• Contemporary Approach to Memory Loss
  Dr Shea Tat Ming, Paul (佘達明醫生)

• Update on Management of Myelodysplastic Syndromes
  Dr Chen Yi Tin (陳以天醫生) & Dr Liu Sung Yu, Herman (廖崇瑜醫生)

• Differential Diagnosis of Hypercalcaemia
  Dr Chan Kwok Wing, Fredriech (陳國榮醫生)
Editorial

With an ageing population, caring for the elderly becomes an increasingly important medical problem. Apart from cardiac diseases, elderly individuals also suffer from degenerative conditions affecting the heart, brain and hormones, as well as malignancy in general. These contribute not only to mortality, but also lead to significant morbidity affecting the patients and carers. In this issue, three specialists in the field give a practical approach to managing memory disturbances, haematological malignancies and hypercalcaemia. While these conditions can affect individuals of all ages, they are more commonly seen in the elderly.

Prevention is better than cure. Good prevention and early therapy offered by physicians to manage risk factors that may be medical, psychological and social are important to ameliorate diseases in the elderly.
Memory can basically be divided into primary (working) memory, secondary (short-term) memory and tertiary (long-term) memory. Primary memory is involved with the acquisition and brief retention of new information in limited capacity storage (eg, holding a telephone number in mind while dialing the number). Secondary memory refers to the system involved in the relatively permanent storage of information (eg, immediate recall and delayed recall). Tertiary memory refers to the memory recall over, for example, a 50-year span of history.

Memory Loss with Ageing

Primary memory remains constant with age, but is likely to be affected by attention and interference (other information that takes up the storage space), as well as limited by the storage capacity. Thus, it is easily impaired by multiple factors such as psychological disturbances (eg, anxiety or depression).

Secondary memory such as immediate recall or delayed recall shows significant age differences. Older persons are less able to acquire information quickly, and even less able to remember acquired information. The main problem for the elderly is remembering names, numbers, objects, appointments, locations and addresses (arbitrary facts), but the ability to recall meaningful information (themes of conversations) remains intact. In demented patients, secondary memory is severely affected.

Tertiary memory remains intact throughout the life span. The performance of skills learned years ago may even surpass the level of previous academic achievement, implying that these memories may improve with exposure over the life span.1

Mild Cognitive Impairment

Mild cognitive impairment (MCI) refers to the transitional state between the cognitive changes of normal ageing as mentioned above, and very early dementia. The most important point is to identify individuals at an earlier point in cognitive decline, so that timely therapeutic intervention may be feasible to prevent further development into frank dementia.

Cognition in human includes language, executive function, visuospatial ability, orientation, attention and concentration, and short-term and long-term memory. Based on the cognitive complaint, MCI can be classified into amnestic (includes memory impairment) or non-amnestic (non-memory impairment) subtypes, which may or may not be

![Figure 1. Current algorithm for diagnosing and subtyping mild cognitive impairment](image-url)

MCI = mild cognitive impairment  
Adapted from reference 2.
associated with impairment of other cognitive domains. (Figure 1) The outcomes of these four MCI subtypes are different according to their presumed aetiology.

Several community-based and population-based studies have estimated the progress rate of MCI to dementia. Amnestic MCI patients were found to have a 10% to 15% chance per year to develop Alzheimer’s disease (AD). In contrast, the population incidence of AD is only 1% to 2% per year. Some MCI patients can regain normal cognition after treatment of anxiety or depression, or removal of the offending medications.

Dementia (Memory Loss due to Illness) is not a Diagnosis

Dementia is a syndrome characterized by symptoms that typically include loss of memory, judgment and reasoning, as well as changes in mood or behaviour. Dementia is not a diagnosis. Instead, it can be due to various illnesses. The most common causes include AD, vascular dementia and dementia with Lewy bodies (DLB, or Lewy body disease). Other less common causes include normal pressure hydrocephalus (NPH), frontotemporal dementia (FTD), hypothyroidism, vitamin B12 deficiency, neurosyphilis and depression.

Alzheimer’s Disease

AD is a slowly progressive disease characterized by the neuropathological lesion of beta amyloid-containing senile plaques and neurofibrillary tangles, which consist of intracellular accumulations of modified tau protein in the form of paired helical filaments. The Alzheimer’s Association lists 10 key warning signs of AD:

1. Memory loss;
2. Difficulty performing familiar tasks;
3. Problems with language;
4. Disorientation to time and place;
5. Poor or decreased judgment;
6. Problems with abstract thinking;
7. Misplacing things;
8. Changes in mood or behaviour;
9. Changes in personality; and
10. Loss of initiative.

The onset of AD is insidious, with gradual impairment of intellect and cognitive function over years. Psychological disturbances such as depression, anxiety and apathy are common. Behaviour problems such as disinhibition, aggression, agitation and delusion pose a big burden on caregivers. Language is usually well preserved until late stage. Gait, unlike in other causes of dementia, is usually unaffected. Severe AD can be recognized when an individual needs full-time care and assistance with basic activities of daily living, such as toileting, dressing and bathing.

