oral steroids are needed

in severe cases. There are no associated maternal or fetal complications,⁵⁹ although infants may later develop atopic dermatitis.²

The pathogenesis is unknown however, the abdominal distension leading to collagen and elastic fibre damage in striae is hypothesized, leading to formation of antigens and triggering inflammatory cascade.⁶⁰ The role of progesterone has been suggested by the increased progesterone receptor immunoreactivity in skin lesions of PEP.⁶¹ The discovery of fetal DNA in skin lesions of women with PEP has furthered the hypothesis that abdominal distension leads to increased permeability of vessels and permit chimeric cell migration in the maternal skin.⁶² Linear IgM dermatosis of pregnancy is an entity characterized by pruritic, red, follicular papules and pustules on the abdomen and proximal extremities seen after 36 weeks gestation and a linear band of IgM deposition on basement membrane zone. It has been characterized as a variant of PEP or PP by different authors.¹²

Pemphigoid Gestationis (PG): (Syn: Herpes Gestationis or HG, Gestational Pemphogoid, Dermatitis Herpetiformis of Pregnancy)

PG is the most clearly characterized pregnancy dermatosis and the one which also affects the fetal skin.⁶³ It is a rare, self-limiting, autoimmune bullous disease with an incidence of 1:1700 to 1:50000 pregnancies.⁶³ Mean onset occurs at 21 weeks gestation, though it occurs in the postpartum period in a fifth of all cases.⁶⁴ Constitutional symptoms, burning and itching herald the onset of the disease. Half of patients develop urticarial lesions on the abdomen, particularly in the periumbilical region, that change rapidly to a generalized bullous eruption usually sparing the face, palms, soles and mucosae. Vesicles may arise in herpetiform or circinate distribution. Face is involved in 10% cases and oral mucosa in 20%.¹² The disease shows spontaneous improvement in late gestation but flares may occur at the time of delivery in 75% of the cases.⁶³ Though the disease may remit after a few weeks after delivery, a protracted course, conversion to bullous pemphigoid or recurrence with menstrual cycle and use of oral contraceptive pills has been reported.⁵⁰ PG tends to recur in subsequent pregnancies in a more severe form and at an early stage with longer stay in postpartum.⁵⁰ Skipped pregnancies have been described.^{63,65} The disease is also linked with hydatiform mole and choriocarcinoma.⁶⁶

The classical histopathological finding is the presence of a subepidermal vesicle, spongiosis and an infiltrate consisting of lymphocytes, histiocytes and eosinophils.⁶⁴ An inverted tear drop appearance due to oedema in the dermal papilla is seen in early urticarial lesions.¹⁵ Direct immunofluorescence reveals a linear deposition of C3 along the dermo-epidermal junction in 100% cases and is diagnostic of the disease, while a salt split skin shows an epidermal staining.⁶⁷ Antithyroid antibodies may be present but thyroid dysfunction is not common.⁶³ Systemic corticosteroids are the mainstay of management. About one in ten children born to women with PG develop blisters due to passive transfer of antibodies, this resolves on its own. Severity of the disease has been correlated with the risk of prematurity and small for gestational age babies.⁶⁸

Pathogenesis of PG involves the production of IgG1 antibodies against NC16A domain of carboxyl terminus of Bullous Pemphigoid Antigen 2 (BPAg2), leading to activation of complement, recruitment of eosinophils to the local site and damage of the basement membrane and consequent blistering.² The aberrant expression of MHC class II antigens of paternal haplotype is believed to stimulate an allogenic response to placental basement membrane and this is believed to cross react with the skin in PG.^{63,69}

Intrahepatic Cholestasis of pregnancy (ICP): (Syn: Obstetric Cholestasis, Pruritus Gravidarum, Icterus Gravidarum, Recurrent Jaundice of Pregnancy, Idiopathic Jaundice of Pregnancy)

Pruritus in pregnancy is fairly common and can be due to various reasons like pregnancy specific dermatoses and other co-existing dermatoses such as scabies, urticaria, atopic dermatitis, drug reactions etc. It was found to be present in more than half

of 170 pregnant women in an Indian study.⁷⁰ This must be differentiated from ICP where the skin lesions arise secondary to itching.

ICP was first described by Kehr in 1907.⁶³ ICP being referred to Pruritus Gravidarum (for pruritus without skin changes occurring early in pregnancy and related to atopic diathesis and no cholestasis) and Prurigo Gravidarum (for pruritus associated with PP like skin lesions and associated with cholestasis) lead to much confusion regarding nomenclature.⁶³ The disease has an incidence of 10-150 cases per 10,000 pregnancies⁷¹, being more common in South America and Scandinavia, probably due to dietary factors.⁵⁰ Patients complain of sudden onset pruritus beginning from the palms and soles and later generalizing to the whole body. Skin lesions are secondary to itching and range from excoriations to prurigo nodularis, extensors are more severely involved. Jaundice is seen in 20% cases only.⁷² Clay coloured stools, dark urine and haemorrhage secondary to vitamin K malabsorption can occur. Family history can be elicited in half of the cases and an association with multiple gestation is described.⁷³ Resolution of ICP occurs soon after delivery. Recurrence in subsequent pregnancies is seen in 45-70% cases and routinely with the use of oral contraceptive pills, though no detectable abnormalities are seen in the duration between two pregnancies.⁶³ Histopathology is non-specific and immunofluorescence is negative. Diagnosis is made by increased serum bile acid levels, transaminases are elevated. Prothrombin time may be prolonged. A 2.7 times increased risk of gallstones is reported in primigravida with ICP compared to non-pregnant women.⁷⁴ ICP is associated with significant fetal morbidity including premature births in 20-60% cases, intrapartum fetal distress including meconium aspiration in 20-30% and fetal mortality in 1-2%.⁷¹ Risk is particularly more if serum bile acid levels exceed 40 micromoles per litre.⁷⁵ Meconium may cause umbilical vein compression and induction of labour at 36 weeks gestation has been recommended in severe cases.⁵⁰ The goal of treatment is reduction of serum bile acids. Ursodeoxycholic acid, given in the dose of 15mg/kg orally daily is the only proven therapeutic agent that decreases fetal mortality.^{63,76} Cholestyramine reduces vitamin K absorption and increases the risk of haemorrhage. Other agents like S-adenosylmethionine, dexamethasone, silymarin, phenobarbitone, epomediol and activated charcoal are not that effective and do not affect fetal risk.⁶³ Topical emollients and antipruritic agents offer symptomatic relief but antihistamines are not that effective.⁵⁰

The key event in the pathogenesis of ICP is elevation of bile acids. Oestrogens are said to have cholestatic properties by reducing hepatocyte bile acid uptake and also by inhibiting basolateral transport proteins.⁵⁰ Progesterone may additionally saturate the transport capacity of these transport proteins in hepatocyte.⁷¹ Genetic predisposition occurs due to mutation in genes encoding bile transport proteins, with cholestasis developing in pregnancy as their capacity to secrete substance is exceeded.⁶³ Bile acids passing through the placenta produce

vasoconstriction of placental veins, fetal cardiomyocyte dysfunction and also abnormal uterine contractility, all leading to fetal hypoxia.⁷¹

CONCLUSION

Pregnancy is associated with a wide variety of cutaneous changes. These may range from common, benign changes termed physiological or more severe, posing significant risk to the mother as well as the baby. Physiological pregnancy changes may be of cosmetic concern to the patient and seldom need anything more than counselling. Pre-existing dermatoses may aggravate during this period, posing a challenge to the treating physician. Women suffering from such diseases need to be warned of complications and risks before trying to conceive. A strict watch for possible complications and appropriate management at an early stage is warranted. Women should also be looked for pregnancy specific dermatoses and their complaints should not be lightly overlooked as non-specific or physiological. Careful history and examination with a judicious use of investigations will help to arrive at a diagnosis and in prompt institution of treatment.

