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"There are three classes of men; lovers of wisdom, lovers of honour, and lovers of gain."

Plato (427 BC – 347 BC)
Greek philosopher

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Editorial

World Cancer Day 2019 – Don't Stop Thinking About Tomorrow

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"The philosophies of one age have become the absurdities of the next, and the foolishness of yesterday has become the wisdom of tomorrow." Sir William Osler

World Cancer Day founded and led by the Union for International Cancer Control (UICC) is a clarion call, with multiple initiatives and campaigns, to governments, health bodies, advocacy groups, grassroot organisations, communities and individuals to conquer the world's biggest disease killer in the 21st century—so as to create a cancer-free world.

A cancer-free world—really? A common question we are asked as oncologists is whether a cure for cancer has been found or is just around the corner. Reflexively, we hear ourselves answer with a long prefix—cancer is not one but a very diverse array of very heterogeneous disease types with underlying common immortalising hallmarks.[1] On deeper reflection, there is much to be gained in framing some of the most pressing issues in cancer care today through the lens of this fundamental question.

In the 21st century, the modern approach to cancer evaluation and treatment emphasises the heterogeneity between and within cancer subtypes which we can classify much more clearly and deeply than 20 years ago. Above and beyond such fine-grained taxonomy, tumour genome sequencing and molecular pathology—currently widely available at much lower cost—are performed with growing frequency to identify targetable genetic alterations or biomarkers to guide more specific therapy—a strategy called precision medicine. Patients are unique individuals; tumours, as entities arising within these individuals, and as the direct result of stochastic events and dynamic evolutionary processes, have equally one-of-a-kind features not captured by common classification schemes based on organ site, cell of origin or histomorphology. Patients should thus be treated based on changes unique to particular individual tumours independent of histologic subtype. Such an approach forms the basis of "basket" clinical trials aiming to match patients to treatments targeting specific aberration(s) that their tumours harbour. While there have been some dramatic successes, druggable oncogenic driver mutations occur in less than 15% of cancers, while the proportion of patients with demonstrated meaningful clinical benefit and improved survival remains low,[2] with significant concerns for the sustainability and feasibility of a broader more universal application.[3] Have we missed the fundamental and therapeutic woods for the trees?

The number of therapeutic agents against many cancers has increased significantly. These advances have undoubtedly improved outcomes for some patients—at times very profoundly—and should certainly be celebrated. A contrarian view may be that a genuinely epochal advance would identify and successfully address the truly fundamental vulnerabilities that underpin all or most neoplastic processes, success that would reflect our consummate apprehension and mastery over malignancy by going beyond the complex genetic makeup of individual tumours to exploit elemental neoplastic dependencies universally—thus pivoting back to addressing cancer as a unitary entity. We would thus contend, controversially, that depersonalising cancer therapy—"a one size fits most" approach—would be much more transformative. The astounding developments in cancer immunotherapy in the past decade raised hopes for just such a major advance. Cancer immunoediting theory provided an elegant overarching framework to think about the immune system's complex relationship with cancer, both suppressing and abetting tumours in different contexts.[4] Monoclonal antibodies against immune checkpoints (for which the 2 lead discoverers earned the Nobel Prize for Medicine in 2018) ushered hope for the most successful therapeutic realisation of immune oncology yet—by resetting an individual's immune system following tumour immune escape; these antibodies would unleash the body's own previously stymied T cells to target neoplastic cells. As a field across a growing number of cancers, the successes with immune checkpoint inhibitors (ICI) have been spectacular and sustained for a very long period in some patients (supersurvivors). But the majority of patients with solid tumours especially, remain resistant to ICI.[5] The impact towards improving survival across so many cancers in such a short timespan notwithstanding, immunotherapy is not a panacea. Perhaps such an all-conquering approach will forever be out of our reach due to the inherent ontogenetic

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diversity and evolutionary dynamism of tumours. This should not diminish the scrupulousness and rigour with which we assess the impact and potential of current paradigms, including precision medicine.

And what of cure? About 50% of all cancers diagnosed globally can be cured. A substantial percentage of haematologic malignancies and germ cell tumours, in addition to the vast majority of early stage solid tumours (in some cases needing adjuvant therapy in addition to surgery) never recur following standard treatment, commonly with combination chemotherapy, bone marrow transplantation, targeted therapy led by the original "magic bullet" imatinib and biological agents. Nonetheless, even in such cases, oncologists can be hesitant to use the word cure, given examples of late recurrences across different tumour types, rare though these events may be.[6] The treatment of metastatic solid tumours is generally characterised as palliative, though ICI has induced durable disease remissions as long as beyond 10 years for some advanced solid tumours such as malignant melanoma. Twenty years ago, advanced melanoma was a universally fatal cancer with only months of median survival[7] and poor treatment options. Modern day cancer immunotherapy raises the possibility of some patients with advanced cancer being cured, or at least having their disease controlled and turned into a quieter, chronic disease, allowing patients to live good quality lives for years. The challenge remains to expand the group of patients for whom these durable remissions are achieved, or at least to identify them better. The significant (if not universal) success of ICI in advanced disease raises interesting questions about its role in earlier stages of disease. For example, the success with ICI in malignant melanoma—the immunogenic solid tumour poster child—has already led to its adoption as adjuvant treatment in resected stage III melanomas. Crucially, only one of the randomised adjuvant ICI trials in melanoma mandated ICI initiation at time of recurrence in the control arm to determine if survival differed between immediate ICI for all and deferred ICI only in those who recurred.[8]

The high cost of some breakthrough cancer therapies is a source of great concern. Cancer drugs overall cost more than drugs in any other medical specialty, and ample data demonstrates the significant adverse impact of financial toxicity on patients.[9] The world's majority of cancer patients come from low- and middle-income countries (LMICs), and access to optimal cancer treatments remains challenging in such LMICs. Over 70% of cancers in LMICs that result in premature death can be averted with achievable measures such as prevention, screening, early detection and basic cancer treatments. Yet even such programmes, medical services and infrastructure are wanting in many such countries. The recent development and approval of tisagenlecleucel—a chimeric antigen receptor (CAR) T cell therapy which genetically engineers a patient's own T cells to express a specific cell surface receptor targeting CD19 (a B cell receptor protein) that induces durable remissions in the majority of refractory B-cell acute lymphoblastic leukaemias—was a huge landmark development in cancer therapy, combining gene therapy and immunotherapy to spectacular effect in a setting that was, up until then, largely hopeless. The extremely high cost of this therapy, however—USD$475,000—raises many questions about how accessible such therapies will be. The unique strategy by the company that developed the therapy (Novartis), of charging only if patients have an initial response to therapy, does not significantly mitigate the impact of the cost on payers. The majority of patients have an initial response to therapy, but up to half of these patients will relapse within 1 year.[10] Unlike the explosion of knowledge in biomarkers to predict efficacy to immune checkpoint inhibitor therapy, predictive biomarkers in T cell therapy are still nascent.[5]

Cancer care is faced with 2 towering challenges—resolving the differences within and between cancers to achieve maximal therapeutic benefit, as well as bending the cost curve in cancer treatment. Successfully addressing them, rests, above all, on the unrelenting commitment to approach cancer equally as a disease of cells and genes, as one of individuals and society.

"I am and I will" is the 'power to the people' tagline for World Cancer Day 2019—asking of individual spirit, motivation and responsibility for our own health. Indeed, there is so much we can do to reduce the risk of cancer—exercise more, maintain an ideal body weight, sleep enough, eat right with less red meat and preserved foods, go for recommended cancer screening, stop smoking, motivate others and spread the good word. With worldwide cancer incidence still rising and poised to be the leading cause of global death this century, international bodies, governments, academic institutions, pharmaceutical companies and other stakeholders will need to implement strong cancer control policies, effective prevention strategies and improve access of evidence-based cancer care to all who need it.

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Editorial

Cancer in 2019 – Progress and Challenges – A Perspective

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Patients with cancer today are doing better than they ever have been in the past. Survival rates are higher; and survival time is longer for most cancers. The drugs and treatment are getting more effective with less toxicity. Supportive care is also getting better. So, patients are not just surviving longer but also living better with good quality of life. Through effective preventive measures and screening programmes, some cancers have even seen a reduction in incidence (for example, smoking-related lung cancer and hepatitis-related hepatocellular carcinoma). Indeed, cancer is no longer a death sentence for most, and some declare that it is the new chronic disease.[1]

In fact, the outlook continues to be rosy. In terms of the understanding of cancer biology and therapeutics, significant advancements are being made. A couple of years ago, immunotherapy was hailed by Science magazine as the scientific breakthrough of the year.[2] In 2018, the Nobel Prize for Medicine was awarded for work on immune checkpoint inhibitors.[3] These immune-based treatments harness the patient's immune system to eradicate tumour cells. The mechanism of the antitumour effect is different from traditional chemotherapy and small molecule inhibitor of signalling pathways (so-called targeted therapies), providing an important addition to the anticancer armamentarium that could potentially overcome resistance to chemotherapy and targeted therapies.

The Science magazine scientific breakthrough for 2018 is for single-cell analysis[4] which has allowed unparalleled insights into the heterogeneity of tumours and the microenvironment in cancer. The ability to study genetics at the single-cell level provides insights into the evolution of tumour cells and the composition of the tumour and its microenvironment, thereby allowing us to understand the clones that survive treatment and which are responsible for relapse. This type of technological precision and scientific advancement—coupled with the unparalleled spectrum of therapeutics targeting different aspects of cancer biology that are available today—offers real opportunity for precision oncology, where specific treatment can be tailored to provide maximal benefits to individual patients based on the biology of their cancer.[5]

With the increase in precision and breadth of biological information (genomics, epigenetics, proteomics, imaging, phenotypic data, etc.) coupled with the large array of therapeutic agents and their potential combination, we are now moving into an era of big data in oncology that lends itself to the use of artificial intelligence.[6] In the last couple of years, important studies have demonstrated the accuracy of artificial intelligence over human experts in diagnosing skin cancers, genetic defects in lung cancers and also optimal drug combinations for individual patients.[7,8]

Challenges

However, there remain significant challenges. Intra-tumoural heterogeneity and evolution result in acquisition of malignant capability of tumour cells and treatment resistance. This remains a common endpoint in most incurable cancers. In addition, these changes always seem to happen one step ahead of the therapy as they are either induced by the treatment or escape the effect of the therapy. To stay ahead, we need to have a way to visualise and assess tumour cells with relative ease and regularity. Clearly, biopsy of primary or residual tumour is not always feasible. The advance of liquid biopsy with the detection of circulating tumour cells or circulating cell-free deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) from tumour cells may be potential avenues to overcome the need for biopsy of the primary tumour. However, whether they are able to reflect the entire heterogeneity in the tumour is unclear.[9] In addition, the limit of sensitivity of the assay in the setting of residual disease may limit its use in the assessment of residual clone.

While the new advancements in scientific knowledge are exciting, it also highlights the complexity of cancer and the limitations in our current knowledge. As knowledge is vital to the development of therapeutic strategies, incomplete knowledge may be one of the key limitations in our current war against cancer. In recent years, the emergence of the

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importance of non-coding RNA in cancer biology (which some years back was considered as genomic "junk"),[10] of the immune system, the host microbiome on the immune system and the impact on tumour development and response to immunotherapy,[11] show that the knowledge base is constantly evolving. How much of the cancer universe is still "dark matter" and how significant these blind spots are remain as ongoing limitations.

Even with the knowledge that we have, we seldom profile tumours in a comprehensive manner. There tends to be an over-reliance on genomics, without an understanding of the functional relevance in a particular tumour. There is an assumption that a driver mutation (which is implied based on statistical analysis of genomic data) would always be important. Indeed, this may not always be the case.

As our knowledge is incomplete, there is a need for platforms where we can test treatment in an unbiased manner, agnostic to assumptions. The development of patient-derived xenografts[12] and oraganoid cultures[13] have provided useful platforms for such testing. The development of platforms to assess drug combinations in a rapid fashion have real clinical potential.[14] Nevertheless, good platforms for testing immunotherapy in vivo or in vitro is still challenging and lacking.