In the past 20 years, basic research has brought about a much needed infusion of optimism and urgency in the treatment of AD. Cholinesterase inhibitors such as donepezil and rivastigmine are currently available pharmacotherapies with modest benefit for patients, but disease modifying drugs are on the horizon. A recent study published in November 2008 showed that drugs such as memantine may slow the decline in glucose metabolism in all brain regions and the progression of hippocampal atrophy. Evidence showed that early diagnosis of AD is important to maximally preserve patients’ quality of life. However, in Hong Kong, patients are usually diagnosed at later stages of the disease when disabling and troubling psychological and behaviour symptoms are already established, causing severe impairment in patients’ daily functioning.

Vascular Dementia

Vascular dementia is characterized by an abrupt onset with stepwise deterioration. The diagnosis is less well defined clinically, with impairment of one or more cognitive domains occurring within months after a stroke. Specific cognitive domains affected depend on the stroke location, and prominent memory loss may or may not be present. Deficits in attention and executive function are common. Patients may have a history of vascular risk factors such as hypertension, hyperlipidaemia, diabetes or atrial fibrillation. In reality, pure vascular dementia may be relatively unusual. Vascular insult commonly coexists with Alzheimer’s plaques or other neuropathologies, and a small infarct may easily unmask underlying early AD.

In addition, patients with vascular dementia may present with neurological signs. Gait disturbances may occur early in the disease. The common gait disorder known as marche de petite, or frontal lobe gait apraxia, is usually associated with small vessel disease of the brain, evidenced in CT of the brain as leukoariorasis.

Dementia With Lewy Bodies and Parkinson’s Disease

Dementia With Lewy Bodies

DLB is a common cause of neurodegenerative dementia, second only to AD. Lewy bodies are neuronal inclusions composed of abnormally phosphorylated neural filament proteins aggregated with ubiquitin and α-synuclein. The prevalence is around 20% by one autopsy study. The diagnosis has become evident only in the past 2 decades due to improvement in antibody staining method.

The clinical diagnosis of DLB was not established until 1995. While progressive cognitive decline is the key symptom, memory complaints are not always evident in the early phase of DLB. The core features include vivid visual hallucination (usually of human figures or animals), fluctuating cognition with changes in mental state within minutes or weeks, and motor features of Parkinsonism. It is sometimes difficult to decide whether the patient is suffering from DLB or Parkinson’s disease dementia (PDD). As an operational guide, PDD is defined as Parkinsonism that occurs more than 1 year before the appearance of dementia features, whereas DLB is defined as...
dementia appearing within 1 year of Parkinsonism. Other common features of DLB include depression, autonomic dysfunction, and rapid eye movement sleep disorder. DLB shows good response to treatment with cholinesterase inhibitors.

DLB is commonly misdiagnosed or underdiagnosed in Hong Kong and Asia, leading to unnecessary morbidity.† DLB is usually misdiagnosed as psychosis due to the vivid hallucination. (Figure 2) Prescription of antipsychotics, whether typical or atypical, would invariably control the symptom, but may lead to further impairment of both cognition and mobility due to neuroleptic sensitivity associated with the drugs. Moreover, many of these patients have to be sent to institutions for nursing care, and some DLB cases are treated as Parkinson’s disease with non-motor features. All these scenarios account for the low prevalence of DLB in Hong Kong.

Approach and Differentiation of Memory Loss

History

The most important aspect of history taking is to identify any significant functional deficits, which would point to a more severe diagnosis. Interviewing a family member or close friends is essential. Functional impairment and psychological disturbance, usually presenting as anxiety and irritability, should be looked for. Behaviour problems such as disinhibition and loss of social skills may point to the diagnosis of dementia.

Physical Examination

A complete neurological examination is a must for the assessment of memory loss. While focal or pyramidal signs suggest vascular causes of memory loss, ataxic fibrillation or valvular lesions may support the possibility of vascular insult. Gait instability would suggest the diagnosis of DLB or NPH.

Mental State Examination

Special attention should be paid to signs of anxiety, depression, inattention and disinhibition during the examination. Clinicians should be alert to restlessness or agitation, as well as negative self-statements, poor effort and tearfulness, as these may indicate the diagnosis of depression.

The Mini-Mental State Examination (MMSE), although widely used, is only validated in demented patients, and is probably not sensitive or specific enough for the diagnosis of MCI. It also has a strong ceiling effect, in which it is not sensitive for mild to moderate cognitive impairment in well-educated individuals or businessmen. The Montreal Cognitive Assessment (MoCA) is a 10-minute screening tool to screen for MCI with a sensitivity of up to 90%. It is well-validated and has been translated into different languages, including Mandarin and Cantonese. Other assessment tools such as the Clock Drawing Test, Hopkins Verbal Learning Test, Wechsler Memory Delayed Recall, Trail Making Test and Rey-Osterrieth Complex Figure test have also been used to assess memory loss.

Diagnostic Tests

Medical diseases that cause memory loss include metabolic abnormalities such as hypernatraemia, hypoglycaemia, hypercalcaemia, uraemia, hypothyroidism, liver failure, infection and vitamin deficiency. A complete workup including metabolic tests such as complete blood count, thyroid function test, vitamin B12 level, electrolytes and VDRL is indicated. Brain imaging such as CT scan and MRI are not routinely used for the diagnosis of memory loss, but they may be indicated when brain pathology is suspected. Positron emission tomography is useful for differentiating FTD from AD. Decreased temporoparietal blood flow on single photon emission computed tomography would suggest a higher risk of conversion from mild memory loss to dementia over the next few years.‡