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Competing Interests

None declared

Author Details

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Optimising stroke prevention in patients with atrial fibrillation in primary care

Yassir Javaid

Abstract

In clinical practice, atrial fibrillation (AF) is the most common cardiac arrhythmia seen, and with an ageing population its prevalence is expected to rise. Guidelines recommend anticoagulant therapy for AF-related stroke prevention, based on an individual's predicted risk of stroke; options include vitamin K antagonists (VKAs) and the non-VKA oral anticoagulants (NOACs), including apixaban, dabigatran, edoxaban, and rivaroxaban. The NOACs fulfil most criteria associated with an ideal anticoagulant and have demonstrated improved benefit–risk profiles compared with warfarin in patients with non-valvular AF. Although patients with AF commonly have other chronic conditions that may complicate treatment, a recent meta-analysis showed a similar treatment effect of NOACs in almost all challenging-to-treat subgroups encountered in clinical practice compared with the general patient population. Encouragingly, data on the real-world efficacy and safety of NOACs are growing and lend support to the increased use of NOACs in this indication.

Keywords: Anticoagulation, atrial fibrillation, real-world, stroke prevention

Summary points

The non-vitamin K antagonist oral anticoagulants have demonstrated favourable benefit–risk profiles in large phase III trials, and these findings have been supported by real-world studies involving unselected patients representative of those encountered in routine clinical practice and including those deemed 'challenging-to-treat'

Accurate detection of atrial fibrillation and assessment of stroke and bleeding risk is crucial in identifying patients who should receive anticoagulation

Elderly populations represent a significant proportion of patients seen in general practice, and advanced age should not be regarded as a contraindication to treatment; acetylsalicylic acid is not considered an effective treatment option to reduce the risk of stroke in patients with non-valvular atrial fibrillation (except for those declining oral anticoagulation), particularly in fragile elderly patients, for whom this drug was historically prescribed

The frequency of follow-up visits, in particular to check compliance, should be tailored according to patients' clinical characteristics and needs, but there is no requirement for routine coagulation monitoring, unlike vitamin K antagonists

ischaemic and other structural heart disease². In addition to being associated with significantly increased rates of mortality³, AF is also associated with significantly increased rates of heart failure, which is both a common cause and consequence of AF and greatly worsens the prognosis⁴. However, it is stroke that is the most devastating consequence of AF, with an average fivefold increased risk⁵.

AF-related strokes are often more severe than other strokes^{6,7} because the clots that embolise from the left atrium or left atrial appendage are often much larger⁸ than from other sources of emboli. These clots usually lodge in large cerebral vessels, commonly the middle cerebral artery, resulting in huge neurological and functional deficits and increased mortality compared with other stroke types. Moreover, the strokes suffered by patients with AF are more likely to lead to extended hospital care than strokes in patients without AF, thus impacting on patients' quality of life⁷.

Current evidence suggests that, in the UK, AF has a causative role in almost 20% of all strokes⁹. This is likely to represent a significant underestimate given that long term electrocardiogram (ECG) monitoring in patients who would previously have been diagnosed as having cryptogenic stroke has demonstrated a significant AF burden in these patients¹⁰.

With improved AF detection and stroke prevention, it is estimated that approximately 8000 strokes could be avoided and 2100 lives saved every year in the UK, resulting in substantial healthcare savings of £96 million^{11,12}.

A key objective of this short review is to provide primary care clinicians with the confidence to manage patients with AF in

Atrial fibrillation: a clinical and economic burden to society

Atrial fibrillation (AF) is the most frequently encountered sustained cardiac arrhythmia, with a prevalence of about 1.5–2% in the general population^{1,2}. Its incidence is predicted to rise sharply over the coming years as a consequence of the ageing population and increased life expectancy in those with

need of anticoagulation, including the safe and appropriate use of the non-vitamin K antagonist oral anticoagulants (NOACs) apixaban, dabigatran, rivaroxaban (approved in the EU, US and several other countries worldwide) and edoxaban (approved in the EU, US and Japan).¹³⁻²⁰ The focus will be on how to accurately identify, risk-stratify and counsel patients on the risks and benefits associated with the different treatment options.

Who to treat. Accurate detection and assessment of stroke and bleeding risk

Many patients with AF are asymptomatic, particularly the elderly, less active patients who may not notice the reduction in cardiac performance associated with AF. Unfortunately, it remains the case that AF is undetected in up to 45% of patients²¹, and stroke is very often the first presentation of AF.

Both the National Institute for Health and Care Excellence (NICE) and the European Society of Cardiology (ESC) guidelines recommend opportunistic screening in patients aged ≥ 65 years by manual pulse palpation followed by ECG in patients found to have an irregular pulse^{1,22}. Opportunistic screening (manual pulse palpation) was shown to be as effective as systematic screening (ECG) in detecting new cases²³, and this simple strategy should be used to screen at-risk patient groups as often as possible. Hypertension and increasing age are the two leading risk factors for developing AF, but other high-risk groups include patients with obstructive sleep apnoea, morbid obesity or a history of ischaemic heart disease²⁴⁻²⁶. In the context of proactive AF detection, many initiatives have been launched worldwide to encourage primary care clinicians to integrate manual pulse checks into their routine practice. The Know Your Pulse campaign was launched by the AF Association and Arrhythmia Alliance during Heart Rhythm Week in 2009 and was quickly endorsed by the Department of Health in the UK and by many other countries. This initiative has assisted in diminishing some of the gaps in AF detection²¹.

The most frequently used tools to evaluate stroke risk in patients with non-valvular AF (AF that is not associated with rheumatic valvular disease or prosthetic heart valves) are the CHADS₂²⁷ and CHA₂DS₂-VASc²⁸ scores, with recent guidelines favouring the use of the latter and emphasising the need to effectively identify 'truly low-risk' patients¹. The CHA₂DS₂-VASc score is superior to CHADS₂ in identifying these truly low-risk patients, who should not be routinely offered anticoagulation¹. Patients with any form of AF (i.e. paroxysmal, persistent or permanent), and regardless of whether they are symptomatic, should be risk stratified in this way. The risk of stroke should also be assessed using CHA₂DS₂-VASc in patients with atrial flutter and probably for the majority of patients who have been successfully cardioverted in the past²². Unless the initial underlying cause has been removed (e.g. corrected hyperthyroidism) and there is no significant underlying structural heart disease, the risk of patients suffering from a recurrence of AF following 'successful' cardioversion remains

high²⁹. The ESC guidelines recommend that anticoagulation should be offered to patients with a CHA₂DS₂-VASc score ≥ 1 based on assessment of risk of bleeding complications and the patient's clinical features and preferences¹.

The new Quality and Outcomes Framework (QOF) for 2015–2016 now recommends the use of CHA₂DS₂-VASc for risk stratification and no longer recommends antiplatelet agents as a therapeutic option for stroke prevention in patients with non-valvular AF³⁰; this should result in significantly more patients receiving anticoagulation for this indication. The changes to QOF 2015–2016 compared with 2014–2015 are summarised in Table 1³⁰.