Lastly, despite great success in drug development for cancer in the last decade, this, on the whole is still quite empirical. As a result, the cost of drug development is high. The process leading to drug approval is also long. Traditional endpoints may take too long to achieve or large numbers of test subjects are needed to achieve statistical power (if the drug only benefits a subpopulation of patients). The identification of good surrogate endpoints and acceptance by regulatory agencies for drug approval would be important. The development of more adaptive trial designs[15] that incorporate biomarkers such as basket trials or umbrella studies are also potentially useful but would require acceptance by regulatory agencies for such trial designs and also a mindset change from academics and industry to collaborate rather than to compete. The recent trend to form large consortiums to tackle these issues are promising.

Challenges for Singapore

For Singapore, translating and implementing all these advances in a rationale and cost-effective manner is a significant challenge. One of the greatest challenges is managing cost of cancer care.

Early stage cancers are curable with simple, short-term treatments such as surgery, while advanced cancers are costly to treat and tend to require continuous treatment with more limited benefits. Early detection is, therefore, key. The most common cancers in Singapore—breast and colorectal—have well established screening methods and programmes. But the uptake rates for these screening are only about 30% in the at-risk population in Singapore. Raising the screening rates would be an important area that needs to be tackled.

There is concern that implementation of precision oncology will lead to higher cost. Certainly, the novel drugs and genomic techniques required are costly but these are being used today anyway (albeit in an empiric manner in most cases). If we can identify the best treatments that provide the most benefits for the individual patient each time, this will maximise the cost-effectiveness and reduce waste.

Many of the tests (for example, positron emission tomography-computed tomography [PET-CT], next generation sequencing-based genomic panels) and treatments (immune checkpoint inhibitors, proton therapy, chimeric antigen receptor-T [CAR-T] therapy) are very costly and do not benefit all cancers. As practitioners, oncologists and haematologists have a responsibility to use these assays and treatments in an appropriate way. It is our duty to educate patients and the public, rather than succumb to over-servicing just because patients ask for them. Developing an appropriate care framework for oncology is therefore critical. This is also an important aspect of keeping costs down.

The issue of costs and the overall roadmap to effectively deliver cancer care in Singapore in the coming years, while taking into consideration the progress and challenges will be tackled by the National Advisory Committee on Cancer (NACC), which has been convened by the Ministry of Health.

Conclusion

As I write this at the start of 2019, we have much to be thankful for in cancer and have much to look forward to. Challenges abound in our war against cancer that will require a concerted effort. The increase in national level collaboration between hospitals, government agencies, academics, industry and other key stakeholders to tackle cancer is gratifying and puts us in a good position to make the next leap.

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Original Article

Klebsiella Pneumoniae Visceral Organ Abscesses – Clinical Characteristics

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Abstract

Introduction: In recent years, *Klebsiella pneumoniae (KP)* has emerged as the predominant cause of pyogenic liver abscess in Asia. *KP*—as the causative microorganism in other visceral organ abscesses—is less described. In this study, we seeked to describe the clinical characteristics of *KP* visceral organ abscesses in our institution and evaluated the prescription practices of physicians with regard to antibiotic therapy. Materials and Methods: A retrospective analysis of patients with culture positive (blood or abscess aspirate) *KP* visceral organ abscesses from May 2014 to April 2016 requiring hospitalisation in Changi General Hospital was conducted. Results: A total of 140 adult patients with *KP* visceral organ abscesses were identified. The commonest site of involvement was the liver (77.9%), followed by genitourinary tract (20.7%). Diabetic patients were more likely to have liver abscesses, genitourinary abscesses, abscesses in 2 or more organs, genitourinary disease with abscess formation outside of the genitourinary tract, and endovascular infection. Patients with extended spectrum beta-lactamase producing *KP*, were more likely to have an obstructive lesion related to the site of the abscess. Overall mortality rate was 7.1%. Amongst survivors, the mean total duration of parenteral antimicrobial therapy was 2.5 weeks before switching to oral antimicrobial agents. Conclusion: Genitourinary tract is the commonest extra-hepatic site for visceral organ abscess in *KP* infections. Parenteral to oral switch of antimicrobial agents appears to be a safe and effective treatment option.

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Key words: Disseminated infection, Genitourinary abscess, Liver Abscess

Introduction

Klebsiella pneumoniae (KP) liver abscesses were first described in the 1980s in Taiwan.[1] Consequently, *KP* emerged as the predominant cause of pyogenic liver abscess in various other countries in East and Southeast Asia. Metastatic infections involving the lung, eye, central nervous system, musculoskeletal system and urinary system have been described.[2-4] Diabetes mellitus is a major risk factor for the development of *KP* liver abscesses and is associated with metastatic complications especially for non-K1/K2 strains.[5,6] *KP*—as the causative microorganism in other visceral organs—is less described despite its propensity for tissue invasion.

In this study, we sought to describe the clinical characteristics of patients with *KP* visceral organ abscesses (VOA) in our institution, with an emphasis on the influence of diabetes mellitus, and evaluated antibiotic prescription practices of managing physicians.

Materials and Methods

A list of patients with blood or abscess aspirate cultures positive for *KP* received from 1 May 2014 to 30 April 2016 was obtained from the Department of Laboratory Medicine, Changi General Hospital. We included all patients seen at our hospital, with blood and/or abscess aspirate cultures positive for *KP,* in whom concomitant imaging evidence of

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VOA was demonstrated through either ultrasound, computed tomography or magnetic resonance imaging. The case records of these patients were then retrospectively analysed to evaluate their clinical characteristics and outcomes.

Statistical analysis was performed using the SPSS version 25 statistical software package. Chi-squared test and Fisher's exact test were used to test for associations in categorical variables whereas the Mann-Whitney U test was used to test for differences in continuous variables. $P < 0.05$ was considered to be statistically significant. The confidence intervals (CIs) are reported with 95% confidence level.

The study was approved by the SingHealth Centralised Institutional Review Board.

Results

Between 1 May 2014 and 30 April 2016, a total of 140 adult patients with *KP* VOA were identified and included in this study. During this study period, we screened a total of 475 *KP*-positive blood cultures from unique patients as well as 1017 non-urine *KP* culture isolates from unique patients. Eighty-four (60.0%) were males. The mean age was 63.6 years (range, 22 to 98 years). Majority were Chinese (n = 106; 75.7%). The majority of *KP* VOA were liver abscesses (109 patients, 77.9%), followed by genitourinary abscesses (29 patients, 20.7%). Amongst the 29 patients with genitourinary abscesses, 1 had mycotic aneurysm, 1 had infective endocarditis, 1 had meningitis and 2 had endophthalmitis.

Seventy-seven (55.0%) patients were diabetics. Table 1 compares between diabetic and non-diabetic patients with *KP* VOA. Diabetic patients were more likely to present with liver abscesses, genitourinary abscesses, abscesses in 2 or more organs, genitourinary disease with abscess formation outside of the genitourinary tract, and endovascular infection.

Amongst the diabetic patients, 10 (13.0%) were newly diagnosed. Sixty-seven (87.0%) patients had known diabetes mellitus, with treatment history available for 63 (81.8%) patients. With regard to their treatment history, 4 (5.2%) patients were on diet control, 41 (53.2%) were on oral hypoglycaemic agents (OHGAs), 6 (7.8%) were on insulin and 8 (10.4%) were on both OHGA and insulin. Four (5.2%) patients were non-compliant to diabetic treatment. Six (14.6%) patients presented with hyperglycaemic crises (4 with diabetic ketoacidosis, 2 with hyperosmolar hyperglycaemic state). Data on glycated haemoglobin (HbA1c) was available for 56 patients. The mean HbA1c value was 9.3% (range, 5.2% to 13.5%). Nine patients had HbA1c <7.0%, 25 patients had HbA1c ranging 7.0% to 9.9% and 22 patients had HbA1c ≥10.0%. Data analysis on these 3 distinct groups of patients did not reveal any significant differences in terms of metastatic complications, systemic complications, recurrence or mortality.

Amongst the patients with non-extended spectrum beta-lactamase (ESBL)-producing *KP* isolates, 35/132 (26.5%) were tested non-susceptible to cefuroxime by

Table 1. Demographic, Clinical, Laboratory, Microbiological Features of Diabetic and Non-Diabetic Patients

	All (n = 140)	Diabetics (n = 77)	Non-Diabetics (n = 63)	*P* Value
Mean age (years)	63.6 ±14.6	63.1 ±13.1	64.3 ±16.3	0.61
Male gender	84 (60.0%)	49 (63.6%)	35 (55.6%)	0.33
Chinese	106 (75.7%)	54 (70.1%)	52 (82.5%)	0.088
Malay	29 (20.7%)	20 (26.0%)	9 (14.3%)	0.090
Indian	2 (1.4%)	2 (2.6%)	0 (0.0%)	0.50
Comorbidities				
Underlying cancer	10 (7.1%)	8 (10.4%)	2 (3.2%)	0.19
Chronic liver disease	9 (6.4%)	7 (9.1%)	2 (3.2%)	0.19
Structural hepatobiliary disease*	30 (21.4%)	13 (16.9%)	17 (27.0%)	0.15
Intestinal pathology†	2 (1.4%)	1 (1.3%)	1 (1.6%)	1.00
Structural urinary abnormality‡	6 (4.3%)	5 (6.5%)	1 (1.6%)	0.22
Fever	111 (79.3%)	58 (75.3%)	53 (84.1%)	0.20
Haemoglobin (g/dL)	12.5 (7.5 – 18.5)	12.4 (7.5 – 18.5)	12.7 (7.7 – 18.1)	0.59
White blood cell count (x10^9/L)	15.1 (1.9 – 38.4)	15.2 (2.2 – 38.4)	15.0 (1.9 – 32.4)	0.91
Platelet count (x10^9/L)	235 (18 – 642)	244 (20 – 642)	224 (18 – 621)	0.23

ESBL: Extended spectrum beta-lactamase
*Includes pancreatic cancer, periampullary carcinoma, cholangiocarcinoma, hepatocellular carcinoma, liver metastasis, biliary stricture, cholecystitis, cholangitis, choledochocyst, previous biliary stenting, previous biliary surgery.
†Includes known colon cancer, diverticular disease.
‡Includes urolithiasis, benign prostate hypertrophy, polycystic kidney disease.