Conclusion

Memory loss is a common clinical presentation, particularly after middle age. It ranges from physiological change of ageing to MCI and frank dementia of various aetiologies. It is important to correctly identify patients with memory loss and their possible aetiologies, and refer them to specialists for further workup and management before the development of troubling psychological, behavioural and functional disturbances or potentially irreversible adverse drug reactions due to misdiagnosis or underdiagnosis.
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Case Study

A 72-year-old lady presented with progressive exertional dyspnoea, palpitation and dizziness. She was pale with no hepatosplenomegaly or lymphadenopathy. There was no clinical evidence of blood loss. Blood test showed: haemoglobin, 6.2 g/dL; red blood cell, 2.29 x 10^12/L; haematocrit, 0.239 L/L; mean corpuscular volume, 102 fl; mean corpuscular haemoglobin, 31.1 pg; mean corpuscular haemoglobin concentration, 33.5 g/dL; red cell distribution width, 15.7%; white blood cell, 3.8 x 10^9/L (neutrophil 78.5%, lymphocyte 12.2%, monocyte 7.6%, eosinophil 1.2%, basophil 0.5%); platelet, 404 x 10^9/L. Liver and renal function tests were normal.

1. Which of the following test(s) is/are the most appropriate further investigation(s)?
   (1) Thyroid function test
   (2) Vitamin B12 and folate level
   (3) Reticulocyte count
   (4) Peripheral blood smear
   (5) G6PD status

   a. (1) + (2) + (3)
   b. (1) + (2) + (4)
   c. (1) + (3) + (5)
   d. (1) + (2) + (3) + (4)
   e. All of the above

Results

Thyroid function test, vitamin B12 and red cell folate level were all normal. Reticulocyte count was 1%. Bone marrow aspiration and cytogenic study were performed. (Figures 1 and 2)

2. What is the most likely diagnosis?
   a. Megabloblastic anaemia
   b. Intravascular haemolysis
   c. Myelodysplastic syndrome
   d. Acute leukaemia
   e. Myelofibrosis

   Cytogenetic study showed deletion of the long arm of chromosome 5. (Figure 2)

3. What is the most appropriate treatment?
   a. Hypomethylating agent
   b. Haematopoietic stem cell transplantation
   c. Erythropoietin
   d. Lenalidomide
   e. Cytarabine

Discussion

Differential diagnoses of macrocytic anaemia include vitamin B12 or folate deficiency, hypothyroidism, haemolytic anaemia, reticulocytosis and myelodysplasia. Checking G6PD in the setting of suspected haemolysis can lead to a falsely normal result. Although G6PD...
deficiency is an X-linked disorder, it can occur in some women due to an extreme degree of X inactivation of the normal chromosome.

Bone marrow examination showed an abundance of small megakaryocytes with hypolobulated nuclei suggestive of underlying 5q- syndrome, which is confirmed by the cytogenetic analysis with deletion of the long arm of chromosome 5. The 5q- syndrome is classified as a myelodysplastic syndrome. Lenalidomide has been shown the most effective treatment of this subtype of myelodysplastic syndrome.

**Myelodysplastic syndromes (MDS)** are a heterogeneous group of conditions characterized by bone marrow failure and risk of progression to acute leukaemia. In MDS, blood stem cells do not mature into healthy red blood cells, white blood cells or platelets. The immature blood cells, called blasts, do not function normally, and patients are at increased susceptibility to infection, anaemia or bleeding.

MDS can arise de novo or, less commonly, after chemotherapy or transplantation. It can affect people of any age, but the risk of developing MDS increases steadily with advancing age. According to the Myelodysplastic Syndromes Foundation, at least 10,000 new MDS cases are being diagnosed in the United States annually.

The previous French-American-British (FAB) classification of MDS is no longer commonly used. According to the new WHO classification, MDS include the following:

- Refractory anaemia;
- Refractory anaemia with ringed sideroblasts;
- Refractory anaemia with excess blasts;
- Refractory anaemia with excess blasts in transformation;
- Refractory cytopenia with multilineage dysplasia;
- MDS associated with an isolated del(5q) chromosome abnormality; and
- Unclassifiable MDS.

The prognosis of MDS can be predicted using the International Prognostic Scoring System (IPSS). Despite being regarded not as a cancer but as a preleukaemic event most of the time, the outcome of MDS patients is dismal. For example, historical comparison showed that patients with MDS have poorer overall survival (OS) than those with lung cancer.

For many years, the only chance of cure is haemopoietic stem cell transplantation. However, as MDS mainly affect the elderly, most of the patients are not transplant candidates and the management is mainly best supportive care. In the past few years, three drugs have been approved by the FDA for the specific treatment of patients with MDS.

### Table 1. Prognosis of MDS based on IPSS

<table>
<thead>
<tr>
<th>Survival and AML evolution</th>
<th>Score value</th>
<th>0</th>
<th>0.5</th>
<th>1.0</th>
<th>1.5</th>
<th>2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prognostic variable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marrow blasts (%)&lt;sup&gt;*&lt;/sup&gt;</td>
<td>&lt;5</td>
<td>5-10</td>
<td>---</td>
<td>11-20</td>
<td>21-30</td>
<td></td>
</tr>
<tr>
<td>Karyotype&lt;sup&gt;#&lt;/sup&gt;</td>
<td>Good</td>
<td>Intermediate</td>
<td>Poor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytopenia†</td>
<td>0/1</td>
<td>2/3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk category (% IPSS population)</th>
<th>Overall score</th>
<th>Median survival (years) in the absence of therapy</th>
<th>25% AML progression (years) in the absence of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (33)</td>
<td>0</td>
<td>5.7</td>
<td>9.4</td>
</tr>
<tr>
<td>Intermediate-1 (38)</td>
<td>0.5-1.0</td>
<td>3.5</td>
<td>3.3</td>
</tr>
<tr>
<td>Intermediate-2 (22)</td>
<td>1.5-2.0</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>High (7)</td>
<td>≥2.5</td>
<td>0.4</td>
<td>0.2</td>
</tr>
</tbody>
</table>

<sup>*</sup> Patients with 20%-30% blasts may be considered as MDS or AML.