Table 1. Summary of changes to UK the Quality and Outcomes Framework (QOF) 2015–2016³⁰

NICE indicator ID	Changes	2014–2015 points	2015–2016 points
NM45: Patients with AF and CHADS ₂ =1 currently treated with anticoagulant therapy or antiplatelet therapy	Retired	6	–
NM46: Patients with AF and a latest record of a CHADS ₂ ≥ 1 currently treated with anticoagulant therapy	Replaced by NM82	6	–
NM82: Patients with AF and CHA ₂ DS ₂ -VASc ≥ 2 currently treated with anticoagulant therapy	Replacement	–	12
NM81: Patients with AF in whom stroke risk has been assessed using the CHA ₂ DS ₂ -VASc risk-stratification scoring system in the preceding 12 months (excluding those with a previous CHADS ₂ or CHA ₂ DS ₂ -VASc ≥ 2)	New indicator	–	12

Key: AF = atrial fibrillation; CHADS₂ = Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes, Stroke (doubled); CHA₂DS₂-VASc = Congestive heart failure or left ventricular dysfunction Hypertension, Age ≥ 75 years (doubled), Diabetes, Stroke (doubled)-Vascular disease, Age 65–74 years, Sex category (female); NICE = National Institute for Health and Care Excellence

The Guidance on Risk Assessment and Stroke Prevention in Atrial Fibrillation (GRASP-AF) clinical audit software detection tool is now very widely used in primary care to improve clinical outcomes in the AF population by identifying patients likely to benefit from anticoagulation. GRASP-AF systematically scans general practice software systems and calculates CHADS₂ and CHA₂DS₂-VASc scores in patients who are coded as having AF, thus enabling physicians to identify high-risk patients who are not adequately treated for stroke prevention³¹. Identification of AF patients who are poorly controlled on warfarin (defined as

having a time in therapeutic range <65% or a labile international normalised ratio [INR], e.g. one INR value >8 or two INR values <1.5 or >5 within the past 6 months)²² is crucial because these patients are more likely to experience major bleeding or stroke. These patients should be reviewed and, if possible, the cause for the poor warfarin control should be identified. The Warfarin Patient Safety Audit tool is another software tool that has been developed to help identify patients with poor warfarin control³².

Primary care clinicians are being urged to objectively assess the bleeding risk of AF patients who are receiving, or about to receive, anticoagulation^{1,22,32}. HAS-BLED is the bleeding assessment scheme advocated by both NICE and the ESC^{1,22}, this has been validated in several independent cohorts and was shown to correlate well with the risk of major bleeding, in particular intracranial bleeding¹. The key aspect of HAS-BLED is that, unlike CHADS₂ and CHA₂DS₂-VASc, it consists of risk factors that are modifiable. It should, therefore, not be a tool to influence the decision of whether to anticoagulate, but instead to identify ways to reduce the risk of bleeding in patients receiving an anticoagulant; for example, optimising blood pressure control, stopping unnecessary antiplatelet or anti-inflammatory agents and reducing alcohol consumption can all significantly reduce HAS-BLED scores and bleeding risk¹. In addition, it needs to be emphasised that the absolute number of patients with AF experiencing a serious bleeding event while receiving anticoagulant therapy is low (~2–3%/year in the XANTUS, PMSS and Dresden NOAC Registry real-world studies), with prospective real-world studies indicating that most bleeding events can be managed conservatively^{33–35}. Whilst concerns have been raised about not having a reversal agent to counter the anticoagulant action of NOACs in patients who experience serious bleeding, the low incidence of major bleeding in real-world and phase III studies and its conservative management in most cases demonstrate that such agents would not be required routinely. Despite these low rates of major bleeding, reversal agents have been developed and successfully completed phase III studies and undergone approval in some markets, including idarucizumab in the UK^{36,37}. Notably, high-risk patients with AF were shown to be more willing to endure bleeding events in order to avoid a stroke and its consequences³⁸, thus reinforcing the message that “we can replace blood but we cannot replace brain tissue”.

Adequate anticoagulation therapy should follow appropriate patient identification

Identifying the right treatment option for patients with AF is likely to improve clinical outcomes. Involving patients in the decision-making process and rationale, and ensuring they understand the net benefit–risk of treatment options, is likely to lead to better compliance and improved clinical outcomes. The ESC guidelines consider patients with valvular AF (patients with AF in the presence of either rheumatic mitral stenosis [very rare now in the UK] or prosthetic heart valves) to be at high

risk, and these patients should be anticoagulated with a VKA regardless of the presence of any other risk factors¹. Warfarin is very effective at reducing the risk of stroke compared with acetylsalicylic acid (ASA)^{39,40}, but an unpredictable dose–response relationship and multiple drug and food interactions can be problematic for some patients, and many patients remain sub-optimally treated⁴¹. ASA is also not considered an effective treatment option to reduce the risk of stroke in patients with non-valvular AF especially in frail, elderly patients in whom ASA was historically prescribed. The GARFIELD-AF registry (10,614 patients enrolled in the first cohort) revealed that real-world anticoagulant prescribing in AF populations deviates substantially from guideline recommendations: 40.7% of patients with a CHA₂DS₂-VASc score ≥2 did not receive anticoagulant therapy, and a further 38.7% with a score of 0 received anticoagulant therapy. At diagnosis, 55.8% of patients overall were given a VKA, just over one quarter (25.3%) received an antiplatelet drug alone, and ~4.5% received a NOAC²⁴. Inappropriate prescribing was further confirmed by data from UK general practices (n=1857, representing a practice population of 13.1 million registered patients) using the GRASP-AF tool. Only 55% of patients with high-risk AF (CHADS₂ ≥2) were receiving oral anticoagulation (OAC) therapy, whereas a further 34% of patients with no known contraindication did not receive OAC therapy⁴².

The NOACs have altered the landscape in terms of stroke prevention management by increasing the available options for patients. These agents exhibit some important practical advantages over traditional therapy (e.g. no requirement for routine anticoagulation monitoring, simple fixed dosing oral regimens, fast onset of action, fewer drug reactions and no food interactions), leading to their increased uptake in primary care.

Key patient groups who are likely to benefit from the NOACs include patients poorly controlled on VKAs, those predicted to require medications that interact with VKAs (e.g. patients who require frequent antibiotics), those without severe renal impairment or those with a prior ischaemic stroke while receiving a VKA with an adequate INR. These agents could also be a good choice for patients living a considerable distance from their local hospital or surgery and commuters. The NICE guidelines state that primary care clinicians should consider clinical features and patient preference before deciding on the most appropriate option for patients²². In addition, cost may be important in some settings. All of the NOACs have demonstrated cost-effectiveness versus warfarin, and although cost models vary by country, there is little doubt that these agents provide cost-effectiveness largely through the number of adverse events avoided and their associated costs⁴³.

Choice of anticoagulant: which to choose?

The demonstration of a favourable benefit–risk profile (stroke prevention vs bleeding events) in large phase III studies involving over 70,000 patients has resulted in the regulatory

approval of apixaban, dabigatran, edoxaban and rivaroxaban⁴⁴⁻⁴⁷ for the prevention of stroke and systemic embolism in patients with non-valvular AF and one or more risk factors.