Table 1. Demographic, Clinical, Laboratory, Microbiological Features of Diabetic and Non-Diabetic Patients (Cont'd)

	All (n = 140)	Diabetics (n = 77)	Non-Diabetics (n = 63)	*P* Value
C-reactive protein (mg/L)	220 (3 missing) (1.6 – 380)	218 (2 missing) (1.6 – 380)	222 (1 missing) (4.4 – 380)	0.68
Procalcitonin (μg/L)	33.6 (17 missing) (0.19 – 100)	33.8 (10 missing) (0.37 – 100)	33.4 (7 missing) (0.19 – 100)	0.80
Bacteraemia	96 (68.6%)	56 (72.7%)	40 (63.5%)	0.26
Abscess location				
Liver	109 (77.9%)	54 (70.1%)	55 (87.3%)	**0.015**
Right lobe	61 (43.6%)	31 (40.3%)	30 (47.6%)	0.76
Left lobe	24 (17.1%)	9 (11.7%)	15 (23.8%)	0.18
Both lobes	24 (17.1%)	14 (18.2%)	10 (15.9%)	0.33
Genitourinary	29 (20.7%)	22 (28.6%)	6 (9.5%)	0.050
Kidney	12 (8.6%)	11 (14.3%)	1 (1.6%)	0.080
Prostate	17 (12.1%)	13 (16.9%)	4 (6.3%)	0.058
Lung	5 (3.6%)	2 (2.6%)	3 (4.8%)	0.66
Brain	4 (2.9%)	4 (5.2%)	0 (0.0%)	0.13
Solitary abscess	75 (53.6%)	38 (50.7%)	37 (49.3%)	0.27
Abscess size ≥5 cm	65 (46.4%)	36 (55.4%)	29 (44.6%)	0.94
Abscess formation in ≥2 organs	9 (6.4%)	8 (10.4%)	1 (1.6%)	**0.041**
Other sites of involvement without abscess formation				
None	97 (69.3%)	51 (66.2%)	46 (73.0%)	0.39
Lung	16 (11.4%)	12 (15.6%)	4 (6.3%)	0.09
Genitourinary	9 (6.4%)	8 (10.4%)	1 (1.6%)	**0.041**
Musculoskeletal	5 (3.6%)	5 (6.5%)	0 (0.0%)	0.06
Endovascular	10 (7.1%)	2 (2.6%)	8 (12.7%)	**0.043**
Septic thrombus	8 (5.7%)	2 (2.6%)	6 (9.5%)	0.14
Eye	7 (5.0%)	3 (3.9%)	4 (6.3%)	0.70
Meninges	3 (2.1%)	3 (3.9%)	0 (0.0%)	0.25
Abscess rupture with locoregional extension	7 (5.0%)	3 (3.9%)	4 (6.3%)	0.70
Disseminated disease involving ≥2 organs	28 (20.0%)	19 (24.7%)	9 (14.3%)	0.13
Systemic complications	74 (52.9%)	43 (55.8%)	31 (49.2%)	0.43
Septic shock	30 (21.4%)	14 (18.2%)	16 (25.4%)	0.30
Respiratory failure	12 (8.6%)	6 (7.8%)	6 (9.5%)	0.71
Acute kidney injury	61 (43.6%)	34 (44.2%)	27 (42.9%)	0.88
Myocardial infarction	18 (12.9%)	10 (13.0%)	8 (12.7%)	0.96
Atrial fibrillation with rapid ventricular response	5 (3.6%)	3 (3.9%)	2 (3.2%)	1.0
Disseminated intravascular coagulopathy	5 (3.6%)	4 (5.2%)	1 (1.6%)	0.38
Recurrence	6 (4.3%)	4 (5.2%)	2 (3.2%)	0.69
28-day mortality	10 (7.1%)	8 (10.4%)	2 (3.2%)	0.19
Antimicrobial resistance				
Second generation cephalosporin resistance	43 (30.7%)	25 (32.5%)	18 (28.6%)	0.62
Beta-lactam-beta-lactamase inhibitor resistance	11 (7.9%)	8 (10.4%)	3 (4.8%)	0.35
Fluoroquinolone resistance	9 (6.4%)	7 (9.1%)	2 (3.2%)	0.19
ESBL-producing strain	8 (5.7%)	6 (7.8%)	2 (3.2%)	0.30
Polymicrobial growth	12 (8.6%)	9 (11.7%)	3 (4.8%)	0.15

ESBL: Extended spectrum beta-lactamase

*Includes pancreatic cancer, periampullary carcinoma, cholangiocarcinoma, hepatocellular carcinoma, liver metastasis, biliary stricture, cholecystitis, cholangitis, choledochocyst, previous biliary stenting, previous biliary surgery.

†Includes known colon cancer, diverticular disease.

‡Includes urolithiasis, benign prostate hypertrophy, polycystic kidney disease.

the disk diffusion method, majority being of intermediate resistance. Of these, 29/35 (82.9%) patients did not have recent hospital contact.

Patients with ESBL-producing *KP* were more likely to have an obstructive lesion related to the site of the abscess (i.e. biliary obstruction for liver abscess, obstructive uropathy for genitourinary abscess) (P <0.001). Amongst the 8 cases of ESBL-producing *KP*, 2 were community-acquired whilst 6 had the *KP* isolated either within 3 months of a recent hospitalisation or after 48 hours of a hospital admission.

Forty-five out of 140 (32.1%) patients had their abscesses conservatively managed with systemic antimicrobial therapy alone whilst 95/140 (67.9%) patients had both abscess drainage and systemic antimicrobial therapy. Amongst the 95 patients who underwent abscess drainage, the majority (93.7%) were performed through radiological guidance; 7.4% needed surgical intervention. The most commonly drained abscess was from the liver (n = 86), followed by the prostate (n =12) and the kidney (n = 3).

Overall mortality rate was 7.1%. Amongst survivors, 129/130 (99.2%) patients had data of antibiotic duration available for analysis. These patients had a mean total duration of systemic antibiotics, parenteral antibiotics and oral antibiotics of 8.6 weeks, 2.5 weeks and 6.2 weeks, respectively; 6/129 (4.6%) survivors received parenteral antibiotics throughout the treatment course despite having oral antibiotic options.

Table 2 shows the predictive value of biomarkers for various clinical features and complications of patients with *KP* VOA. A higher leucocyte count is predictive of disseminated disease (P = 0.028), abscess formation in ≥2 sites (P = 0.032), lung abscess (P = 0.002), genitourinary involvement without abscess formation (P = 0.009), respiratory failure (P = 0.002) and polymicrobial infection (P = 0.048). A lower leucocyte count is predictive of liver abscess (P = 0.004). A lower platelet count is predictive of acute kidney injury (P = 0.001) (data not shown). A higher C-reactive protein is predictive of abscess ≥5 cm (P <0.001). A higher procalcitonin is predictive of bacteraemia (P = 0.008), prostate abscess (P = 0.030) and systemic complications (P = 0.002).

Table 3 shows the factors predictive of mortality in our patient cohort. We found that having a lung abscess, presenting with respiratory failure, acute kidney injury and atrial fibrillation with rapid ventricular response, as well as having a polymicrobial infection are predictors of mortality. Presenting with fever or having a liver abscess appears to be protective.

In addition, having a polymicrobial infection appears predictive of likelihood of recurrence, with a trend towards significance (odds ratio 6.20, 95% CI 1.01-38.1; P = 0.083).

Discussion

In this single-centre retrospective study in Singapore, we found that liver and genitourinary sites were the predominant visceral organs involved in *KP* VOA. The presence of diabetes mellitus is predictive of abscess formation in the liver, genitourinary tract, multi-organ abscesses and endovascular involvement.

Although a previous study showed that glycaemic control in diabetic patients is an important determinant in predicting the presence of metastatic complications in liver abscess,[7] our study failed to demonstrate a similar association for *KP* VOA. However, we showed that the presence of diabetes mellitus significantly increases the risk of dissemination, evidenced by the increased risk of multi-organ abscess and endovascular complications.

While *KP* pyogenic liver abscesses are well described in the literature, the phenomenon of *KP* genitourinary abscesses is less commonly reported. *KP* has been reported to be the predominant cause of prostatic abscesses in some centres, but available case series are small. In 2 centres in Southern Taiwan, 10/17 prostatic abscesses diagnosed during a 11-year period were due to *KP*.[8] A Korean single-centre study over 7 years identified 6/14 cases of prostatic abscesses to be due to *KP*.[9] The largest series of *KP* renal abscess came from Taiwan, which reported a total of 24 cases identified over 17 years.[10] Our series identified 17 *KP* prostatic abscesses and 12 *KP* renal abscesses across a 2-year period, with at least 5/29 patients exhibiting features of complicated, difficult-to-treat infections (mycotic aneurysm, infective endocarditis, meningitis and endophthalmitis), otherwise rarely reported in the literature.[11-14] Of note, in 2 Singaporean studies of 101 and 129 cases of *KP* bacteraemia (the latter study is also from our centre), 17% and 16% of cases were found associated with pyogenic liver abscesses, respectively.[15-16] No mention was made, however, of any association with other VOA in both series. Our study strengthens the case in point about *KP* genitourinary abscesses as an emerging clinical entity.

In our study, we find that the majority of our abscess-forming *KP* isolates are susceptible to most of the commonly prescribed antibiotics (<10% resistance to fluoroquinolones and third generation cephalosporins). A significant percentage of resistance to cefuroxime (30.7%) is observed, however, limiting the empiric use of this agent in patients with VOA without microbiological diagnosis. The optimal duration and mode of antimicrobial administration in the management of *KP*-associated abscesses remain unknown. Most experts would opt for a combination of percutaneous drainage coupled with several weeks of parenteral antibiotics. As demonstrated in our study, percutaneous drainage appears to be the preferred modality for source control over surgery in our centre. In our cohort, only a small

Table 2. Relation between White Blood Cell Count, C-Reactive Protein, Procalcitonin and Various Clinical Parameters

Parameter	Category	Total, n (%)	White Blood Cell Count (x10^9/L)		C-Reactive Protein (mg/L)		Procalcitonin (μg/L)	
			Median (Q1 – Q3)	*P* Value	Median (Q1 – Q3)	*P* Value	Median (Q1 – Q3)	*P* Value
Bacteraemia	Yes	96 (68.6)	13.7 (10.4 – 19.5)	0.96	234.5 (162.9 – 279.4)	0.85	24.5 (3.3 – 91.3)	**0.008**
	No	44 (31.4)	15.2 (10.7 – 18.4)		224.0 (141.4 – 290.5)		5.9 (1.4 – 35.8)	
Abscess								
Size ≥5 cm*	Yes	65 (46.4)	14.0 (9.7 – 17.9)	0.68	259.4 (196.1 – 328.7)	**<0.001**	16.1 (2.0 – 75.7)	0.91
	No	64 (45.7)	13.7 (10.6 – 19.3)		192.9 (119.2 – 263.4)		17.4 (2.1 – 45.4)	
Location ≥2 organ sites	Yes	9 (6.4)	17.5 (16.4 – 29.1)	**0.032**	224.3 (187.9 – 347.6)	0.54	5.2 (6.7 – 29.1)	0.15
	No	131 (93.6)	13.2 (10.4 – 19.0)		235.5 (156.2 – 284.1)		16.7 (2.1 – 60.4)	
Liver	Yes	109 (77.9)	13.2 (10.2 – 17.8)	**0.004**	242.1 (163.8 – 290.2)	0.11	16.8 (2.0 – 57.0)	0.94
	No	31 (22.1)	17.5 (10.7 – 23.7)		197.5 (135.8 – 252.6)		11.8 (3.4 – 49.4)	
Kidney	Yes	12 (8.6)	17.3 (12.6 – 21.8)	0.15	224.0 (177.9 – 278.2)	0.88	10.2 (6.4 – 65.3)	0.98
	No	128 (91.4%)	14.1 (10.4 – 19.2)		234.5 (161.6 – 285.7)		16.7 (2.0 – 56.4)	
Prostate	Yes	17 (12.1)	17.5 (12.7 – 21.5)	0.97	192.9 (128.2 – 221.8)	0.60	2.6 (1.0 – 15.8)	**0.030**
	No	123 (87.9)	13.2 (10.3 – 18.5)		241.9 (162.8 – 289.6)		16.9 (2.8 – 63.9)	
Systemic complications†	Yes	74 (52.9)	15.3 (10.0 – 21.2)	0.33	240.9 (164.7 – 292.9)	0.14	25.6 (7.5 – 98.1)	**0.002**
	No	66 (47.1)	13.2 (10.6 – 17.6)		211.8 (145.3 – 269.3)		4.42 (1.53 – 31.0)	
Polymicrobial infection	Yes	12 (8.6)	20.9 (11.1 – 26.4)	**0.048**	211.8 (107.2 – 263.0)	0.42	8.7 (1.6 – 63.9)	0.46
	No	128 (91.4)	13.6 (10.4 – 18.1)		236.9 (163.3 – 285.7)		16.8 (2.0 – 55.7)	
Outcomes								
Recurrence	Yes	6 (4.3)	17.8 (9.3 – 22.0)	0.52	168.9 (111.6 – 229.9)	0.18	30.7 (14.8 – 65.5)	0.34
	No	134 (95.7)	14.4 (10.4 – 19.1)		238.2 (163.2 – 285.4)		16.3 (2.0 – 56.4)	
28-day mortality	Yes	10 (7.1)	19.5 (10.4 – 26.3)	0.18	209.5 (151.8 – 259.0)	0.67	24.6 (3.3 – 36.5)	0.85
	No	130 (92.9)	14.4 (10.4 – 18.6)		235.5 (163.1 – 286.7)		16.2 (2.0 – 56.9)	

Q: quartile

*11 abscesses not measured.