<sup>#</sup> Cytogenetics: Good = normal, -Y alone, del(5q) alone, del(20q) alone; poor = complex ≥3 abnormalities) or chromosome 7 anomalies; intermediate = other abnormalities. [This excludes karyotypes t(8;21), inv16, and t(15;17), which are considered to be AML, not MDS.]

† Cytopenias: Neutrophil count <1,800/mcL, platelets <100,000/mcL, haemoglobin <10 g/dL. Adapted from reference 1.

### Table 2. Comparison of survival between MDS and lung cancer patients

<table>
<thead>
<tr>
<th>IPSS score</th>
<th>Risk group</th>
<th>Median survival (years)</th>
<th>Stage</th>
<th>Median survival (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Low</td>
<td>5.7</td>
<td>1a</td>
<td>8</td>
</tr>
<tr>
<td>0.5-1</td>
<td>Intermediate-1</td>
<td>3.5</td>
<td>2a</td>
<td>5.4</td>
</tr>
<tr>
<td>1.5-2</td>
<td>Intermediate-2</td>
<td>1.2</td>
<td>3a</td>
<td>2.4</td>
</tr>
<tr>
<td>≥2</td>
<td>High</td>
<td>0.4</td>
<td>4</td>
<td>1.2</td>
</tr>
</tbody>
</table>

IPSS = International Prognosis Scoring System
Adapted from references 2 and 3.

### Table 3. Drugs approved by FDA for treatment of MDS

<table>
<thead>
<tr>
<th>Indication</th>
<th>Azacitidine</th>
<th>Lenalidomide</th>
<th>Decitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td>All MDS subtypes (FAB classes)</td>
<td>Low-risk MDS IPSS low or intermediate-1 with deletion 5q: transfusion dependent</td>
<td>All MDS subtypes (FAB classes) IPSS: intermediate-1, intermediate-2, high</td>
<td></td>
</tr>
<tr>
<td>Route</td>
<td>Subcutaneous/intravenous</td>
<td>Oral</td>
<td>Intravenous (1-3 hours)</td>
</tr>
<tr>
<td>Dosing</td>
<td>75 mg/m²/day for 7 days Q4W</td>
<td>10 mg/day</td>
<td>45 mg/m²/day for 3 days Q6W (divided by 3 doses/day)</td>
</tr>
<tr>
<td>Mode of action</td>
<td>DNA hypomethylation</td>
<td>Immune modulation</td>
<td>Angiogenesis inhibition</td>
</tr>
</tbody>
</table>

FAB classes = French-American-British classes; IPSS = International Prognostic Scoring System

**Answers:** 1. d; 2. c; 3. d
Mechanism of Action of Hypomethylating Agents

Aberrant methylation of cytosines within the CpG promoter regions by DNA methyltransferases (DNMT) may silence critical components of normal cell growth and differentiation programmes. Hypomethylating agents covalently bind to the DNMT during S phase, irreversibly inhibiting their function and leading to the loss of methylation. Examples of hypomethylating agents include azacitidine and decitabine. They are believed to act by hypomethylation of DNA and direct cytotoxicity on abnormal haematopoetic cells in the bone marrow. By inhibiting hypermethylation, the silent genes that are critical to cell differentiation and proliferation are restored.

Azacitidine

Azacitidine was approved by the FDA in May 2004 for the treatment of all MDS subtypes according to the FAB classification. Patients received 75 mg/m$^2$ for 7 days every 4 weeks subcutaneously. Patients who received azacitidine had an overall response of 15.7% compared to 0% in the observation group.

The AZA-001 study showed that the use of azacitidine for a median of 9 cycles compared to that of conventional care regimens (CCR) significantly improved median OS (24.5 months vs 15 months, $p=0.0001$; hazard ratio, 0.58; 95% confidence interval, 0.43-0.77) and almost doubled the 2-year survival rate (50.8% vs 25.2%). Survival benefit was observed across relevant patient subgroups, including elderly patients (age >65 years), those with acute myeloid leukaemia (AML), and patients with poor risk cytogenetics.4

Moreover, 45% of patients who were transfusion-dependent at baseline became transfusion-independent (vs 11.4% with CCR). The median duration of independence was 13.0 months.$^4$

Decitabine

Decitabine is also a nucleoside analogue. It was approved by the FDA in May 2006 for the treatment of all MDS subtypes according to the FAB classification, with IPSS risk category of intermediate-1 or above. Its mechanism of action is similar to that of azacitidine.