Overall, NOACs have demonstrated an improved benefit compared with warfarin, with lower rates of intracranial haemorrhage (for all NOACs) and similar or superior efficacy for stroke prevention⁴⁴⁻⁴⁸. Statistically significant relative risk reductions (RRRs) in the incidence of fatal bleeding events were seen with low-dose dabigatran (110 mg twice daily [bd]; RRR=42%), both tested doses of edoxaban (30 mg once daily [od] and 60 mg od; RRR=65% and 45%, respectively) and rivaroxaban (20 mg od; RRR=50%)^{46,47,49}; rates of fatal bleeding were also lower in patients treated with apixaban compared with warfarin (34 patients vs 55 patients, respectively)⁴⁴. These data are promising, especially considering the current lack of a specific antidote for any of the NOACs, and it is likely that the very short half-life of these drugs play an important role in mitigating the bleeding risk.

Owing to a lack of head-to-head comparisons between the NOACs in phase III clinical trials, patient characteristics, drug compliance, tolerability issues and cost may be important considerations¹. In addition, subanalyses of phase III trial data for rivaroxaban, apixaban and dabigatran indicate that the challenging-to-treat patient groups often encountered by primary care clinicians can be treated effectively and safely with the NOACs (Table 2). A recent meta-analysis showed a similar treatment effect for almost all subgroups encountered in clinical practice; NOACs appeared to be at least as effective as VKAs in reducing the risk of stroke and systemic embolism and no more hazardous in relation to the risk of major bleeding events, irrespective of patient co-morbidities⁵⁰.

Table 2. Novel oral anticoagulants studied in key patient subgroups*

Subgroup analysis	Rivaroxaban	Dabigatran	Apixaban
Factors related to disease	ROCKET AF	RE-LY	ARISTOTLE
Heart failure	✓ ⁵⁹	✓ ⁶⁰	✓ ⁶¹
Renal impairment	✓ ⁶²	✓ ⁶³	✓ ⁶⁴
Prior stroke	✓ ⁶⁵	✓ ⁶⁶	✓ ⁶⁷
VKA-naïve	✓ ⁶⁸	✓ ⁶⁹	✓ ⁷⁰
Prior MI or CAD	✓(prior MI) ⁷¹	✓(CAD or prior MI) ⁷²	✓CAD ⁷³
PAD	✓ ⁷⁴	—	—
PK/PD	✓ ⁷⁵	✓ ⁷⁶	—
East Asian patients	✓ ⁷⁷	✓ ⁷⁸	⁷⁹
Elderly	✓ ⁸⁰	✓ ⁴⁹	✓ ⁸¹

Major bleeding predictors	✓ ⁸²	—	—
Obesity	—	—	—
Diabetes	✓ ⁸³	✓ ⁸⁴	✓ ⁸⁵
Valvular heart disease	✓ ⁸⁶	—	✓ ⁸⁷
Paroxysmal versus persistent AF	✓ ⁸⁸	✓ ⁸⁹	✓ ⁹⁰

*No subgroup analyses have been presented for edoxaban **Key:** AF = atrial fibrillation; ARISTOTLE = Apixaban for Reduction In STroke and Other ThromboemboLic Events in atrial fibrillation; CAD = coronary artery disease; CHADS₂= Congestive heart failure, Hypertension, Age ≥75 years, Diabetes, Stroke (doubled); MI = myocardial infarction; PAD = peripheral artery disease; PK/PD = pharmacodynamics/pharmacokinetics; RE-LY = Randomized Evaluation of Long-term anticoagulation therapy; ROCKET AF = Rivaroxaban Once daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation; VKA = vitamin K antagonist

Because patient selection in clinical trials is based on strict inclusion/exclusion criteria, patient populations in such studies are not always representative of patients routinely seen in real-world practice. In addition, bleeding events may be managed differently in clinical trials versus routine clinical practice. Real-world data are, therefore, needed to help validate drug safety and effectiveness in unselected patient populations. Following phase III clinical trials and the widespread approval of the NOACs in stroke prevention in patients with non-valvular AF, real-world experience has been steadily accumulating. The current real-world data for rivaroxaban, apixaban and dabigatran have been very reassuring and bridge the evidence gap between clinical studies and real-world experience^{33-35,51-57}.

The lack of routine coagulation monitoring with NOACs does not remove the necessity for regular follow-up. Instead, the frequency of visits can be tailored according to patients' clinical characteristics and needs. NOACs are all partially eliminated by the kidneys; therefore, regular monitoring of renal function is important either to use a lower recommended dose of these drugs or to avoid them. For example, renal function should be monitored every 6 months in patients who have stage III chronic kidney disease (creatinine clearance [CrCl] 30–60 ml/min)⁵⁸. Apixaban, rivaroxaban and edoxaban are not recommended in patients with CrCl <15 ml/min, and dabigatran is contraindicated in patients with CrCl <30 ml/min^{13,15,17,19}. Reduced-dose regimens of NOACs are recommended for patients at higher risk of bleeding events, including those with reduced renal function. For example, a reduced apixaban dose of 2.5 mg bd is indicated in patients with at least two of the following characteristics: age ≥80 years,

body weight ≤ 60 kg or serum creatinine ≥ 1.5 mg/dl (133 $\mu\text{mol/l}$); a reduced rivaroxaban dose of 15 mg od is indicated in patients with CrCl 15–49 ml/min⁵⁸; edoxaban is recommended at a reduced dose of 30 mg od in patients with CrCl 15–50 ml/min and contraindicated in patients with CrCl >95 ml/min⁵⁸; and a reduced dose of 110 mg bd dabigatran should be considered in patients with CrCl 30–50 ml/min who are at a high risk of bleeding⁵⁸. Follow-up visits should also systematically document patient compliance, thromboembolic and bleeding events, side-effects, co-medications and blood test results⁵⁸.

Conclusions

The NOACs have demonstrated favourable benefit–risk profiles in large phase III trials, and these findings have been supported by real-world studies involving unselected patients, including those deemed challenging to treat. The NOACs also address many of the limitations associated with VKA use, thus assisting with their integration into clinical practice for stroke prevention in patients with non-valvular AF. In addition, the results from subgroup analyses should provide primary care clinicians with the confidence to manage stroke-prevention strategies in a wide variety of patients with AF.

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Competing Interests

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Multiple ring enhancing lesions in brain: Neurocysticercosis or Tuberculoma? An extremely unusual / uncommon radiological presentation of a common disease: central nervous system tuberculosis

Manjunath M N, Bhakyalakshmi, Lakshmi, Chaitanya and Sharanya

Abstract

Cerebral tuberculomas is a rare and serious form of tuberculosis (TB) due to the haematogenous spread of Mycobacterium Tuberculosis (MT). Symptoms and radiologic features are nonspecific, leading sometimes to misdiagnosis. Multiple ring-enhancing lesions in the brain often raise many questions about the true diagnosis. It can present as tuberculous meningitis with complications such as infarctions of cerebral cortex, cranial nerve dysfunction, brain stem being the site of greatest involvement, hydrocephalus, cerebral edema and tuberculoma. The clinical progression of tuberculous meningitis may be rapid or gradual. Rapid progression is more often seen in young children. The diagnoses can be difficult early in its course and radiographic studies can aid in diagnosis. Tuberculoma may be confused with Neurocysticercosis radiologically, however various distinguishing features exist.

We present a case of CNS tuberculosis presenting as multiple tuberculomas causing great difficulty to distinguish with other similar radiological lesions.