†Includes shock, respiratory failure, acute kidney injury, myocardial infarction, disseminated intravascular coagulopathy.

Table 3. Factors Predictive of Mortality in Patients with Visceral Abscess

	Odds Ratio (95% CI)	*P* Value
Fever as presenting complaint	0.143 (0.0370 – 0.549)	**0.006**
Liver abscess	0.25 (0.0670 – 0.928)	**0.043**
Lung abscess	10.6 (1.54 – 72.7)	**0.041**
Respiratory failure	10.2 (2.38 – 43.5)	**0.005**
Acute kidney injury	5.8 (1.19 – 28.5)	**0.021**
Atrial fibrillation with rapid ventricular response	10.6 (1.54 – 72.7)	**0.041**
Polymicrobial infection	5.76 (1.27 – 26.1)	**0.041**

number of patients (4.6%) received parenteral antibiotics throughout the course of their treatment despite having oral antibiotic options. The mean parenteral treatment duration of 2.5 weeks amongst survivors, followed by oral switch and a low recurrence rate of 4.3% seem to support early use of oral antibiotics as a therapeutic option. Indeed, Chen et al, reported safe and efficacious use of oral antibiotics in an open-label randomised controlled trial in a group of patients with liver abscesses, predominantly due to *KP*.[17] ESBL-producing strains causing invasive *KP* VOA appears low at 5.7% in our cohort. Many of our patients in this cohort presented as community-acquired infections and over half presented with systemic complications such as organ failure. Our finding of ESBL-producing *KP* infections being significantly associated with an obstructive lesion related to the site of the abscess, may potentially allow clinicians to make early informed decisions about ESBL coverage in their empiric antimicrobial regimen. This observation is also consistent with Shi et al's study of 817 pyogenic liver abscess patients, where ESBL-producing *Enterobacteriaceae* occurred mainly in individuals with biliary disorders.[18]

Our results show that presence of fever and having a liver abscess was protective. We postulate that patients with fever tended to present earlier, have blood cultures performed and also received antibiotics more promptly. Several other studies have highlighted lower mortality in septic patients with higher body temperature,[19-21] possibly enhancing immune-cell function and promoting antimicrobial activity.[22-23] It is plausible that patients with liver abscess tend to have drainage performed more promptly, allowing better source control, hence improving mortality. Indeed 86/109 (78.9%) of the liver abscesses in our study were drained compared to 15/29 (51.7%) of genitourinary abscess, which is the second most common site of involvement for abscesses.

Our study is one of the largest series of patients with *KP* VOA with their clinical outcomes described. We acknowledge several limitations. This is a retrospective single-centre study, which may give rise to selection bias in our patient population. There is also a lack of serotyping and identification of genotypic virulent factors in our clinical isolates. The actual number of *KP* VOA is possibly even higher, given that there were bacteraemic patients who were too ill to undergo abdominal imaging and demised early in their clinical course.

Conclusion

Our study concludes that the genitourinary tract is the commonest extra-hepatic site for VOA in *KP* infections, with diabetes mellitus as a clear risk factor for both hepatic and genitourinary abscesses in this series. Early parenteral to oral switch of antimicrobial agents appears to be a safe and effective treatment option.

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Original Article

Assessing for Mood and Anxiety Disorders in Parents of Clinically-Referred Children: Laying the Foundation for a Family-Based Approach to Mental Health in Singapore

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Abstract

Introduction: Family history of psychopathology is a risk factor for mood and anxiety disorders in children, but little is known about rates of parental psychopathology among treatment-seeking youth with affective disorders in the Asia Pacific region. This study examined patterns of emotional and behavioural problems in parents of clinically-referred youth in Singapore. We hypothesised that parents would have higher rates of affective disorders compared to the Singapore national prevalence rate of 12%. Materials and Methods: In this cross-sectional study, 47 families were recruited from affective disorders and community-based psychiatry programmes run by a tertiary child psychiatry clinic. All children had a confirmed primary clinical diagnosis of depression or an anxiety disorder. Parents completed the Mini International Neuropsychiatric Interview (MINI) to assess for lifetime mood and anxiety disorders. They also completed the Adult Self Report (ASR) and Adult Behavior Checklist (ABCL) to assess current internalising and externalising symptoms. Results: Consistent with our hypothesis, 38.5% of mothers and 10.5% of fathers reported a lifetime mood or anxiety disorder. Nearly 1/3 of mothers had clinical/subclinical scores on current internalising and externalising problems. A similar pattern was found for internalising problems among fathers, with a slightly lower rate of clinical/subclinical externalising problems. Conclusion: Our findings are consistent with previous overseas studies showing elevated rates of affective disorders among parents—particularly mothers—of children seeking outpatient psychiatric care. Routine screening in this population may help to close the current treatment gap for adults with mood and anxiety disorders.

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Key words: Affective disorders, Depression, Family history

Introduction

Background

Parental psychopathology is a documented risk factor for mood disorders in children[1,2] and it may be due to a combination of genetic vulnerabilities and psychosocial factors such as parenting style and attachment.[3,4] While there is evidence for the heritability of mood and anxiety disorders, parental psychopathology can also profoundly affect the environment in which the child is raised.[2,5] Epigenetic pathways are involved in the long lasting effects of maternal psychopathology and child outcomes.[6] In addition, children with depression and anxiety disorders may be more likely to elicit certain parenting styles, such as overprotection, in turn creating an environment that

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maintains affective symptoms.[7] Children's symptoms can also become an increased risk and/or perpetuating factor for psychopathology in parents.[8]

The intergenerational association between maternal and offspring depression and anxiety persists well into adulthood.[6,9] In a 30-year follow-up study of children of parents with depression, it was found that they had a threefold increased risk for depression and anxiety when compared to children whose parents did not have depression.[10] Maternal depression and anxiety measured in late adolescence was consistently associated with offspring depression and anxiety across daughters' transition to adulthood.[6] Recent clinical data has suggested that treatment of maternal depression can reduce the number of psychiatric diagnoses and problem behaviours in their children.[11] For example, in a United States (US) study of 168 mothers with major depression who were treated with 9 sessions of interpersonal or supportive psychotherapy, improvement in mothers' depressive symptoms after psychotherapy predicted an improvement in their children's functioning 3 to 6 months later, an effect that was independent of the youth's treatment.[11] Taken together, these studies suggest that a family-based approach to assessment and treatment of mental health conditions is warranted. However, screening family members of clinically-referred youth is not routinely done in clinical practice.

To our knowledge, no studies have been conducted on the rates of psychopathology in parents seeking psychiatric evaluation for their children in an Asian setting. Data from overseas studies indicate that parents of treatment-seeking youth have high rates of internalising conditions. In a US study, Ferro et al[12] found that among mothers who brought their children to paediatric psychiatry clinics for depression and anxiety, 14% screened positive for current major depression, 17% for panic disorder, and 17% for generalised anxiety disorder. In a United Kingdom sample, Cooper et al[13] found that 57% of mothers and 33% of fathers of children with anxiety disorders had lifetime major depressive disorder, while 68% of mothers and 45% of fathers had lifetime anxiety disorders. Middeldorp et al[14] found that among parents of children who presented for outpatient psychiatric services in the Netherlands, approximately 20% of mothers and fathers had elevated scores on internalising problems. In a study by Swartz et al,[15] over 60% of mothers seeking outpatient psychiatric care for their children met criteria for Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) mood and anxiety disorders. Vidair and colleagues[16] examined rates of parental psychiatric symptoms in a sample of 848 youth aged 6 to 17 years who were assessed at a tertiary outpatient psychiatric clinic in the US. Results indicated that over 18% of mothers and fathers experienced elevated psychiatric symptoms. Maternal and paternal symptoms were significantly associated with the severity of the child internalising and externalising symptoms. The investigators proposed that screening parents for psychopathology should be part of a child's psychiatric evaluation. A similar multi-informant approach has also been advocated by Hudziak and colleagues.[17]

Study Aims and Hypotheses

To date, there have been no studies using a family-based approach to examine patterns of parental mood and anxiety disorders among clinically-referred youth in Singapore. According to the Singapore Mental Health Study (SMHS), approximately 12% of the population had at least 1 lifetime affective, anxiety, or alcohol use disorder.[18] Data from the SMHS also showed that the lifetime prevalence of major depressive disorder was higher among women (7.2%) than men (4.3%).[19] However, an estimated 59.6% of people with major depressive disorder and 56.5% of those with generalised anxiety disorder did not seek medical treatment for their conditions,[20] indicating a large treatment gap for adults with mood and anxiety disorders in Singapore.

It is possible that parents are more comfortable seeking mental healthcare for their children than they are seeking psychiatric care for themselves. Hence, assessment and referral of parents of treatment-seeking youth when presenting at the child outpatient clinic may provide another route to diagnosis and treatment for those with mental health issues who might otherwise remain unidentified and untreated. This study aimed to characterise patterns of psychiatric diagnosis and mental health problems among parents of clinically-referred youth with mood and anxiety disorders in Singapore with the goal of informing future family-based assessment and intervention strategies.

Building on previous findings regarding the intergenerational transmission of depression and anxiety, we hypothesised that parents of youth with mood and anxiety disorders would: 1) have higher rates of lifetime mental health disorders compared to the national prevalence rate of 12%, and 2) show elevations on current multi-informant ratings of internalising and externalising problems, as well as mood and anxiety symptoms.

Materials and Methods

Study Design and Setting

The study design was cross-sectional in nature. We enrolled 47 children, aged 6 to 19 years of age from a public outpatient subspecialty clinic serving children with mood and anxiety disorders and 2 community outreach teams based at the Department of Child and Adolescent Psychiatry at the Institute of Mental Health (IMH) in Singapore.[21] The outpatient psychiatry clinic is a tertiary-level service that is organised into 3 subspecialty clinics. The Mood and Anxiety Clinic offers medication management by psychiatrists, in

addition to cognitive behavioural therapy and family therapy provided by clinical psychologists and social workers. The community-based multidisciplinary teams consist of psychiatrists, social workers, and psychologists who provide assessment, consultation-liaison, and psychotherapy services to schools for children and adolescents with suspected mental health conditions.[22]

Participants and Procedures

Recruitment was based on the inclusion and exclusion criteria described in Table 1 pertaining to child participants. Of the 47 children, 3 failed to complete the study procedures and were therefore excluded from analysis. The 44 identified participants and their parents completed structured clinical interviews[23,24] and validated multi-informant rating scales[25-28] to assess the presence of lifetime DSM-IV diagnoses and current mental health/behavioural problems. Figure 1 shows the recruitment flowchart.

Procedures

All study procedures took place during 1 to 2 study visits, which included obtaining vital signs, body mass index (BMI), and child medical/psychiatric history, administration of structured clinical interviews regarding the child (Diagnostic Interview Schedule for Children IV; DISC-IV)[24] and parents (Mini-International Neuropsychiatric Interview-IV; MINI-IV),[23] and administration of multi-informant rating scales assessing current parent symptoms (Adult Self-Report; ASR, Adult Behavior Checklist; ABCL).[25,28]

To minimise burden on participants and their families, we attempted to complete all study procedures during 1 study visit. If both parents were not available, we allowed the recruitment of the child and 1 parent. Participants were also given the option of bringing home the rating scales for completion to reduce the amount of time spent during the study visit. To cater for the Chinese-speaking families, Mandarin versions of the structured clinical interviews and rating scales were also administered, when necessary. A total of 5 parents completed the rating scales and interviews in Mandarin.