In a phase III randomized, open-label, multicenter controlled trial evaluating 170 adult patients with MDS meeting the FAB classification criteria, 89 patients were randomized to receive decitabine (intravenously at 15 mg/m$^2$ over a 3-hour period, every 8 hours, for 3 consecutive days; cycle repeated every 6 weeks) plus supportive care and 81 patients to supportive care alone. Response criteria were classified using the MDS International Working Group (IWG) criteria. The overall response rate (complete response + partial response) in the intention-to-treat population was 17% in the decitabine group and 0% in the supportive care group. (Table 4) All but one of the decitabine-treated patients who responded did so by the fourth cycle.5

<table>
<thead>
<tr>
<th>Table 4. Response to decitabine treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>IWG response rate, onset and duration</td>
</tr>
<tr>
<td>Decitabine (n=89)</td>
</tr>
<tr>
<td>Supportive care (n=81)</td>
</tr>
<tr>
<td>Overall response rate (CR + PR)</td>
</tr>
<tr>
<td>CR</td>
</tr>
<tr>
<td>PR</td>
</tr>
<tr>
<td>Haematological improvement</td>
</tr>
<tr>
<td>Median time to response (CR + PR)</td>
</tr>
<tr>
<td>Median duration of response (CR + PR)</td>
</tr>
</tbody>
</table>

CR = complete response; IWG = International Working Group; PR = partial response
Adapted from reference 5.

<table>
<thead>
<tr>
<th>Table 5. Efficacy of lenalidomide in MDS patients with del(5q)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients 5q- 10 mg QD (n=103)</td>
</tr>
<tr>
<td>Transfusion independence (&gt;8 weeks)</td>
</tr>
<tr>
<td>Minor (&gt;50% decrease in transfusion)</td>
</tr>
<tr>
<td>Transfusion independence + minor</td>
</tr>
<tr>
<td>Median time to response</td>
</tr>
<tr>
<td>Median haemoglobin increase</td>
</tr>
<tr>
<td>Median duration of transfusion independence</td>
</tr>
<tr>
<td>Cytogenetic response</td>
</tr>
</tbody>
</table>

IPSS = International Prognostic Scoring System
* Eligibility: del(5q), IPSS low or intermediate-1
Adapted from reference 6.

Lenalidomide

Lenalidomide is an immunomodulatory drug with an array of biological activities, including suppression of proinflammatory cytokine production by monocyte enhancement of natural killer cells and T cell activation, and inhibition of angiogenesis. It was approved by FDA for the treatment of a specific entity of MDS – the 5q- syndrome. The 5q- syndrome is characterized by female preponderance, severe anaemia, thrombocytosis, typical dysmegakaryopoiesis, rare AML transformation and favourable outcome.

In the MDS-003 trial, a large, multicentre phase II trial in MDS with del(5q), patients received lenalidomide 10 mg daily or 10 mg daily for 21 days every 4 weeks. The median age was 71 years, and 66% of the patients were female. The median interval from diagnosis was 2.5 years. Transfusion independence was obtained in 68% of the patients, and a further 8% of patients had a minor (>50% decrease in transfusion) response.$^5$ (Table 5)

Conclusion

Apart from conventional supportive care, novel agents are now available for patients with MDS. A certain subgroup and proportion of MDS patients may benefit from these new therapeutic agents.

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References:
1. Fenaux P et al, ASH 2007 Abstract no. 817
3. Vidaza full prescribing information
Hypercalcaemia can result from enhanced entry of calcium into the extracellular fluid from bone resorption, from excessive absorption of calcium from the gastrointestinal tract, from enhanced renal calcium conservation, or from a combination of all three mechanisms. Hypercalcaemia may be caused by a large number of disorders. \(^1\) (Table 1) The two most common causes are malignancy and primary hyperparathyroidism, accounting together for approximately 90% of all hypercalcaemic patients. In the general population, primary hyperparathyroidism is more common than malignancy. In a hospitalized population, up to 70% is due to malignancy.\(^2\) The differential diagnosis of hypercalcaemia is focused initially on the distinction between primary hyperparathyroidism and malignancy. A careful history and physical examination always help in the early evaluation.

Primary hyperparathyroidism is caused by hypersecretion of parathyroid hormone (PTH), whereas hypercalcaemia of malignancy is caused by a number of factors produced by the tumour or by direct metastatic skeletal invasion. Thus, the distinction to be made is between PTH-dependent and PTH-independent hypercalcaemia. Although the two disorders are different, there are similarities in the clinical features. Along with hypercalcaemia, there is an increase in urinary cyclic adenosine monophosphate (cAMP) and hypophosphataemia. In malignancy, the hypercalcaemia tends to be more severe and is characterized by increased bone resorption and suppressed bone formation.\(^3\)

Although not diagnostically useful, hypercalcaemia of malignancy can be associated with a mild hypochloremic alkalosis. In contrast, primary hyperparathyroidism is more characteristically associated with a mild hyperchloremic acidosis. In primary hyperparathyroidism, the hypercalcaemia tends to be mild, although acute severe hypercalcaemia of primary hyperparathyroidism is well known. In hyperparathyroidism, both bone resorption and bone formation are enhanced.\(^4\)

Another difference between primary hyperparathyroidism and cancer-associated hypercalcaemia is the level of 1,25-dihydroxyvitamin D, the active metabolite of vitamin D. In primary hyperparathyroidism, 1,25-dihydroxyvitamin D tends to be in the upper range of normal, and in 35% of patients, it is frankly elevated. This is due to the actions of PTH to stimulate the conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D. In hypercalcaemia of malignancy, the 1,25-dihydroxyvitamin D levels are normal or suppressed. The mechanism of this suppression is controversial.\(^5,6\)

The most helpful way to distinguish between hypercalcaemia of malignancy and primary hyperparathyroidism is measurement of the PTH concentration. Immunoradiometric (IRM) or immunochemical luminometric assays (ICMA) for intact PTH detect elevated levels in 85% to 90% of patients with primary hyperparathyroidism.\(^7\) PTH levels will be suppressed in hypercalcaemia due to causes other than primary hyperparathyroidism, lithium and thiazide use and familial hypocalciuric hypercalcaemia. Even when the malignancy is associated with PTH-related protein (PTHrP), PTH levels will be suppressed because IRMA and ICMA assays for PTH show no cross-reactivity with PTHrP.