Keywords: Tuberculoma, Neurocysticercosis, Gene-Xpert, Ring enhancing lesions

Abbreviations: MT- Mycobacterium Tuberculosis, AFB- Acid fast bacilli, ATT- Anti tubercular therapy, EVD- External ventricular drain

Case Summary

Three and half year old male child presented to PICU, Narayana health BANGALORE, with a short history of fever of 8 days with headache and cough for 2 days. At admission the child was febrile, dull looking, haemodynamically stable with no meningeal signs or focal neurological deficit. He was admitted and evaluated for the cause of fever. Same day child developed generalized seizures along with fever, hence a possibility of meningitis or electrolyte imbalance (hyponatremia) kept as child had initial serum sodium of 128meq/l. The cause of hyponatremia was looked into and child managed with antiepileptic drugs and 3% normal saline infusion. The initial sepsis screen was in-conclusive and CSF analysis showed 3 lymphocytes with low glucose and elevated protein levels, hence partially treated meningitis was considered (as h/o admission to a hospital for 3 days prior to admission in our hospital). The antimeningitic dose of IV antibiotics were given. On day 3 of admission child developed meningeal signs with worsening sensorium, hence neuro imaging was done (MRI brain) which showed multiple well defined ring enhancing lesion at bilateral central and cerebellar hemisphere, thalamus, pons with mild perilesional edema. This radiological picture suggested a possibility of neurocysticercosis, however the clinical picture did not match with the same, hence pediatric neurology opinion was taken and simultaneous workup for tuberculosis were started. Child was also started on IV steroid. A strong possibility of CNS toxoplasmosis was kept by neurologist based on radiological picture. The workup for TB

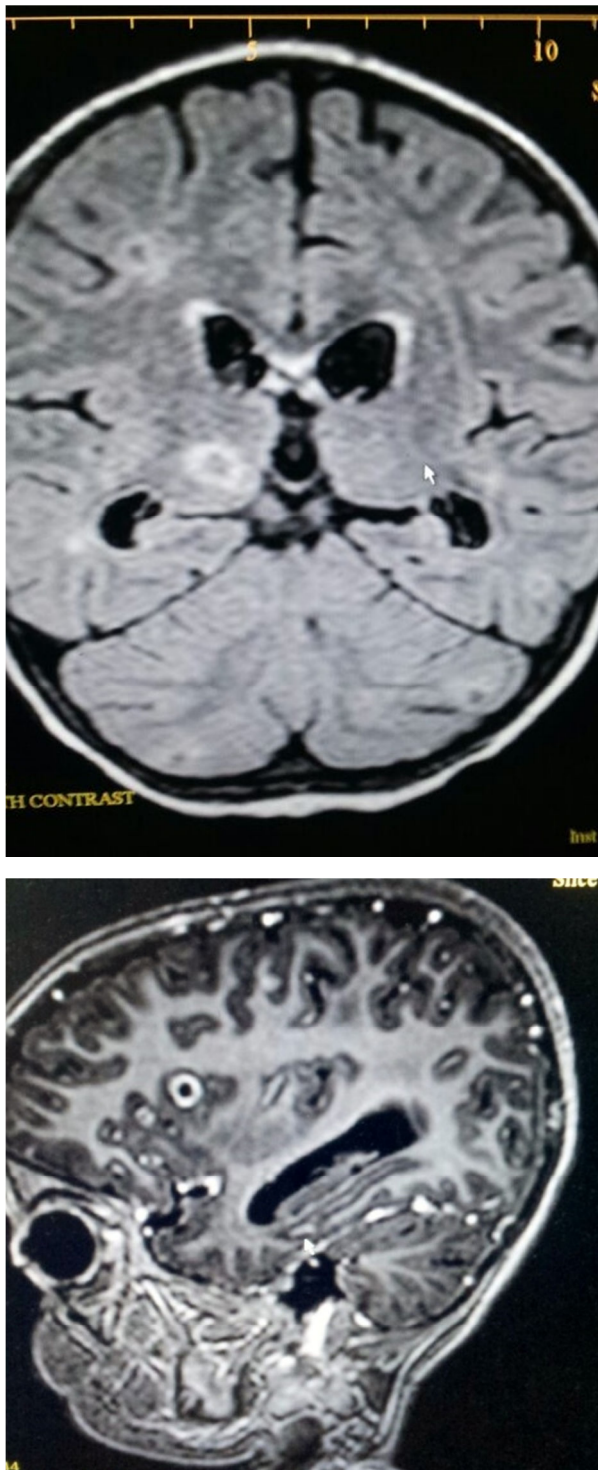
was inconclusive (negative mantoux, normal ESR, negative gastric aspirate for AFB) however child was empirically started on category II ATT in view of deteriorating clinical state. Repeat CSF evaluation showed increasing cell counts and similar biochemical picture as before, the sample was also send for Gene-Xpert (DNA amplification study). On day 6 of admission child developed lethargy and drowsiness hence antiedema measures were initiated. Same day he developed tonic posturing with unequal pupil, hypertension and bradycardia indicating raised Intracranial pressure (ICP), for which he was intubated and ventilated and urgent repeat CT head was done which showed increase in ventricular size and hydrocephalus. Immediately EVD was put by neurosurgeons after which there was gradual improvement in child's condition and he was extubated within 48 hours. The reports showed negative HIV and toxoplasma serology and positive CSF gene study for AFB confirming the diagnosis of CNS tuberculosis, hence ATT and antiedema measures were continued and the EVD was later converted into VP shunt. Child by 2nd week of illness became afebrile with improved sensorium and function.

Discussion

Tuberculosis remains a leading cause of morbidity and mortality in the developing world. CNS involvement is thought to occur in 2-5% of patients with tuberculosis and up to 15% of those with AIDS related tuberculosis^{1,2}. Although CNS involvement by tuberculosis is seen in all age groups, there is a predilection for younger patients, with 60-70% of cases occurring in patients younger than 20 years of

age². Haematogenous spread from the lungs or gastrointestinal tract is most common, leading to small subpial or subependymal infective foci. These are termed Rich foci and form a reservoir from which intracranial manifestations may arise^{3,4}. Tuberculomas often present with symptoms and signs of focal neurological deficit without evidence of systemic disease. The radiologic features are also nonspecific and differential diagnosis includes malignant lesions, sarcoidosis, pyogenic abscess, toxoplasmosis and cysticercosis.^{5,6}

Fig 1 & 2: MRI showing multiple ring enhancing lesions



Regarding treatment, the Center for Disease Control and Prevention recommends 12 months of treatment for CNS TB

when the MT strain is sensitive to all drugs.⁷ However numerous variables can affect the response of the disease to therapy and it has been suggested that treatment duration should be tailored to the radiological response.⁸ After 12 months of treatment more than two-thirds of the patients still have contrast enhancing lesions. Although it is not clear if this represents an active lesion or just inflammation, continuing treatment is probably prudent. Total resolution of the tuberculoma is observed when scans demonstrate no enhancing lesions or only an area of calcification.⁸

In the case described above child had tubercular meningitis, multiple tuberculomas, hydrocephalus and raised ICP. Although clinical presentations were suggestive of same, however the radiological picture and initial CSF finding raised suspicion is diagnosis. As tuberculoma and NCC shows many common clinical features, there are few distinguishing features such as the cysticercosis is smaller, less perilesional edema, multiple numbers and less of midline shift as compared to tuberculoma. However in our patient the multiple tuberculomas gave a suspicion of NCC. It was only gene expert which confirmed our diagnosis.