Table 1. Inclusion/Exclusion Criteria for Children

Inclusion	Exclusion
• 6 to 19 years of age	• Unstable medical condition
• English- or Mandarin-speaking	• Severe psychiatric disorders (i.e. ASD, schizophrenia, other psychotic disorders)
• Primary clinical diagnosis of mood and/or anxiety disorder	• Current active suicidal and/ or homicidal ideation with plan/intent
• Willing and able to complete questionnaires	• Unable to comprehend rating scales
	• Borderline personality traits

ASD: Autism spectrum disorder

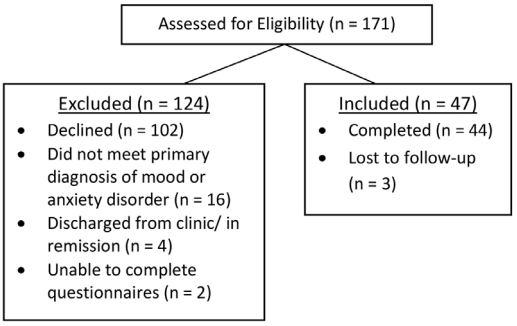

Fig. 1. Recruitment flow chart.

Following completion of the study assessments, all participants and their caregivers were offered an optional review of their results, general psycho-education about mood and/or anxiety disorders, and possible treatment options. Parents with prominent symptoms who were not already being treated were referred to IMH psychiatry or community mental health services for further evaluation and treatment. All of the study procedures were on voluntary basis and were approved by the National Healthcare Group Domain Specific Institutional Review Board.

Parent and Child Assessments

For child diagnostic assessments, we used the National Institute of Mental Health DISC-IV, a well validated structured parent interview designed to assess mental disorders in youth based on DSM-IV criteria.[24] The DISC-IV has been widely used to assess inclusion criteria in research studies involving children and adolescents. Our research team used the DISC-IV in several prior studies of the local population.[29-31] For adult interviews, we used the MINI-IV, a reliable and valid semi-structured interview designed to assess the DSM-IV disorders most commonly encountered in psychiatric outpatients.[23,24] The Principal Investigator had extensive experience using the MINI-IV in prior studies of adults in the US[32] and Singapore.[33,34]

For the multi-informant rating scales, we used the Achenbach System of Empirically Based Assessments (ASEBA), a comprehensive system for assessing adaptive and maladaptive functioning in a cross-cultural context.[25] We used 2 adult rating scales: the spouse-report ABCL and the self-report ASR.[28] Subscales of these measures assess broadband internalising and externalising symptoms, behavioural problem domains, and symptoms corresponding to DSM-IV diagnoses. Our research team participated in the cross-cultural validation of the ASEBA scales and we have used them in several studies of the local population.[26, 35-38] The thresholds for clinical and subclinical scores for the ABCL and ASR correspond to the 97th and 93rd percentiles, respectively, of men and women in the general population.

Results

Participant Characteristics

Out of the 44 families, there were 5 child-father pairs, 25 child-mother pairs and 14 child-father-mother triads. All 44 children had a clinical DSM-IV diagnosis of either depression (36.4%) and/or anxiety disorders (63.6%). Of these 44 patients, 38.6% (n = 17) were male and 61.4% (n = 27) were female. Ethnicity was 84.1% (n = 37) Chinese, 6.8% (n = 3) Indian and 9.1% (n = 4) other race/ethnicity. The age (mean, SD) of child, father, and mother participants were 14.8 (3.4), 49.4 (5.9), and 46.9 (5.4) years, respectively. Other child demographic and clinical characteristics can be found in Table 2.

Table 2. Demographic and Clinical Characteristics of Child Participants

Demographic Characteristics	
Ethnicity of child (n, %)	
Chinese	37 (84.1)
Indian	3 (6.8)
Others	4 (9.1)
Gender of child (n, %)	
Male	17 (38.6)
Female	27 (61.4)
Religion (n, %)	
Buddhist/Taoist	18 (40.9)
Christian/Catholic	19 (43.2)
Muslim	2 (4.5)
No religion	12 (27.3)
Education level of child (n, %)	
Primary	11 (25.0)
Secondary	19 (43.2)
Polytechnic or junior college	12 (27.3)
Not in school	2 (4.5)
Clinical Characteristics	
Maternal medication use during pregnancy (n, %)	
None	23 (52.3)
Stimulants	3(6.8)
Antidepressants	14 (31.8)
Others	3 (6.8)
Child's psychiatric diagnosis (n, %)	
Major depressive disorder	16 (36.4)
Panic disorder	5 (11.4)
Social anxiety disorder	6 (13.6)
Generalised anxiety disorder	7 (15.9)
Obsessive-compulsive disorder	6 (13.6)
Separation anxiety disorder	1 (2.3)
Selective mutism	2 (4.5)
Specific phobia	1 (2.3)
Past history of suicide attempt (n, %)	7 (15.9)
Age of onset (M, SD)	11.9 (3.6)
Children's Global Assessment Scale score (M, SD)	62.9 (9.1)
Duration of illness in years (M, SD)	2.7 (0.6)

Parental Mental Health Disorders

Tables 3 to 5 show the prevalence of lifetime mood and anxiety disorders and current mental health symptoms among parents. Consistent with our hypothesis, 38.5% of mothers and 10.5% of fathers met diagnostic criteria for a lifetime mental health disorder as assessed by the Mini-International Neuropsychiatric Interview-IV (MINI-IV) (see Table 3). Several of the parents also reported comorbid depressive and anxiety disorders. Comorbid depression and agoraphobia was found in 2.6% of mothers, comorbid depression and obsessive-compulsive disorder in 2.6% of mothers, comorbid depression and social anxiety disorder in 2.6% of mothers. Comorbid depression, panic disorder, and mood disorder with psychotic features was found in 2.6% of fathers. Comorbid depression, panic disorder, agoraphobia, and social phobia was found in 2.6% of mothers.

Parental Internalising, Externalising and Affective Symptoms

Self-Report

For internalising symptoms, 27% of mothers and 31.6% of fathers scored in the clinical or subclinical range. For externalising symptoms, 32.4% of mothers and 15.8% of fathers scored in the clinical or subclinical range. For depressive problems, 18.2% of mothers and 9.4% of fathers scored in the clinical and subclinical range. For anxiety problems, 9% of mothers and 11.6% of fathers scored in the clinical and subclinical range. For suicidal ideation, 17.9 % (n = 7) of mothers and 5.2% of fathers (n = 1) answered "Sometimes True" to the item "I think about killing myself." Table 4 presents ASEBA subscale scores for self-reported internalising, externalising, syndrome scales, and DSM-oriented scales.

Spouse-Report

For internalising symptoms, 31.6% of mothers and 23.7% of fathers scored in the clinical or subclinical range. For externalising symptoms, 21% of mothers and 18.4% of fathers scored in the clinical or subclinical range. For depressive problems, 11.4% of mothers and 4.7% of fathers scored in the clinical and subclinical range. For anxiety problems, 9.1% of mothers and 7% of fathers scored in the clinical and subclinical range. Table 5 presents ASEBA subscale scores for spouse-reported internalising, externalising, syndrome scales, and DSM-oriented scales. For the ABCL and the ASR, internalising and externalising problems scores were considered clinical if they were above the 90th percentile and subclinical if they were between the 84th to 90th percentiles.

Table 3. Parent Lifetime MINI-IV Diagnoses

	Father (n = 19)	Mother (n = 39)
MINI-IV diagnosis (n, %)		
Major depressive disorder	0 (0)	9 (23.1)
Panic disorder	0 (0)	1 (2.6)
Social anxiety disorder	0 (0)	1 (2.6)
Bipolar disorder	0 (0)	0 (0)
Post-traumatic stress disorder	0 (0)	0 (0)
Agoraphobia	1 (5.3)	0 (0)
Obsessive-compulsive disorder	0 (0)	0 (0)
Generalised anxiety disorder	0 (0)	0 (0)
Any mood or anxiety disorder	2 (10.5)	15 (38.5)

MINI-IV: Mini-International Neuropsychiatric Interview-IV

Table 4. Mental Health Symptoms among Parents (Self-Report)

	Mother		Father	
	Clinical	Subclinical	Clinical	Subclinical
Syndrome scores (n, %)				
Anxious/ depressed	5 (11.4)	2 (4.5)	1 (2.3)	2 (4.7)
Withdrawn	4 (9.1)	4 (9.1)	2 (4.7)	0 (0)
Somatic complaints	1 (2.3)	6 (13.6)	2 (4.7)	2 (4.7)
Thought problems	1 (2.3)	3 (6.8)	1 (2.3)	2 (4.7)
Attention problems	2 (4.5)	3 (6.8)	3 (7.0)	0 (0)
Aggressive problems	1 (2.3)	6 (13.6)	2 (4.7)	0 (0)
Rule-breaking behaviour	0 (0)	1 (2.3)	1 (2.3)	0 (0)
Intrusive	0 (0)	1 (2.3)	1 (2.3)	0 (0)
Internalising problems	7 (15.9)	3 (6.8)	5 (11.6)	1 (2.3)
Externalising problems	7 (15.9)	5 (11.4)	2 (4.7)	1 (2.3)
Total problems	9 (20.5)	2 (4.5)	3 (7.0)	1 (2.3)
DSM-oriented scale (n, %)				
Depressive problems	3 (6.8)	5 (11.4)	2 (4.7)	2 (4.7)
Anxiety problems	2 (4.5)	2 (4.5)	0 (0)	5 (11.6)
Somatic problems	1 (2.3)	5 (11.4)	1 (2.3)	2 (4.7)
Avoidant personality problems	2 (4.5)	5 (11.4)	0 (0)	3 (7.0)
ADHD problems	3 (6.8)	1 (2.3)	1 (2.3)	1 (2.3)
Antisocial personality problems	0 (0)	0 (0)	0 (0)	4 (9.3)

ADHD: Attention deficit hyperactivity disorder; DSM: Diagnostic and Statistical Manual of Mental Disorders

Table 5. Mental Health Symptoms among Parents (Spouse-Report)

	Mother		Father	
	Clinical	Subclinical	Clinical	Subclinical
Syndrome scores (n, %)				
Anxious/ depressed	2 (4.5)	3 (6.8)	1 (2.3)	2 (4.7)
Withdrawn	3 (6.8)	2 (4.5)	3 (7.0)	4 (9.3)
Somatic complaints	2 (4.5)	1 (2.3)	0 (0)	5 (11.6)
Thought problems	1 (2.3)	1 (2.3)	2 (4.7)	2 (4.7)
Attention problems	1 (2.3)	2 (4.5)	3 (7.0)	1 (2.3)
Aggressive problems	1 (2.3)	2 (4.5)	2 (4.7)	3 (7.0)
Rule-breaking behaviour	0 (0)	0 (0)	2 (4.7)	1 (2.3)
Intrusive	0 (0)	0 (0)	1 (2.3)	2 (4.7)
Internalising problems	5 (11.4)	1 (2.3)	2 (4.7)	7 (16.3)
Externalising problems	1 (2.3)	3 (6.8)	5 (11.6)	2 (4.7)
Total problems	4 (9.1)	2 (4.5)	5 (11.6)	2 (4.7)
DSM-oriented scale (n, %)				
Depressive problems	4 (9.1)	1 (2.3)	0 (0)	2 (4.7)
Anxiety problems	0 (0)	4 (9.1)	0 (0)	3 (7.0)
Somatic problems	3 (6.8)	0 (0)	2 (4.7)	3 (7.0)
Avoidant personality problems	3 (6.8)	1 (2.3)	3 (7.0)	3 (7.0)
ADHD problems	1 (2.3)	0 (0)	3 (7.0)	3 (7.0)
Antisocial personality problems	0 (0)	0 (0)	2 (4.7)	4 (9.3)

ADHD: Attention deficit hyperactivity disorder; DSM: Diagnostic and Statistical Manual of Mental Disorders

Discussion

To our knowledge, this is the first study in the Asia Pacific region to document rates of psychiatric symptoms among parents of children attending an outpatient psychiatric clinic. Consistent with our hypothesis, 38.5% of mothers and 10.5% of fathers met diagnostic criteria for a lifetime mental health disorder as assessed by the MINI-IV. A higher percentage of mothers had greater tendency towards internalising problems while a higher percentage of fathers had greater tendency towards externalising problems. Our findings are consistent with previous overseas studies that reported a high rate of depression and anxiety among

parents of children seeking outpatient psychiatric care.[12-16] For example, Ferro et al found that 31% of mothers of children with depression met diagnostic criteria for a current psychiatric disorder.[12] Similarly, Swartz et al found that 35% and 42% of mothers of children presenting for psychiatric evaluation met diagnostic criteria for depression and anxiety respectively.[15] In addition, our findings that 31.6% of mothers and 23.7% of fathers scored in the clinical or subclinical range for internalising symptoms are in keeping with Middeldorp et al who found that 20% of both mothers and fathers of children presenting for psychiatric evaluation displayed such symptoms,[14] and with Vidair et al who found that 18.8% of mothers and 18.4% of fathers reported elevated internalising symptoms.[16]

Local data to explain the high rate of depression and anxiety among parents are relatively limited. In the adult population in Singapore, depression has been associated with being a single mother,[39] and having poorer quality of life with respect to physical and mental health functioning.[40] Generalised anxiety disorder has been associated with increased psychiatric comorbidity, history of threatening life events, and increased odds of being divorced.[41] These factors may contribute to poor parenting and adverse family environments. Maladaptive ruminations[42] and feelings of shame in depression[43] may also contribute to a greater tendency towards internalising problems among adult Singaporeans.