<table>
<thead>
<tr>
<th>Differential Diagnosis of Hypercalcaemia</th>
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<tbody>
<tr>
<td><strong>Primary hyperparathyroidism</strong></td>
</tr>
<tr>
<td>• Sporadic (adenoma, hyperplasia or carcinoma)</td>
</tr>
<tr>
<td>• Familial</td>
</tr>
<tr>
<td>- Isolated</td>
</tr>
<tr>
<td>- Cystic</td>
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<tr>
<td>- Multiple endocrine neoplasia type 1 or 2</td>
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<tr>
<td><strong>Malignancy</strong></td>
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<tr>
<td>• Parathyroid hormone-related protein</td>
</tr>
<tr>
<td>• Excess production of 1,25-dihydroxyvitamin D</td>
</tr>
<tr>
<td>• Other factors (cytokines, growth factors)</td>
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<tr>
<td><strong>Granulomatous diseases</strong></td>
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<tr>
<td>• Sarcoidosis</td>
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<tr>
<td>• Tuberculosis</td>
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<tr>
<td>• Histoplasmosis</td>
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<tr>
<td>• Coccidiodermosis</td>
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<tr>
<td>• Leprosy</td>
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<tr>
<td><strong>Nonparathyroid endocrine disorders</strong></td>
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<tr>
<td>• Thryotoxicosis</td>
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<tr>
<td>• Phaeochromocytoma</td>
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<tr>
<td>• Addison’s disease</td>
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<tr>
<td>• Vasointestinal polypeptide hormone-producing tumour</td>
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<tr>
<td><strong>Medications</strong></td>
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<tr>
<td>• Thiaizide diuretics</td>
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<tr>
<td>• Lithium</td>
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<tr>
<td>• Vitamin D or its analogues</td>
</tr>
<tr>
<td>• Hypervitaminosis A</td>
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<tr>
<td>• Milk-alkali syndrome</td>
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<tr>
<td><strong>Familial hypocalciuric hypercalcaemia</strong></td>
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<tr>
<td><strong>Immobilization</strong></td>
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<td><strong>Parenteral nutrition</strong></td>
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<tr>
<td><strong>Aluminium excess</strong></td>
</tr>
<tr>
<td><strong>Acute and chronic renal failure</strong></td>
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</tbody>
</table>

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Key words: Hypercalcaemia (高鈣血症), primary hyperparathyroidism (原發性甲狀旁腺功能亢進症), malignancy (惡性腫瘤)
Primary Hyperparathyroidism

Incidence
Since the advent of routine screening of serum calcium levels with the multichannel biochemical autoanalyzer in Western countries, increased number of cases of primary hyperparathyroidism with less severe clinical effects have been reported. From 1974 to 1981, primary hyperparathyroidism was a relatively uncommon disease in Hong Kong, with a prevalence of 3.1 per 100,000 hospital population. Shortly after installation of the autoanalyzer, the prevalence rose only slightly to 3.7 per 100,000 hospital population during the period from 1982 to 1986. Ten years later, the prevalence had increased by more than five times to 18.7 per 100,000 hospital population in the year of 1996. The frequency of parathyroidectomy has also increased from one per year in 1987 to one per month in 1996 in another regional hospital. However, the true prevalence of the disease in Hong Kong may be higher as hyperparathyroidism is more commonly seen in the outpatient setting. Regular screening for calcium level should be done in patients who are concerned with their bone health.

Clinical Manifestations
Data from the two regional hospitals in Hong Kong are combined for analysis. The cohort consisted of 74 patients (50 female, 24 male) diagnosed with primary hyperparathyroidism from 1987 to 1996. The mean age at presentation was 58 years. Fifty-five percent (n=41) of the patients were incidentally discovered to have hypercalcemia and were asymptomatic at presentation. The other patients presented with one or more of the following symptoms: constipation, polyuria, abdominal pain, bone pain or neuropsychiatric symptoms. In addition, 16.2% (n=12) of patients presented with renal lithiasis, and 5.4% (n=4) of patients had X-rays with features that were typical of subperiosteal bone resorption or osteitis fibrosa cystica. (Figure 1)

All patients had elevated serum calcium levels at a mean value of 3.0 mmol/L. Eighty-seven percent (n=64) of the patients had clearly elevated PTH concentrations. Thirteen percent of them had PTH concentrations at the upper limit of the normal range, which were inappropriately high in association with hypercalcemia. The mean PTH level was at about two to three times of normal, at 160 pg/mL. The mean serum phosphate level was at the lower limit of the normal range, at 0.7 mmol/L (normal: 0.7 to 1.0 mmol/L). Serum alkaline phosphatase level was elevated in 40% of patients. The 24-hour urinary calcium levels were elevated in 30 patients (41%).