Hence clinical cases like Tuberculoma, the radiological findings of which can usually be distinguished from other common illness like Neurocysticercosis or Toxoplasmosis, sometimes pose challenge in terms of radiological diagnosis suggesting the need for detailed evaluation to reach the diagnosis and guide treatment.

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None declared

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Lymphoplasmacyte rich meningioma-a rare morphological variant of meningioma

Manveen Kaur, Varsha Dalal, Karam Chand Sharma, Avninder Singh

Abstract

Lymphoplasmacyte-rich meningioma (LPM) is a rare variant of meningioma accounting for less than 1% of all meningiomas. It is characterized by extensive infiltrate of lymphocytes and plasma cells often obscuring the meningeothelial component. We report a case of a 21-year-old male who presented with a solid cystic lesion in the right fronto-parietal region. Histopathological and immunohistochemical examination finally helped in reaching the diagnosis of lymphoplasmacyte-rich meningioma. Recognition of this entity is of paramount importance to guide appropriate therapy and management.

Keywords: lymphoplasmacyte, meningioma, intracranial

Abbreviations: LPM- Lymphoplasmacyte- rich meningioma; WHO- World Health Organisation; IHP- idiopathic hypertrophic pachymeningitis; EMA- Epithelial membrane antigen

Introduction

Meningiomas are common intracranial neoplasms with a wide range of histopathological appearances. The WHO classification of tumours of the central nervous system recognises 15 subtypes of meningiomas, of which meningeothelial, fibrous and transitional subtypes are most common. Lymphoplasmacyte-rich meningiomas (LPM) are rare WHO subtype that belong to Grade I meningiomas.¹ The estimated incidence is less than 1% of all meningiomas.² LPM usually occurs in young and middle age patients, with most common locations being cerebral convexities, skull base, parasagittal area within the superior sagittal sinus, cervical canal, optic nerve and tentorium.³ Histopathological examination shows extensive infiltrates of lymphocytes and plasma cells often obscuring the meningeothelial component.

Case report

A 21-year-old man presented with a history of headache since 4 months. It was a dull pain not associated with vomiting, seizures or visual symptoms. The patient did not have any features suggestive of cranial nerve involvement. Physical examination was unremarkable except for the presence of papilloedema. Non-contrast CT scan showed a large isodense lesion with peri-lesional oedema and eccentric enhancing nodular component in the right fronto-parietal region (Figure 1). A radiological diagnosis of glioma with mass effect and shift to left was rendered. A right frontoparietal free bone flap craniotomy was performed. Operatively, a well encapsulated tumour probably arising from the dura mater was found. Gross total removal of the tumour was done and the excised tumour

was sent for histopathological examination with a provisional clinical diagnosis of meningioma.

Histopathological examination revealed a tumour arranged as sheets and whorls of meningeothelial cells without any mitoses or atypia. A dense infiltrate of lymphocytes and plasma cells was seen in large areas of the tumour (Figure 2).

On immunohistochemistry, tumour cells were positive for epithelial membrane antigen (EMA) (Figure 3) and vimentin. The lymphoplasmacytic infiltrate contained mixture of CD3 and CD20 positive lymphocytes. A diagnosis of lymphoplasmacyte- rich meningioma was given.

Discussion

Meningiomas are common neoplasms accounting for 24-30% of all primary intracranial tumours. They arise from the arachnoidal cells, and are typically attached to the inner surface of the duramater.¹ Most of the meningiomas are benign, corresponding to WHO grade I and associated with a favourable clinical outcome. LPM is a rare low grade histopathological subtype of meningioma, usually seen in younger patients, with the mean age of onset being 34 years.^{4,5} The patients with LPM have variable clinical manifestations according to the location of the tumour. The common presentations include headache, hemiparesis, seizure, vomiting, dizziness, visual disturbance, dyscalculia, dysgraphia and slurred speech.³ Although the natural history of LPM is often over one year, few cases might occur in short duration due to inflammatory cell infiltration and oedema.⁶ Systemic haematological abnormalities such as hyperglobulinemia and

iron refractory anaemia have been documented in some patients with LPM, believed by some to be due to the plasma cell infiltrate.^{3,6,7}



Figure 1: Non-contrast CT scan showing a large isodense cystic lesion with perilesional oedema and eccentric enhancing nodular component in the right frontoparietal region

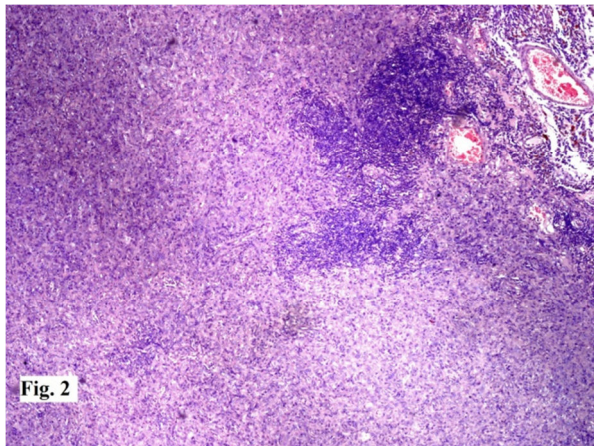


Figure 2: Tumour arranged as sheets and whorls of meningothelial cells without any mitoses or atypia. A dense infiltrate of lymphocytes and plasma cells seen in large areas of the tumour (H & E x 100)

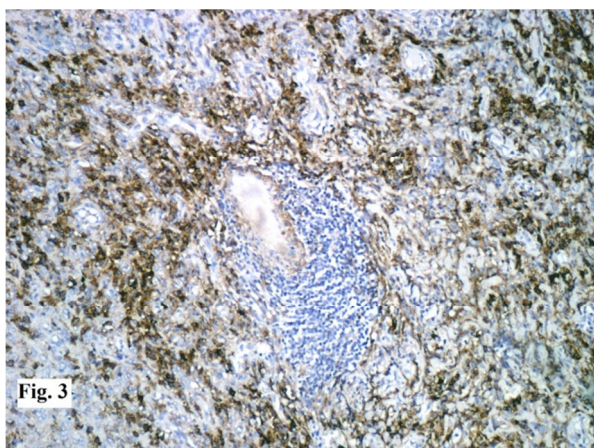


Figure 3: Tumour cells positive for epithelial membrane antigen (x 200)

Radiologically, LPMs are usually globular, highly vascular, contrast-enhancing, and dural based tumours. The typical

characters of LPM on MRI are isointense lesions on T1-weighted images and hyperintense lesions on T2-weighted images, with a strong homogenous enhancement after the administration of gadolinium; obvious peritumoural brain oedema and dural tail signs.³ Sometimes, cystic component and heterogeneous enhancement may also be encountered, making pre-operative diagnosis difficult, as in our case.⁸

On microscopic examination, this tumour is characterised by a conspicuous infiltrate of lymphocytes and plasma cells, sometimes completely obscuring the tumour cells. The massive infiltration of lymphocytes and plasma cells has been postulated to play a central role in the development of brain oedema associated with LPM. The origin of this tumour (neoplastic or inflammatory) is unclear, so it is considered closer to intracranial inflammatory masses rather than typical meningiomas.⁷

The differential diagnoses include collision tumour of meningioma and plasmacytoma, inflammatory pseudotumour, idiopathic hypertrophic pachymeningitis (IHP), and intracranial plasma cell granuloma.^{3,7} The use of staining for EMA and vimentin is useful in indicating the meningothelial origin of the tumour, and differentiates LPM from other intracranial lesions.⁹

The pathological findings of IHP usually include thickened fibrotic dura mater with marked infiltration of lymphocytes and plasma cells, occasionally accompanied with small islands of meningothelial proliferation mimicking those of LPM. Localised nodular lesion can sometimes rule out this diagnosis in that IHP usually shows diffused lamellar thickenings or plaque-like features.⁴

Chordoid meningiomas often contain regions that are histologically similar to chordoma, with cords or trabeculae of eosinophilic, vacuolated cells in a background of abundant mucoid matrix background.³ Detailed histological studies can aid the differential diagnosis. The plasma cell component is not neoplastic and thus plasmacytoma with reactive meningothelial hyperplasia or a collision tumour involving meningioma and plasmacytoma can both be excluded.¹⁰

The knowledge of this rare entity is important to avoid its underdiagnosis as an inflammatory pseudotumour or plasma cell granuloma and overdiagnosis as a plasmacytoma.