Some strengths and limitations of our study should be highlighted. Strengths include the use of a multi-informant approach to gather information on psychiatric symptoms among parents, use of validated rating scales and structured diagnostic interviews, and administration of study assessments by highly trained research staff. These methods allow for a more accurate and reliable understanding of psychopathology in our sample. Our study also has a number of limitations. First, our findings are generalisable only to a self-selected group of parents bringing their children for treatment at an outpatient psychiatric clinic and may not be generalisable to other groups of fathers or mothers. Second, 60% of eligible participants declined participation in our study. It is unknown whether they differ in demographic and clinical characteristics to the participants who were recruited. The fact that only 45% of fathers and 89% of mothers were assessed could also have introduced a bias into the findings. The lower rate of participation by fathers limits the extent to which our results reflect the true rates of affective disorders in this group. Furthermore, men with depression are less likely to seek help and more likely to attempt suicide with high perceived lethality.[44] It is quite possible that fathers who were depressed or anxious would be less likely to participate in a study evaluating their emotional and behavioural health. Nevertheless, our findings are consistent with previous literature demonstrating higher rates of psychopathology among parents of children attending outpatient psychiatric clinics. In addition, a control group (parents of children without psychiatric illnesses) was not included. Due to the ethnic composition of our study sample, no Malay families were included. Future studies should include a larger sample to reflect the ethnic composition in Singapore more accurately. Finally, there were also lacking demographic details (aside from parent age and ethnicity), so we would be unable to examine the extent to which these are associated with parental psychopathology, and we were unable to examine the temporal relationships and strength of association between child and parent symptoms (i.e. duration and severity). Finally, due to the cross-sectional study design, we cannot assess the causative relationship between child and parental psychopathology.

Our study also highlights several possibilities for future research. First, prior research has demonstrated the negative physical[45] and mental health[46] consequences that parental smoking may have on children. Hence, future studies may be useful to elucidate the role of parental smoking and alcohol misuse and how this may mediate the intergenerational transmission of psychopathology. Second, information regarding parents' demographics (e.g. education, occupation, family income), psychiatric history and treatment received may also help identify treatment gaps. Among Singaporean adults, depression and anxiety have been associated with unemployment,[47] chronic diseases[48] and caregiving for older parents with chronic diseases such as stroke.[49] Further information on the causes of depression and anxiety in parents whose children are receiving psychiatric treatment will also help with designing appropriate interventions for these parents.

Conclusion

The data presented here may be seen as an important first step in designing appropriate family-based prevention and intervention strategies for children and families in Singapore. Our preliminary results indicate that, consistent with findings from overseas studies, parents (particularly mothers) of clinically-referred children with mood and anxiety disorders have higher lifetime rates of affective disorders as compared to adults in the general population. They are also at risk for clinically significant elevations in internalising and externalising symptoms, which may impact their current functioning and ability to manage their child's illness. These findings highlight an increasing need for coordinated care to identify and treat mental illnesses such as depression and anxiety.[50] Research on Singaporean adults with anxiety and depression demonstrated that poor self-rated mental health status predicted the tendency of

patients to seek help.[51] Child and adolescent psychiatrists are in a strong position to encourage parents to be screened for anxiety and depression. Advances in technology, including the use of smart phone applications that focus on mental health, may be useful in the early identification and management of depression.[52,53] Improving the child's environment through treatment of parental mental health problems is likely to have positive outcomes on child symptoms and functioning and vice versa. In the long term, identification of modifiable environmental risk factors may also allow for family-based environmental interventions.

Acknowledgments

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Deformity Correction Using the "Sandwich" Technique for a Non-Union Hoffa Fracture

Dear Editor,

Fredrich Busch was the first author to describe a coronal plane fracture of the lateral femoral condyle. It was, however, Albert Hoffa who was credited with discovering this fracture. Recent recommendations have been made to rename isolated, intra-articular, coronal plane fractures of the distal femur, or the "Hoffa fracture" to "Busch-Hoffa fractures".[1] These fractures have been reported to more commonly involve the lateral side.[2] The configuration of this fracture causes it to be inherently unstable; hence poor outcome is usual with non-operative management, with malunion being recognised as a common late complication even after surgical management.[2,3,4,5] This paper discusses the case of a young adult male presenting with a grade II (Letenneur classification)[9] Hoffa fracture—his management, complications and outcomes.

Case Report

A 34-year-old male construction worker presented after a 300 kg concrete beam fell from a crane onto his thighs. He sustained a right closed mid shaft of femur fracture and left closed Hoffa fracture (Fig. 1). The right femur fracture was fixed with a retrograde intramedullary nail. Stable and adequate reduction was achieved, and the Hoffa fracture was fixed with a percutaneous 4.5 mm partially threaded cannulated cancellous screw (Fig. 2), utilising a minimally invasive surgical technique so as to minimise deep tissue dissection.

Postoperatively, he was allowed to full weight-bear on the right lower limb. He was not allowed to weight-bear for a month on the left lower limb, before the transition to partial weight-bearing.

At the 3 month follow-up mark, he complained of a valgus deformity of the left lower limb. Radiographs (Figs. 3 and 4) showed a non-united fracture with implant loosening. A long leg film revealed a valgus deformity of 8 degrees. The decision was made for surgical revision to correct the deformity and to provide stable fixation for healing of this intra-articular fracture.

The fracture site was approached via an anterolateral incision during the revision operation. This extensile approach allowed for direct visualisation of the lateral femoral condyle and fracture site, direct reduction and screw fixation via the same exposure. There was evidence of fibrous non-union at the fracture site, and a 2 mm articular step deformity. The fracture site was separated, freshened and elevated to restore the height of the articular surface. It was noted that the fracture fragment had undergone disuse osteolysis, and hence was reduced in size and height. An autologous tricortical anterior iliac crest bone graft was then harvested and fashioned to be used as a strut and "sandwiched" into the fracture site between both condylar segments to maintain the articular height (Fig. 5). The fixation was temporarily reduced with a Kirschner-wire (K-wire). The cable technique was then used to assess the patient's lower limb alignment, which was found to be satisfactory. This was followed by the definitive fixation with two 4 mm headless compression screws that were applied in a posterior to anterior, caudal to cranial direction to secure the graft and fracture fragments.

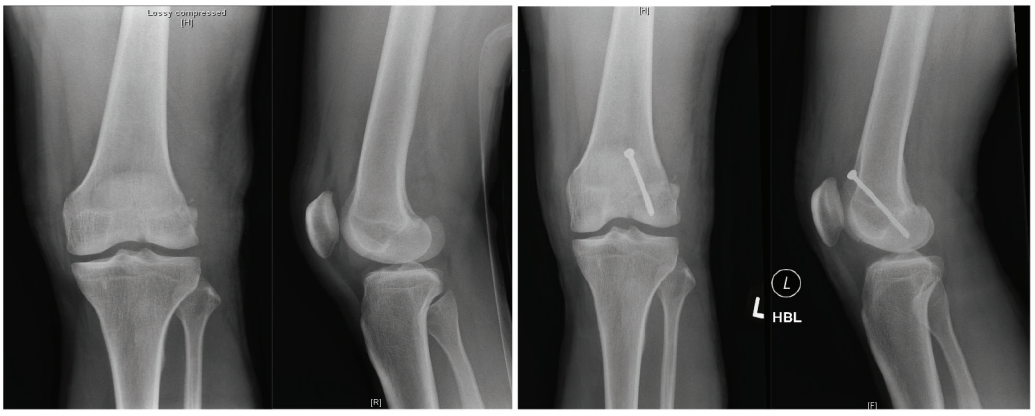

Fig. 1. Hoffa fracture of left femoral condyle, before and after index operation (left and right, respectively).

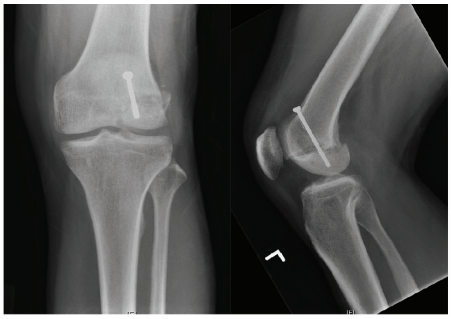

Fig. 2. Radiograph at 3 months showing malunion with implant loosening.

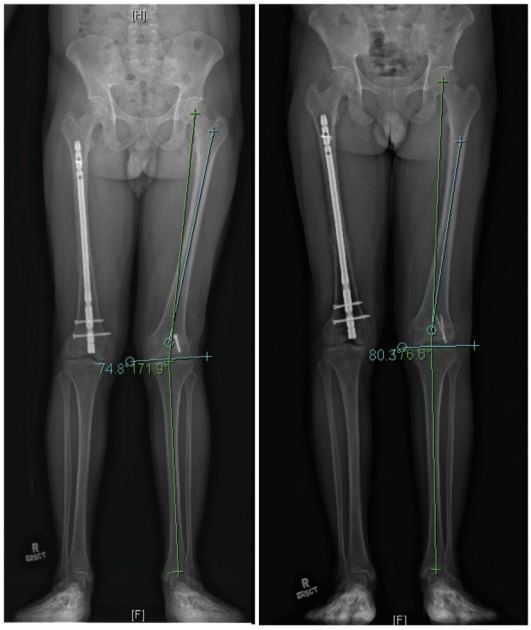

Fig. 3. Long leg film showing genu valgus deformity due to malunion, and its rectification following revision surgery (left and right, respectively).

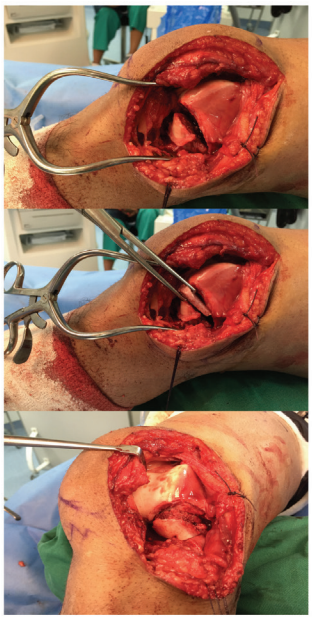

Fig. 4. Steps of revision surgery. Top image: Defect after debridement and correction of the step deformity. Middle image: Tricortical autologous iliac crest insertion. Bottom image: Restoration of articular height after graft sandwiched into fracture site.

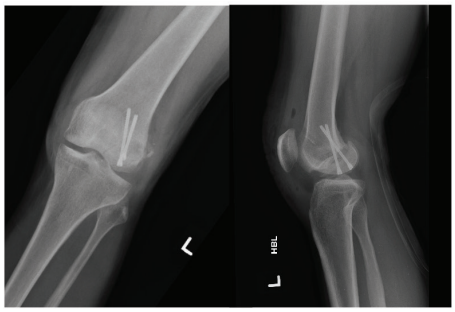

Fig. 5. Postoperative (revision surgery) radiographs showing restoration of lateral condyle.