The clinical manifestation of patients with primary hyperparathyroidism in Hong Kong is more similar to that of patients in New York than those in Beijing. (Table 2) In the United States, primary hyperparathyroidism typically presents as asymptomatic hypercalcemia in women within 10 years of menopause. Most often, it is discovered accidentally in the course of a routine multichannel chemistry screening test. Primary hyperparathyroidism in Beijing presents much more differently. Patients are at least a decade or two younger at presentation compared to those in the West. The clinical presentations are more severe, with higher calcium and PTH levels. Asymptomatic primary hyperparathyroidism commonly seen in the West is exceedingly rare in Beijing. Radiological evidence for osteitis fibrosa cystica is seen in more than half of the cases. Up to 40% of patients have renal stones. In contrast, more than half of the patients with primary hyperparathyroidism present as asymptomatic hypercalcemia in Hong Kong. Radiological evidence of bone disease is seen in only 5.4% of the cases. The incidence of renal stones is also similar to that in the United States, at 15% to 20%. The difference in socioeconomic development, availability of multichannel biochemical autoanalyzer, and also vitamin D nutrition in the population may explain the discrepancy.

![Figure 1. Typical features of subperiosteal bone resorption in patients with primary hyperparathyroidism on X-ray](image)

<table>
<thead>
<tr>
<th>Time period</th>
<th>New York</th>
<th>Hong Kong</th>
<th>Beijing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number</td>
<td>143</td>
<td>74</td>
<td>134</td>
</tr>
<tr>
<td>Gender ratio (F:M)</td>
<td>3.4:1</td>
<td>2.1</td>
<td>2.6:1</td>
</tr>
<tr>
<td>Age at presentation</td>
<td>65</td>
<td>58</td>
<td>37</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>80%</td>
<td>55%</td>
<td>3%</td>
</tr>
<tr>
<td>Skeletal disease</td>
<td>1.4%</td>
<td>5.4%</td>
<td>56%</td>
</tr>
<tr>
<td>Nephrolithiasis</td>
<td>17%</td>
<td>16.2%</td>
<td>41%</td>
</tr>
<tr>
<td>Calcium level</td>
<td>2.8 mmol/L</td>
<td>3.0 mmol/L</td>
<td>&gt;3.0 mmol/L</td>
</tr>
<tr>
<td>PTH level</td>
<td>1.5-2x</td>
<td>2-3x</td>
<td>20x</td>
</tr>
<tr>
<td>Fractures</td>
<td>Infrequent</td>
<td>Infrequent</td>
<td>Frequent (35%)</td>
</tr>
</tbody>
</table>

PTH = parathyroid hormone
Adapted from references 11 and 12.
Hypercalcaemia in Malignancy

Hypercalcaemia is one of the most common paraneoplastic syndromes associated with cancer, complicating the clinical course of 5% to 10% of patients with advanced malignancy. The mechanisms responsible for hypercalcaemia of malignancy are diverse, and different types of malignancy are associated with different mechanisms.

Hypercalcaemia Associated With Local Osteolysis

The underlying mechanism of hypercalcaemia in patients with breast cancer, multiple myeloma and some cases of lymphoma involves locally active factors that induce osteoclast activation and subsequent excessive release of calcium into extracellular space. These local osteoclast-activating factors might be secreted by tumour cells alone or in association with activated host cells. Among many potential candidate molecules, prostaglandins, proteases, lysosomal enzymes, interleukin-1 and tumour necrosis factor have received attention.

Humoral Hypercalcaemia of Malignancy

This group comprises about 80% of patients with malignancy-associated hypercalcaemia. The syndrome of humoral hypercalcaemia of malignancy (HHM) is clinically analogous to primary hyperparathyroidism. Hypercalcaemia and hypophosphataemia are typically present in HHM, as in primary hyperparathyroidism. Over the past 20 years, it has become clear that in most cases of HHM, the cause is PTHrP, a molecule that bears both striking resemblance and remarkable difference from PTH.

Seminal studies from three laboratories in the 1980s have established the identity of PTHrP. PTHrP is a larger molecule than the 84-amino acid PTH molecule than the 84-amino acid PTH. The single gene that codes for PTHrP can lead to one of three peptides of varying length: 1-139, 1-141, and 1-173. The first 13 amino acids of PTHrP are highly homologous to PTH. Thereafter, the primary structure diverges. However, the high degree of homology at the amino-terminal end of both molecules is believed to be responsible for their shared actions at bone and kidney. In fact, PTH and PTHrP appear to stimulate the same signal transduction mechanisms via a common receptor, the PTH/PTHrP receptor. Squamous cell carcinoma (eg, nasopharynx, lung, oesophagus, cervix, vulva and skin) is most commonly associated with PTHrP production. Adenocarcinoma (eg, breast and renal cell carcinoma, transitional carcinoma of the bladder, ovarian carcinoma) can also be associated with this syndrome. Other malignancies such as human T-cell lymphoma/leukaemia have also been associated with PTHrP production.

Hodgkin's disease is most consistently associated with 1,25-dihydroxyvitamin D when hypercalcaemia develops. Breslau and colleagues have reported three patients with Hodgkin's lymphoma in whom, in the absence of any lytic bone lesions, hypercalcaemia developed along with high serum concentrations of 1,25-dihydroxyvitamin D and suppressed PTH levels. Other groups have reported similar findings in patients with non-Hodgkin's lymphoma and acquired immunodeficiency syndrome.