Competing Interests

None declared

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Correspondence - Another case report of a unusual reaction to IV Pethidine

Premila Hirubalan and Pierre Christian Ip-Yam

A 38 year old BMI 20.2 ASA 2 female underwent an elective robotic-assisted laparoscopic extirpation of endometriosis and dissection of endometriomas. Her medical history included hypertension, migraine, atopic dermatitis, sciatica, cervical spine spondylosis and dysplastic spondylolisthesis of L4/5. Of note, the patient had allergies to Aspirin (causing angioedema), Morphine and Tramadol (both causing generalized rash).

An 18gauge IV cannula was inserted into the cephalic vein at the left wrist, and connected to a bag of Hartmann's solution. The patient was induced with Propofol 100mg, Rocuronium 30mg and a Remifentanyl infusion running at Ce 1ng/mL. Cefazolin 2g and Dexamethasone 4mg were also administered post-intubation. No rashes were noted on the patient's skin, and her arms were subsequently enclosed with green towels by her sides for the duration of the surgery. During the procedure, the patient was sustained in a steep trendelenberg position, with her face and eyes checked periodically. No rashes were noted on any exposed skin. Peri-operatively, she was maintained with O₂/air/Desflurane, top-up doses of Rocuronium, and titration of the Remifentanyl infusion. At the end of the surgery, the patient was administered Ondansetron 4mg and Pethidine 50mg (in 2mL), and reversed with Neostigmine 2.5mg and Glycopyrrolate 0.4mg. The patient's arms were subsequently exposed in preparation for transfer, and it was noted that she had developed severe erythema and inflammation in specific tributaries of the cannulated vein (Figure 1). The patient was extubated uneventfully five minutes later, and did not complain of any symptoms systemically or pertaining to the cord inflammation. She was monitored in recovery for three hours post-op, and the inflammation subsided significantly 90 minutes post-op (Figure 2) and completely 150 minutes post-op (Figure 3).

There have not been many reports of such a reaction in published materials, and we take this opportunity to provide further pictorial evidence of the possible sequelae of IV administration of a high concentration Pethidine solution. The variances in analgesia effectiveness and potential side effects between Morphine and Pethidine are negligible². As such, and given that Pethidine is commonly used as a mode of analgesia on our wards and in the peri- and immediate post-operative periods when other classes of drugs are contraindicated, we hope to provide further pictorial support of such an extraordinary reaction for other interested clinicians. It is also interesting to note that in both cases the patient was female,

around 40 years old, had a thin body structure, had an atopic tendency, and the concentration of injected solution was higher than 10mg/mL. Additionally, these are known factors believed to increase reaction severity^{3 4}. We acknowledge that 3 other drugs were administered at the same approximate time as Pethidine, and as such any of the 4 medications could be culprit to the reaction, although this is unlikely as our patient had been given those medications in previous procedures with no issues or complications.

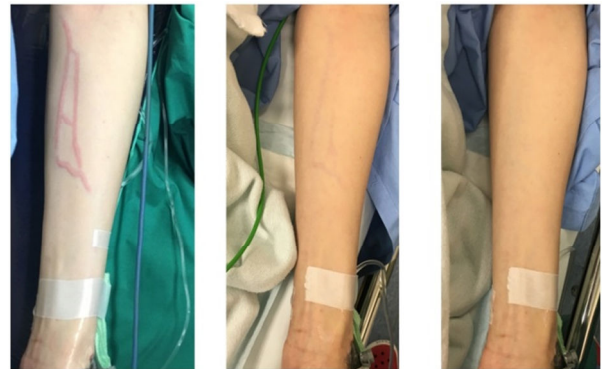


Figure 1: Post-op, Figure 2: 90 mins post-op, Figure 3: 150 mins post-op

Competing Interests

None declared

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Colonic Metastasis from a Breast Carcinoma, an Unusual Colonoscopic Finding

Wadah Ali, Zakir K Mohamed and D Thekkinkattil

Abstract

Breast cancer is a leading cause of cancer deaths in females in the UK. Distant metastases are the commonest cause of death and the lung, liver and bones are the most common sites. Metastases to the gastrointestinal (GI) tract are rare with colonic metastases even rarer and as such may pose a diagnostic challenge. They are much less common than primary intestinal tumours. Here, we report an interesting case of a patient who presented with colonic metastasis over six years following treatment of a breast carcinoma.

Keywords: Breast cancer, colon metastasis, colonoscopy

CASE REPORT

A 61-year-old lady underwent a modified radical mastectomy and axillary clearance in 2008 for a carcinoma of the left breast. Histopathology examination revealed two tumours within the left breast; a 16mm Grade 2 lobular carcinoma with probable vascular invasion and a 9mm Grade 1 infiltrating ductal carcinoma with no vascular invasion. She had clear resection margins. 21 out of 34 removed lymph nodes were positive for metastatic deposits. The tumour was oestrogen receptor positive and HER2 negative. She was staged as T1 N3a Mx and the tumour had a Nottingham Prognostic Index of 5.32. Metastatic workup revealed no distant metastasis.

Postoperatively, she required aspiration of a seroma but her recovery was otherwise satisfactory. She received adjuvant chemotherapy in the form of three cycles of Fluorouracil, Epirubicin and Cyclophosphamide and 3 cycles of Docetaxel. In addition, she had postoperative radiotherapy to the chest wall and supraclavicular fossa (40 Gy in 15 Fractions over 3 weeks) and hormonal therapy with Letrozole 2.5mg once daily.

The patient opted to undergo a prophylactic right mastectomy in 2010. She was regular in follow up and appeared to be free of disease recurrence for 6 years.

Her past surgical history included abdominal hysterectomy and bilateral salpingo-oophorectomy for fibroid disease as well as varicose vein stripping. She is a non-smoker and doesn't consume alcohol. She had a family history of colon and cervical cancer in her uncle and sister respectively.

The patient visited the surgical outpatient clinic complaining of abdominal cramps, altered bowel habits and fatigue of a few months duration. There was no associated rectal bleeding, haematemesis, melaena, weight loss or urinary symptoms. Physical examination was unremarkable but she was noted to have gradually worsening renal function. Her symptoms were at first attributed to side effects of intravenous antibiotic

treatment, which she received during an admission for cellulitis. She had already undergone an upper GI endoscopy which showed oesophagitis and ulceration; biopsies were within normal limits. She received treatment with proton pump inhibitors but her symptoms persisted.

A non-contrast abdominal CT scan was done, on account of her poor renal function, which showed bilateral hydronephrosis and thickening of the postero-superior aspect of the bladder wall. Considering the limitations of the non-contrast study, there were no other abnormalities. A colonoscopy was also done to investigate her altered bowel habit and it revealed a benign-looking stricture in the sigmoid about 25cm from the anal verge which was easily bypassed by the scope.



Figure 1. Benign stricture on flexible sigmoidoscopy

Biopsies of the sigmoid stricture showed an infiltrate of small to medium sized tumour cells in the submucosa, which had an Indian file pattern. They were positive for AE1/AE3 (pancytokeratins) and negative for CD68. They were positive for CK7 and negative for CK20, strongly positive for oestrogen receptors and HER2 negative. Taken in conjunction with the

patient's past history of an invasive lobular carcinoma of the breast, the appearance was consistent with a metastatic lobular carcinoma.

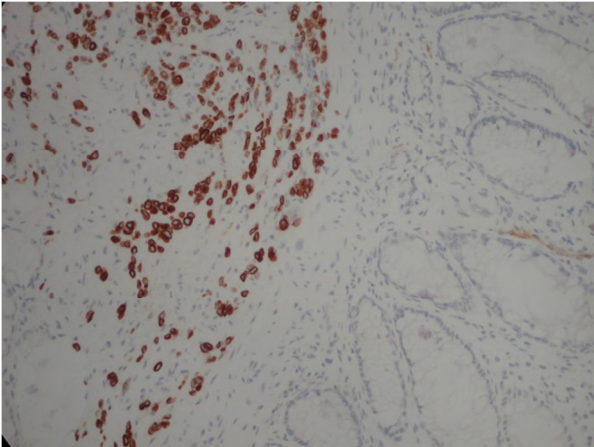


Figure 2. Clusters and cords of cells with positive cytoplasm for the cytokeratin immunostain CK7. Although the classical 'Indian filing' of lobular carcinoma is not well seen, the image clearly demonstrates that the large bowel glands are negative (normally CK20+, CK7-) and that the infiltrate is beneath the glandular mucosa (i.e. not originating from dysplastic glands within the mucosa and raising the possibility of infiltration from outside the bowel wall). The magnification is x200. Lobular carcinoma is usually CK7 +, CK20 -, ER +.

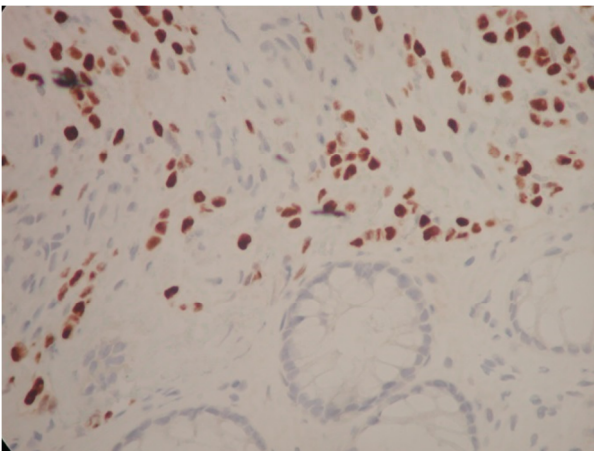


Figure 3. The same cells with their nuclei staining positively with an immunostain to oestrogen receptors. There are a few short chains of 'Indian filing' with the cells appearing rather rectangular in shape with straight margins. You can make out slight 'moulding' of the nuclei as they press against one another. The magnification is x 400.

The patient required a right nephrostomy and a cystoscopy with left double J ureteric stent insertion to address her hydronephrosis and deteriorating renal function before undergoing restaging of her disease.

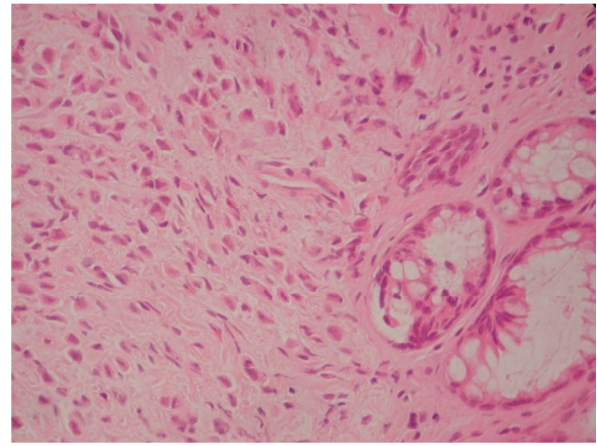


Figure 4. Haematoxylin and Eosin section at 400 magnification. This shows a diffuse infiltrate of single cells with eccentric nuclei.

DISCUSSION

In patients with history of breast cancer, isolated GI metastases are less common than benign disease processes or second primaries of the GI tract.^{1,2} In a retrospective review, 73 out of 12001 cases of breast cancer had gastrointestinal metastases, out of which 24 were to the colorectum³ and invasive lobular carcinoma was the commonest histological subtype.^{3,4} However, sixteen percent of patients with breast cancer have GI metastases at postmortem examination¹.

There might be a long interval of time between the diagnosis of breast cancer and development of gastrointestinal metastasis which together with their rare occurrence and nonspecific clinical and radiological manifestations adds to the diagnostic challenge. The median interval between the diagnosis and the development of GI metastasis was reported to be 6 years (range 0.25 to 12.5 years) by Schwarz *et al*⁵ with 25 years being the longest reported in the literature.⁶ Because of this long interval the history of a primary breast cancer can be missed. This also highlights the importance of long term follow up and maintaining an index of suspicion when these patients develop GI symptoms.

In our case, the interval between the diagnosis of breast cancer and colonic metastasis was 81 months. Her GI symptoms were initially attributed to side effects of antibiotic treatment for cellulitis and dyspepsia before investigating her with a colonoscopy. Even at colonoscopy the appearance was that of a smooth benign-looking stricture which did not seem to harbour any sinister pathology

Histological examination is probably the most reliable tool to make a diagnosis and it is prudent in such cases to compare the specimen with the original breast tumour. In this case, there were two primary tumours; an invasive ductal carcinoma as well as a lobular carcinoma but the metastatic disease favoured the lobular component, which is consistent with other published reports in the literature. The reasons why metastases favour lobular carcinoma are poorly understood. One explanation is the loss of E-cadherin expression, a molecule involved in

cellular adhesion, in invasive lobular carcinoma⁷. A similar case in which the primary was a mixed ductal and lobular type with lobular subtype colonic metastasis was reported by Uygun *et al.*⁸ Immunohistochemistry can also help in establishing a diagnosis. Metastatic breast cancers tend to be positive for Oestrogen or Progesterone receptors as well as Gross Cystic Disease Fluid Protein-15.^{9, 10} It is, however, worth noting that primary colonic cancers can be oestrogen receptor positive in 30 to 70% of cases.¹¹

Accurate histopathological diagnosis probably saved our patient an unnecessary surgical treatment for a primary colonic neoplasm as the main focus of her treatment should be systemic therapy for metastatic breast cancer.

CONCLUSION

GI tract metastases from breast cancer are a rare occurrence. The patients may present after a long interval from the original diagnosis and the clinical and radiological features are nonspecific with the diagnosis often established on histological examination. Moreover, the history of breast cancer may not be elicited in all cases and these patients may present to a gastroenterologist or colorectal surgeon rather than a breast surgeon or oncologist. Therefore, remaining vigilant to this possibility is advised in any patient with a history of breast cancer who presents with unexplained GI symptoms.

Competing Interests

None declared

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