Postoperative radiographs showed restoration of the lateral femoral condyle surface and correction of the valgus deformity (Fig. 6). He was allowed gentle range-of-motion of the knee but was kept non-weight-bearing on the left lower limb.

At 3 months, radiographs showed that the fracture had healed with good anatomical restoration. He also demonstrated knee range-of-motion of 10 to 130 degrees. He was allowed to fully bear weight at this point. No early complications such as infection and loss of reduction were noted postrevision surgery.

Discussion

A Hoffa fracture is characterised as an intra-articular fracture in the coronal plane of the posterior aspect of the femoral condyle. These fractures are rare and account for less than 1% of distal femoral fracture and generally result from direct high energy trauma[6] resulting in a shearing force on posterior femoral condyle.[7]

In this case, the mechanism of injury was likely that the patient had his knees flexed beyond 90 degrees when the concrete beam fell onto his thighs. High impact forces were thus transmitted to the lateral femoral condyle, resulting in it bearing an axial loading force.

Hoffa fractures are commonly missed (up to 31%),[8] with many conservatively treated cases resulting in common complications of malunion or non-union.[2] Malunion of such fractures can lead to progressive joint deformity and secondary degenerative joint disease. Surgical fixation is

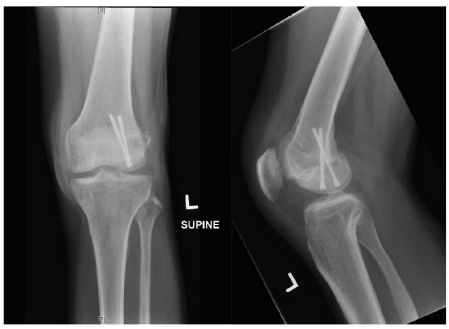

Fig. 6. Three months postrevision surgery.

hence the recommended method of treatment for Hoffa fractures.[2,3,4,5] This would allow the stable reconstruction of the affected femoral condyle, restoring joint congruence. This restoration will enable early postoperative motion of the knee[9] which speeds up the rehabilitation process. Various case reports have suggested treating Hoffa fracture malunion with corrective osteotomy[10] and xenogenous bone grafting.[11] These case studies briefly described similar patients with Hoffa fractures which had gone untreated or the complication of non-union, who had undergone salvage surgery using xenogenous bone grafts to restore anatomical reduction and articular congruence, with good outcome.[11,12,13]

We report the early results of a technique for deformity correction in a non-united Hoffa fracture. Literature has suggested that corrective osteotomy is effective in the correction of malunited intra-articular of various long bones.[9,14] Our paper highlights the novel surgical method of using a bone graft alone to elevate the depressed articular cartilage, without the need for a larger procedure like an osteotomy. We have included intraoperative photographs on the surgical steps to provide detailed demonstration on how to perform this technique. Close follow-up and hence early detection of the non-united fracture allowed for prompt intervention. The old fracture line was therefore easily identified and separated, hence avoiding the need for a larger procedure such as an osteotomy. The result was that of complete bony union at the fracture site, with good anatomical restoration. Radiographs showed reduction of the valgus knee deformity. The patient also reported resolution of knee pain and was able to demonstrate an improvement in knee flexion to 130 degrees.

Recent literature has closely examined Hoffa fractures and provided suggested treatment approaches based on the fracture configuration. Xie et al[15] reviewed 75 Hoffa fractures, characterising them based on their configuration and reconstruction. Its findings support the knowledge that the fracture more frequently occurs in the lateral femoral condyle, extending in the anterolateral to posteromedial direction. Articular comminution is more commonly seen in lateral condyle fractures and concentrated on the weight-bearing zone of the articular surface, suggesting higher likelihood of subsequently developing osteoarthritis. Such findings were noted in our patient's case.

Previously, there had been no standardised surgical approach in the treatment of Hoffa fractures, except by Holmes et al[16] which described an anterior midline approach with parapatellar arthrotomies according to fracture location. Recently, Pires et al[17] proposed a treatment algorithm for Hoffa fractures based on the modified Letenneur classification of coronal plane distal femur fractures. In this paper, for type II fractures, Pires et al proposed a posterolateral approach to fix the fracture fragment with screws in the posterior to anterior direction, furthermore recommending against the anterior approach due to difficulty in holding the small osteochondral fragments with a few screw threads. Our index operation, however, was approached via a parapatellar incision, holding the fracture fragment with a K-wire prior to securing the fracture fragment with a screw inserted in the anterior to posterior direction. Busch-Hoffa fractures are treated using the principle of absolute stability, which was achieved in our index operation with our surgical approach. Achieving stability would enable early range-of-motion and satisfactory functional outcomes. Though Jarit et al[18] demonstrated in a cadaveric study that the posterior to anterior orientation of screws provide more strength to failure than antero-posterior oriented screws, the study also estimated the ultimate axial strength of antero-posterior oriented screws to be 1025N after 100,000 cycles of loading. Such large amounts of force are seldom encountered during the rehabilitation process; hence we believe that either direction of insertion is feasible.

The parapatellar approach, via a midline incision was decided in our index operation to reduce soft tissue disruption via percutaneous fixation. The screw was inserted in an anterior to posterior direction, which offered extra-articular fixation. The principle followed here is that the intra-osseous blood supply to the posterior femoral condyle is tenuous, and is likely disrupted in displaced fractures, making preservation of the extra-osseous blood supply.[19] Minimising surgical vascular insult potentially minimises the risk for condylar avascular necrosis and non-union. We, however, identify that this approach may limit visualisation of posterior comminution and the ease of reduction.

Literature has also suggested that posterior to anterior screws may offer more biomechanical advantage and further improve rotational stability,[2] but placement might be difficult, and it has to be ensured that screw heads are countersunk if they are inserted from a cartilage-bearing. Pivoting on this point, it was decided that the salvage surgery utilised countersunk screws inserted in the posterior to anterior direction.

Postsalvage operation radiographs revealed that the screws appear to cross on the lateral film, while remaining divergent on the antero-posterior film. We acknowledge that perfectly parallel screws in both planes, if inserted perpendicular to the fracture line, offer highest degree of compression.[20] However, as these are shear fractures, this configuration of screws may predispose to failure if exposed to excessive shear forces, especially in comminuted fractures.[21] Moreover, fracture geometry and the size of fragments may preclude this in some cases.

Onay et al[22] reported a 54% incidence of osteoarthritis and a mean Knee Society Score of 78.4 (range, 53-95 points) in patients who sustained Hoffa fractures. Patients with

such injuries have an increased likelihood of developing osteoarthritis following injury due to the high-energy forces from the trauma sustained. Our patient had gone 3 months with the complication of fracture non-union, which raises his probability of developing osteoarthritis. Moreover, the use of a tricortical bone graft in contact with the articular surface further predisposes to osteoarthritis developing. However, it was important in our case to restore anatomical reduction, and hence knee stability, to enable early range-of-motion and satisfactory functional outcomes, which would otherwise not be possible given the non-ideal state of the bone stock in the fracture non-union site.

We identify the short follow-up duration of the patient as a limitation. This was due to our patient being a foreigner, who had returned to his home country postsurgery, and subsequently defaulted follow-up appointments after that at 3-months. We recommend a reasonable follow-up duration for a fracture to be at least 1 year, and ideally 2 years, to verify and manage early and late complications, if any.

Conclusion

We wish to highlight the importance of a stable and accurate anatomical reduction of Hoffa fractures in the index surgery to prevent complications such as malunion and non-union. This will aid in the rehabilitation and restoration of motion and function of the knee. In addition, we recommend close follow-up to detect complications promptly, and allow for early intervention. This may prevent the need for a larger procedure such as corrective osteotomy. The above described novel "sandwich" technique of inserting a bone graft into the fracture site is a viable treatment option for malunited Hoffa fractures.

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"High" on Muscle Spray – Ethyl Chloride Abuse

Dear Editor,

Volatile substance abuse (VSA) is intentional inhalation of volatile substances for psychoactive effects. As volatile substances have lawful commercial, household and medical uses, it is easily accessible. VSA is recognised to occur more frequently in marginalised societies, in people with low socioeconomic levels and in males.[1] Despite the prevalence of VSA in most countries—especially among young adults and youth—it is often overlooked. In Great Britain, there have been 834 VSA-related deaths since 2001, and 64 recorded in 2016 alone.[2] The harms of VSA addiction and adverse effects of ethyl chloride is often underappreciated due to the poor knowledge on VSA and the general perception that VSA is not a "true form" of drug abuse. There is limited medical literature on ethyl chloride abuse, most of them from the 1980s and 1990s. While there are reports on other VSAs, reports on ethyl chloride abuse are few. Ethyl chloride abuse has been reported in the mainstream media in Singapore[3] but awareness among the general public and health care professionals remains poor.

Case Report

A 24-year-old Singaporean Chinese gentleman presented to a local hospital with a 2-day history of nausea, vomiting and abdominal cramps. He did not have any past medical history and was not taking any medications. He admitted to abusing a "muscle spray" a few times a week for the past 2 months. He explained that the substance is sprayed onto a piece cloth and the fumes are inhaled.

On examination, he had an unsteady gait, intention tremors and bilateral nystagmus on horizontal gaze. The rest of his physical examination was normal.

Electrocardiogram, arterial blood gas, full blood count, renal profile, electrolytes and liver profile were unremarkable. Urine toxicology screen was negative. Computed tomography (CT) scan of the brain was normal. The content of the "muscle spray" was checked and it was found to contain ethyl chloride. A diagnosis of ethyl chloride poisoning was made. He was started on intravenous hydration and monitored in hospital.

On day 2 of admission, his symptoms improved but he still had unsteady gait. A contrasted magnetic resonance imaging (MRI) of the brain was performed; the results of which were normal.

He was discharged on day 4 of admission after being seen by the neurologist who concurred with the diagnosis of ethyl chloride poisoning. He was seen in the outpatient clinic 2 weeks after discharge, at which point his symptoms had completely resolved.

Discussion

There are a few case reports—as early as 1985—on ethyl chloride misuse. There have also been 2 case reports of ethyl chloride inhalation causing death.[4,5]

Ethyl chloride (C_2H_5Cl) or chloroethane is a colourless, halogenated, hydrocarbon gas which was first discovered in 1759 and widely used as a general anaesthetic in the late 19th and early 20th centuries.[6] However, its use as general anaesthesia declined due to its controversial safety profile, unpleasant recovery period and the revelation of other superior agents.[7] From as early as the 1890s, ethyl chloride has been used as topical anaesthesia. It condenses under slight pressure—so when sprayed to the skin, it produces an intense cold sensation as it rapidly evaporates due to its low boiling point. Due to this property, till date, it has been used extensively in products to induce local anaesthesia and relieve muscle pain. Ethyl chloride has also been used as a solvent, refrigerant and in the manufacturing of dyes and chemicals.

Ethyl chloride inhalation produces a temporary sensation of intoxication and at higher levels, causes incoordination and unconsciousness. Other features of inhalation include stomach cramps, eye irritation, nausea and vomiting. Long-term inhalation can lead to neurological effects such as incoordination, giddiness, dysarthria, unsteady gait, disorientation, short-term memory loss and hallucinations.[8]

There are limited studies on the longer term sequelae of ethyl chloride poisoning. There is some evidence of depression of cardiac tissues due to vagal stimulation. There are also studies showing mildly deranged liver function tests and impaired leukocyte phagocytosis with ethyl chloride inhalation.[3] Animal studies have shown associations with fetotoxicity and carcinogenicity mainly involving the skin, brain, liver, lung, uterus and endometrium.[9]

Ethyl chloride is rapidly absorbed by the lungs and is lipophilic, enabling easy access to the central nervous system which can explain the neurological symptoms.[10] Also, lipophilicity may lead to delayed clearance from the body.

The diagnosis of ethyl chloride poisoning is based on history and clinical examination. There are currently no modalities to check for ethyl chloride levels in serum or urine in Singapore. However, there are studies on detection of ethyl chloride levels from urine which have shown favourable results.[11]

Management options for ethyl chloride poisoning are limited. The mainstay of treatment is removal of the patient from further exposure and supportive care. Patients need to be monitored for cardiac arrhythmias and neurological progression. Patients who are unconscious or develop respiratory depression will require respiratory support. Progression of symptoms and signs should prompt further investigations and consideration of alternative diagnoses as effects of ethyl chloride generally clear rapidly.[12] The neurological effects usually improve within a week following cessation of ethyl chloride inhalation.[13]

Concomitant abuse of other substances needs to be always considered. Some patients may experience worsening of symptoms as a result of withdrawal effects.[13]

Conclusion

There is high propensity for abuse due to the easy availability of muscle analgesic sprays as over-the-counter drugs making ethyl chloride readily available. A check on online shopping websites in Singapore revealed that muscle analgesic sprays containing ethyl chloride produced by Walter Ritter GmbH + Co.KG and Gebauer Company can be liberally purchased. The harms of VSA must be highlighted and awareness among the general public and health care professionals needs to be raised to curb its abuse.

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Lower Lid Mass in a Neonate

A 4-week-old boy was referred to our dermatology unit for evaluation of a left lower lid mass which was present since birth. Physical examination revealed a large, non-pulsatile mass in the left infra-orbital region, with bluish discolouration of the overlying skin. In the first 2 months after birth, the mass was noted to show reduction in size, prompting the diagnosis of a rapidly involuting congenital hemangioma (RICH). However, at 5 months of age, the mass showed interval increase in size. In addition, there was increased bluish discolouration of the overlying skin. In view of the unexpected clinical course, further imaging was performed. Ultrasound of the left orbit revealed a well defined, heterogenous soft tissue mass in the medial aspect of the lower eyelid. Minimal internal vascularity was noted on Doppler interrogation (Figs. 1A-1B). Magnetic resonance imaging (MRI) confirmed the presence of a mildly enhancing heterogenous soft tissue mass, confined within the inferior extra-conal compartment of the left orbit. A small cystic area was seen within its medial aspect but no definite fluid-fluid level or fat was seen. There were also no apparent signal voids on T1-weighted and T2-weighted images to suggest the presence of calcifications. No intracranial extension was demonstrated (Figs. 1C-1E).

What is the most likely diagnosis?

A. Congenital hemangioma
B. Venous lymphatic malformation
C. Dermoid cyst
D. Epidermoid cyst
E. Heterotopic neuroglial tissue

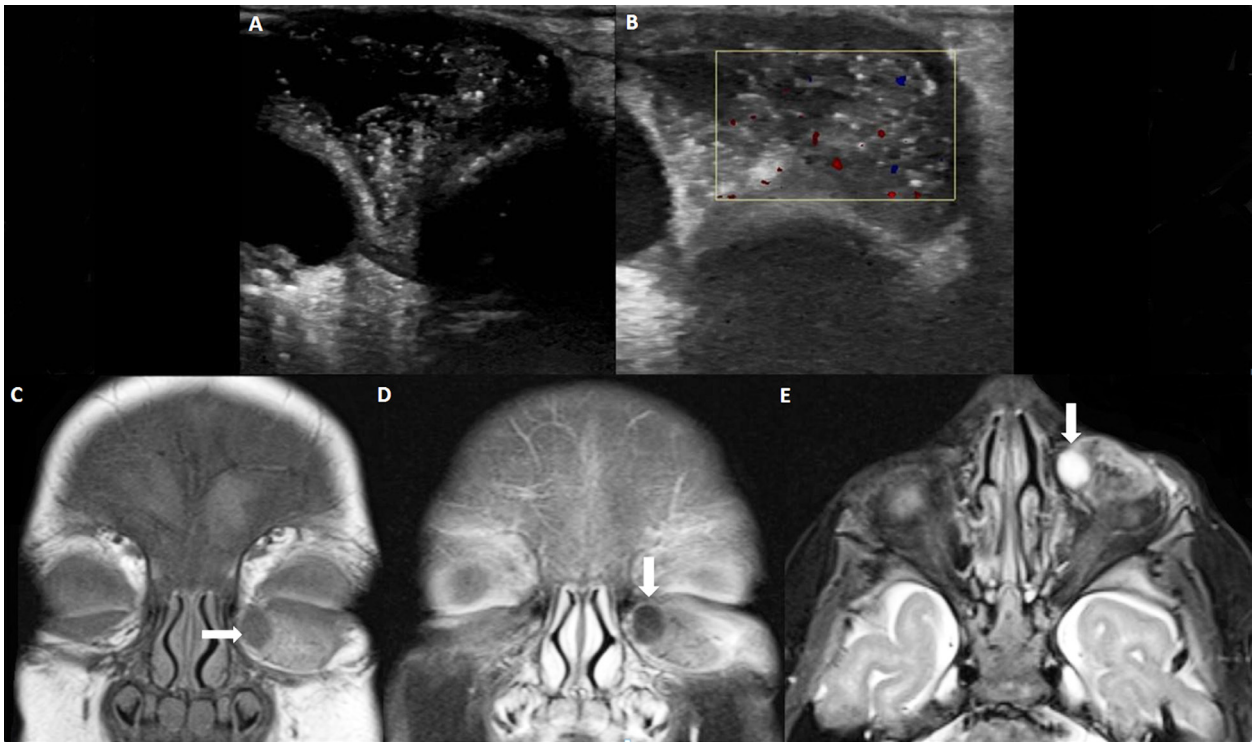

Fig 1. A: Ultrasound (US) of the left orbit showed a well defined, heterogenous soft tissue mass in the medial aspect of the infra-orbital region. B: Minimal internal vascularity was noted on Doppler interrogation. C: Coronal T1-weighted magnetic resonance imaging (MRI). D: Coronal T1-weighted postcontrast MRI. E: Axial T2-weighted MRI confirmed the presence of a mildly enhancing heterogenous soft tissue mass, confined within the antero-inferior extra-conal compartment of the left orbit. A small cystic area (white arrow) was seen within its medial aspect but no definite fluid-fluid level, fat or calcification was seen.

Answer: E

Discussion

Heterotopic neuroglial tissue is an uncommon entity, typically sited along the nasal midline structure. Its occurrence within the orbits is rare, with only few published cases. Presentation within the first year of life is common, and may be mistaken for other entities such as congenital hemangiomas, venolymphatic malformations, dermoid and epidermoid cysts, all of which are common orbital masses in the infantile period. A superficial lesion such as in our case, often presents as a mass while a deeper lesion may present with visual disturbances, proptosis or papilloedema. Diagnosing this lesion on clinical grounds is extremely challenging. Even with high resolution MRI, a definite diagnosis is often elusive due to the lack of characteristic imaging features. The presence of calcifications is not uncommon.[1] It may also appear cystic due to cerebrospinal fluid (CSF) production.[2] Although imaging may not be diagnostic, it is crucial for preoperative planning, primarily to exclude the presence of bony defects and intracranial communication, of which, if present, may necessitate a different surgical approach.[3] Definitive diagnosis requires histological demonstration of neuroglial cells as well as a positive glial fibrillary acidic protein (GFAP) immunohistochemical stain.[1,3,4] Neurons are usually sparse (as in our case) or absent. If abundant neurons are seen, one must exclude an encephalocele. Heterotopic neuroglial tissue is believed to grow at a similar rate comparable to the normal surrounding tissues. Hence, complete surgical excision is the mainstay of treatment, failing which, a recurrence rate of approximately 10% has been reported. Although there is no reported case of malignant transformation, they may possess low-grade neoplastic potential.

Congenital hemangiomas develop in utero and there is no postnatal growth, unlike infantile hemangiomas and heterotopic neuroglial tissue.[5] Doppler ultrasound classically reveals high vascularity.[6] Large flow voids on the surface of the lesion, arterial aneurysms and arteriovenous shunting may also be present. On MRI, it is seen as a heterogenous mass with inhomogenous enhancement. Cystic spaces and intralesional calcifications may also be present.[7,8] The presence of postnatal growth as well as absence of high vascularity on Doppler interrogation in our patient make this diagnosis unlikely.

Venous lymphatic malformation is another common orbital lesion within the paediatric population. Children with orbital venous lymphatic malformation typically present in childhood with slowly progressive proptosis, periorbital swelling and displacement of globe. It appears on MRI as an enhancing mass that crosses anatomic boundaries, such as the conal fascia and orbital septum. It usually has a predominant cystic component with fluid-fluid levels,[7,8] not seen in our patient. Phleboliths may also be present.

Dermoid cysts are benign heterotopic neoplasms termed 'choristomas' and account for up to 9% of paediatric orbital tumours. They occur in 3 primary locations in the head and neck—in the frontotemporal, periorbital and naso-glabellar regions. Within the periorbital region, the lateral orbit (adjacent to the lateral canthus) is the most common location. MRI appearance is variable and depends on the specific contents of the cyst. If there is lipid material within the cyst, it will appear hyperintense on T1-weighted imaging. Cysts containing higher levels of protein can appear hyperintense on both T1 and T2 imaging. Occasionally, calcifications may be present in dermoid cyst. Ruptured dermoids may also show adjacent inflammatory changes.[8] Epidermoid cysts, also a choristoma, are seen as cystic lesions, typically with restricted diffusion on diffusion-weighted imaging.

As the lesion was present at birth, demonstrated postnatal growth and appeared as a solid mass with minimal internal vascularity on imaging, ectopic neuroglial tissue was deemed the most likely diagnosis. Excisional biopsy was performed and microscopic examination revealed disorganised collections of mature neurons and glial cells (Fig. 2).

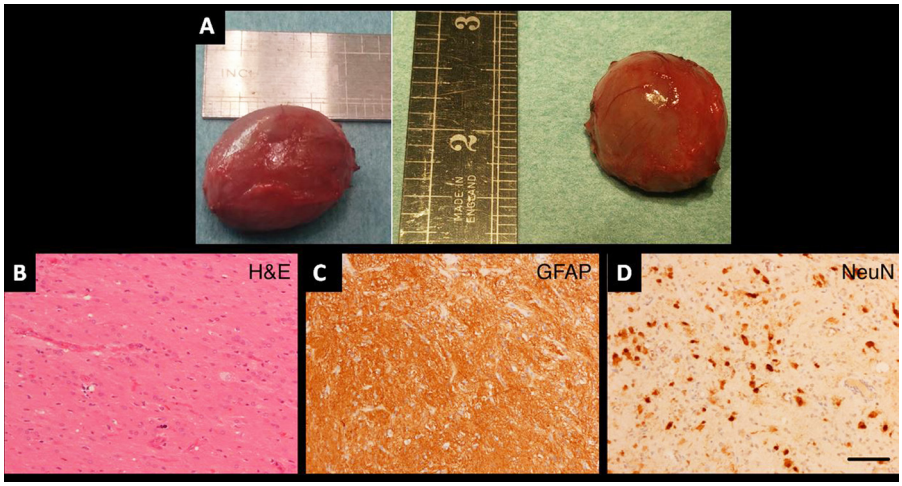

Fig. 2. A: Gross examination of the specimen showed a firm nodule measuring approximately 2.0 cm x 2.5 cm x 1.5 cm. B: Histopathological section revealed disorganised collections of mature neurons and glial cells. C: Diffusely positive glial fibrillary acidic protein (GFAP) on immunohistochemical staining was noted. D: Mild neuronal nuclei (NeuN) immunoreactivity was observed due to the presence of neurons. Findings were in keeping with neuroglial heterotopia.

Several interposed areas of haemorrhage and hemosiderin deposition were seen. Diffusely positive glial fibrillary acidic protein (GFAP) on immunohistochemical staining was noted. Mild neuronal nuclei (NeuN) immunoreactivity was also observed, due to the presence of neurons. Findings were in keeping with heterotopic neuroglial tissue.

Conclusion

Although rare, awareness of heterotopic neuroglial tissue as a cause of periorbital mass is important in expediting the diagnosis so as to enable an effective management strategy.

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