Hypercalcaemia in Granulomatous Diseases

In contrast to the megadosage of vitamin D that is usually required to produce vitamin D toxicity, hypercalcaemia can develop rather easily in patients with granulomatous diseases without excessive intake of exogenous vitamin D. These individuals are said to be hypersensitive to vitamin D. The cause of hypercalcaemia is the poorly regulated extrarenal synthesis of 1,25-dihydroxyvitamin D by the granulomatous tissue itself. The mechanisms by which the active vitamin D metabolites cause hypercalcaemia include increased intestinal calcium absorption and enhanced osteoclastic bone resorption. Hypercalcaemia has been reported in association with the following granulomatous diseases: sarcoidosis, tuberculosis, histoplasmosis, coccidioidomycosis, leprosy and silicone-induced granuloma.

Nonparathyroid Endocrine Causes of Hypercalcaemia

Thyrotoxicosis

Hypercalcaemia occurs in approximately 5% of patients with thyrotoxicosis. The hypercalcaemia rarely exceeds 2.80 mmol/L. The elevated circulating calcium concentration is believed to result from excessive osteoclastic activity induced by the thyrotoxic state. Hypercalcaemia will remit with normalization of thyroid function.

Phaeochromocytoma

Phaeochromocytoma may be accompanied by hypercalcaemia, usually in association with coexisting primary hyperparathyroidism in multiple endocrine neoplasia type 2 (MEN-2). The occasional remission of hypercalcaemia after successful removal of phaeochromocytoma suggests the possibility that the phaeochromocytoma is the source of a hypercalcaemia factor, such as PTHrP.

Addison's Disease

Addison's disease is a rare cause of hypercalcaemia. The elevated serum calcium level is due to loss of the antagonistic properties of glucocorticoids on calcium absorption and bone mobilization, as well as dehydration that is always present in untreated adrenal insufficiency. The coexistence of tuberculosis, which used to be the most common cause of Addison's disease, should also be considered as a cause of hypercalcaemia in these patients.

Islet Cell Tumours

Benign and malignant islet cell tumours that secrete vasoactive intestinal peptide present with a characteristic clinical picture including watery diarrhoea, hypokalaemia and achlorhydria. Approximately 50% of these patients have hypercalcaemia, which can be severe. Similar to the setting of hypercalcaemia in phaeochromocytoma, the vasoactive intestinal peptideoma might coexist with hyperparathyroidism as part of MEN-1 syndrome. However, there are patients in whom hypercalcaemia remits after re-
section of the pancreatic tumour. Studies have shown that PTHrP is responsible for the mechanism of hypercalcaemia in these patients.

**Drug-associated Hypercalcaemia**

Vitamin D toxicity may be due to any one of the three forms of vitamin D (i.e., the parent D compound, 25-hydroxyvitamin D, or 1,25-dihydroxyvitamin D). The half-life of vitamin D ranges from 20 days to months. In contrast, the biological half-life of the less lipophilic compound 25-hydroxyvitamin D is shorter, at approximately 15 days. The half-life of the least lipophilic compound, 1,25-dihydroxyvitamin D, is much shorter, at approximately 15 hours. In general, the duration of toxicity is related to the half-life of the vitamin D compound.

Hypercalcaemia attributed to hypervitaminosis A has been described in patients who have ingested large amounts of vitamin A (i.e., more than 50,000 IU/D) for weeks or months. The diagnosis of vitamin A intoxication is made by measurement of circulating total vitamin A, or more specifically by measurement of the percentage of vitamin A in the retinyl ester form.

Thiazide diuretics can be associated with hypercalcaemia, in part because of their actions to increase renal tubular re-absorption of calcium. The PTH level tends to be elevated. There are a number of patients whose hypercalcaemia does not remit when the diuretic is discontinued. These patients are invariably shown to have primary hyperparathyroidism.

Lithium carbonate, used as a therapy for several psychiatric disorders, has been associated with significant effects on serum calcium concentration, leading to variable degrees of hypercalcaemia. The slight increase in serum calcium concentration could be a result of a lithium-induced alteration in the set point for calcium in the parathyroid cell.

Historically, the milk-alkali syndrome resulted when large amounts of milk and sodium bicarbonate were used together to treat symptoms of peptic ulcer disease. Nowadays, most reported cases have involved ingestion of very large amounts of elemental calcium (3 to 6 g) or 75 to 15 g of calcium carbonate daily.

**Familial Hypocalciuric Hypercalcaemia**

Familial hypocalciuric hypercalcaemia (FHH) is an autosomal dominant disorder with a high degree of penetrance. The hypercalcaemia is often seen in affected individuals in childhood. It usually runs an asymptomatic benign course. The disease is characterized by hypercalcaemia and hypocalciuria. The PTH level is usually normal, although it has been elevated in several cases. FHH can easily be confused with primary hyperparathyroidism. When a patient with FHH undergoes subtotal parathyroidectomy, operation does not cure the hypercalcaemia. Family screening helps to differentiate FHH from primary hyperparathyroidism. Low 24-hour urinary calcium excretion, with a ratio of calcium to creatinine clearance of less than 0.01, suggests the diagnosis of FHH.
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References:


