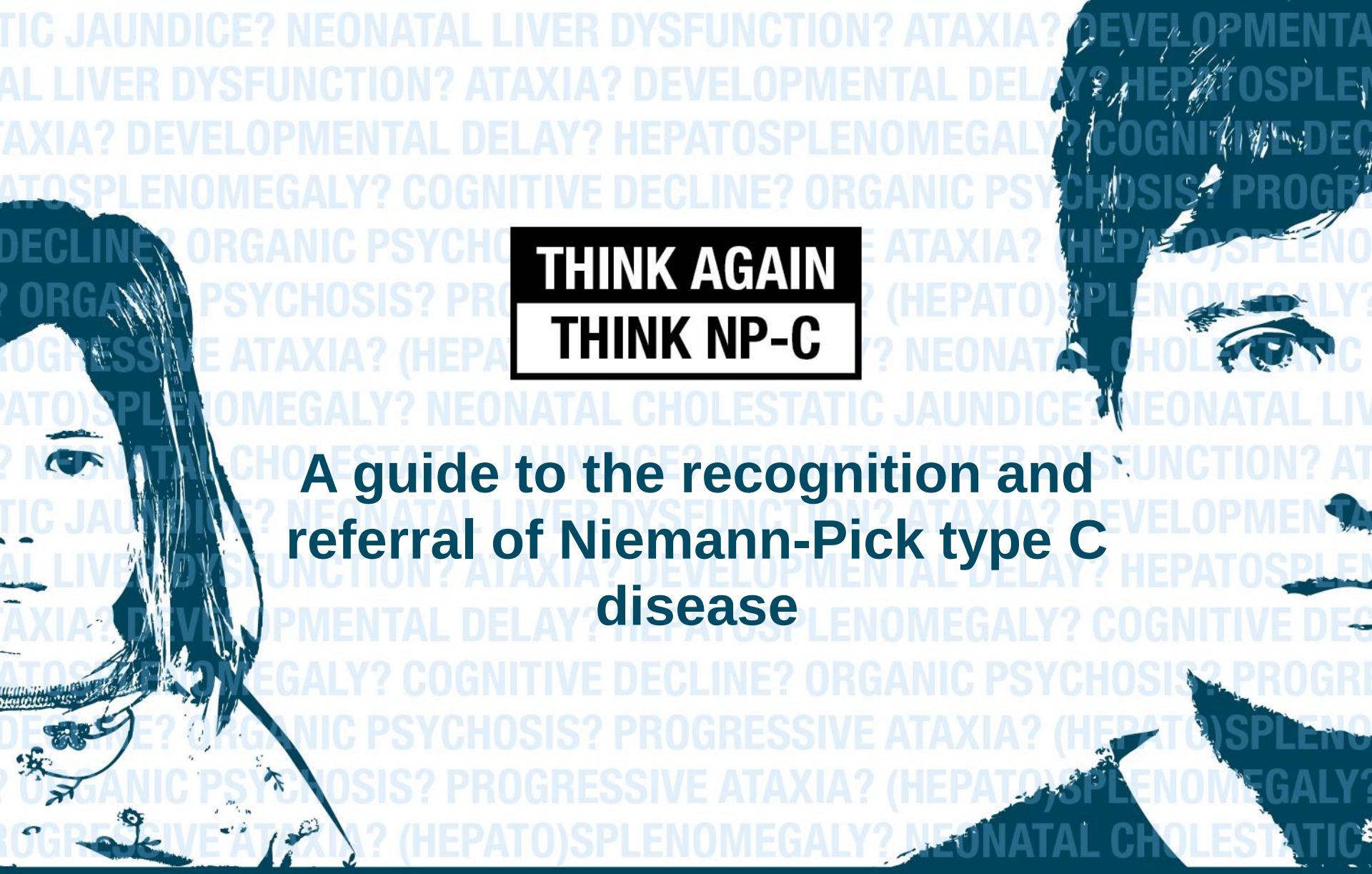

A guide to the recognition and referral of Niemann-Pick type C disease

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A guide to the recognition and referral of Niemann-Pick type C disease (NP-C)

- Introduction
- Background to NP-C
- Symptoms of NP-C
- Recognising NP-C
- Suspect NP-C?

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Introduction

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NP-C is a treatable disease. It affects all ages.

NP-C is commonly **undetected or misdiagnosed** due to its highly variable clinical presentation[1,2]

Early diagnosis means patients can **access support**, which can improve their quality of life and the lives of those around them[2]

Early diagnosis is also important as **NP-C is a treatable disease**. Treatment can help to manage the symptoms and can slow down the progression of the disease[2]

Therefore, it is critical that we aim to achieve earlier diagnosis of NP-C

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References: 1. Wraith et al. *Mol Genet Metab* 2009; 2. Patterson et al, *Mol Genet Metab* 2012

Two steps to achieving early diagnosis of NP-C

Recognition

of signs and symptoms by paediatricians, neurologists, hepatologists, psychiatrists and ophthalmologists and acting on that suspicion

Confirmation

of diagnosis using detailed physical and neurological assessment followed by specialist tests

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THINK AGAIN THINK NP-C is dedicated to improving recognition of the signs and symptoms of NP-C to speed up diagnosis

- This project is led by the **International Niemann-Pick Disease Alliance (INPDA)** in collaboration with a multidisciplinary advisory committee and Actelion Pharmaceuticals Ltd
- The campaign aims to support healthcare professionals with little or no knowledge of NP-C to **recognise the key signs and symptoms** of the disease
- This will help patients by **speeding up diagnosis** to ultimately optimise care and treatment outcomes

Early diagnosis means patients can access treatment and support[1]

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References: 1. Patterson et al, *Mol Genet Metab* 2012

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Background to NP-C

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NP-C is a progressive, irreversible and chronically debilitating lysosomal storage disease[1,2]

It is an **inherited autosomal recessive disease** caused by mutations in the *NPC1* or *NPC2* gene[2]

These mutations lead to a **defect in lipid transportation** within the cell, which leads to intracellular accumulation of lipids in the brain, liver and spleen and causes the symptoms of NP-C[1-3]

NP-C is characterised by **progressive, disabling neurological symptoms** and premature death in most patients[1]

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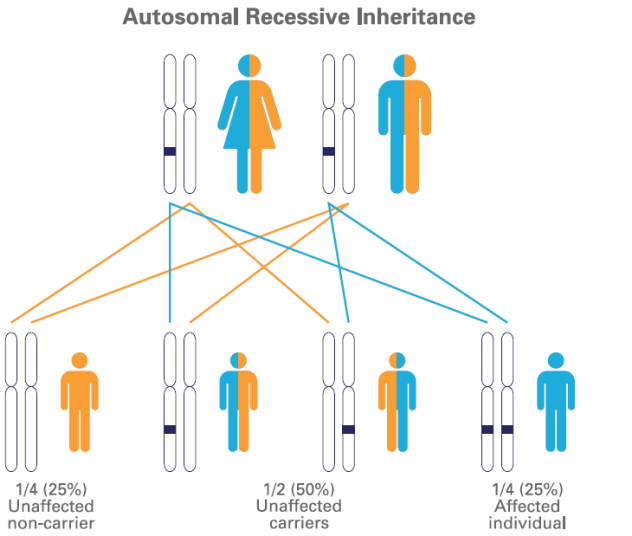
References: 1. Patterson et al, *Mol Genet Metab* 2012; 2. Vanier, *Orphanet J Rare Dis* 2010; 3. Wraith and Imrie, 2007

NP-C can present at any age, affecting infants, children, adolescents and adults[1]

- The incidence of NP-C is approximately **1 in 120,000 live births**[1]
- The incidence is thought to be underestimated due to a lack of clinical awareness of the disease and the difficultly in recognising NP-C because of its **highly heterogeneous clinical presentation**[2]
- As an **autosomal, recessive condition**, in each pregnancy there is a 25% probability that the offspring of two NP-C carriers will receive both mutated NP-C genes and inherit the disease[3]



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References: 1. Vanier, *Orphanet J Rare Dis* 2010; 2. Patterson et al, Lancet 2007; 3. Wraith and Imrie, 2007

All patients with NP-C ultimately develop a progressive and irreversible neurological disease[1,2]

Early onset of neurological symptoms i.e. in childhood **leads to faster deterioration** and earlier death than for those affected in adolescence or adulthood[1]

NP-C has a tremendous impact on **patients' quality of life**, with detrimental effects on schooling and work as well as everyday activities[3]

Those affected inevitably **lose their independence** and have to rely heavily on family members for support[3,4]

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References: 1. Patterson et al, *Mol Genet Metab* 2012; 2. Vanier, *Orphanet J Rare Dis* 2010; 3. Klunemann et al, *Eur Neurol Rev* 2011; 4. Wraith and Imrie 2007.

NP-C is commonly undetected or misdiagnosed[1]

Highly variable clinical presentation (characterised by a wide range of symptoms that individually are not specific to the disease) leads to a lack of detection and diagnosis[2]

Symptoms can be categorised as **visceral (systemic), neurological or psychiatric** and present at different ages and in different combinations[2]

Due to its challenging presentation the disease often remains undetected for many years, with an **average delay in diagnosis of 5-6 years** from onset of neurological symptoms[3]

<u>Linking the symptoms together</u> can facilitate fast and differential diagnosis of NP-C, which can speed up patient access to treatment that can slow down the progression of the disease or stabilise the disease and improve their quality of life[2]

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References: 1. Wraith et al, Mol Genet Metab 2009; 2. Patterson et al, *Mol Genet Metab* 2012; 3. Mengel et al, *Orphanet J Rare Dis* 2013

NP-C is a treatable disease[1,2]

Management strategies include **non-specific, symptomatic treatments** and **NP-C-specific therapies**[1,3]

Symptomatic therapies aim to improve a patient's quality of life. However, they have no impact on disease progression or long-term outcomes[1]

Recent advances in the understanding of NP-C pathophysiology have led to the development of an **NP-C-specific treatment, miglustat,** that can slow down the progression of the disease[1,4,5]

Early diagnosis of NP-C means that patients can access treatment and is crucial for timely intervention[1]

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References: 1. Patterson et al, *Mol Genet Metab* 2012; 2. Wraith and Imrie 2007; 3. Vanier, *Orphanet J Rare Dis* 2010; 4. Pineda et al, Mol Genet Metab 2009; 5. Patterson et al, Lancet 2007

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Symptoms of NP-C

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Symptoms of NP-C can be highly variable and can be grouped as systemic (visceral), neurological or psychiatric[1-3]

Systemic (visceral) symptoms

- **Hepatomegaly** (enlarged liver)
- **Splenomegaly** (enlarged spleen)
- **Prolonged neonatal jaundice**
- **Neonatal cholestasis** (accumulation of bile components in the bloodstream)

Neurological symptoms

- **Vertical supranuclear gaze palsy (VSGP)** (eye movement problems)
- **Ataxia** (balance disorder)
- **Cognitive dysfunction** (problem with information processing or memory)
- **Dysphagia** (difficulty swallowing)
- **Gelastic cataplexy** (episodes of sudden muscular weakness)
- **Dystonia** (sustained muscle contraction)
- **Dysarthria** (slurred and irregular speech)
- **Hypotonia** (decreased muscle tone)
- **Developmental delay**
- **Seizures** (partial or generalised)

Psychiatric symptoms

- **Early-onset psychosis** (hallucinations and delusions)
- **Prominent visual hallucinations**
- **Incomplete response to treatment**
- **Pre-senile cognitive decline and/or dementia**
- **Disruptive or aggressive behaviour** in adolescence or adulthood

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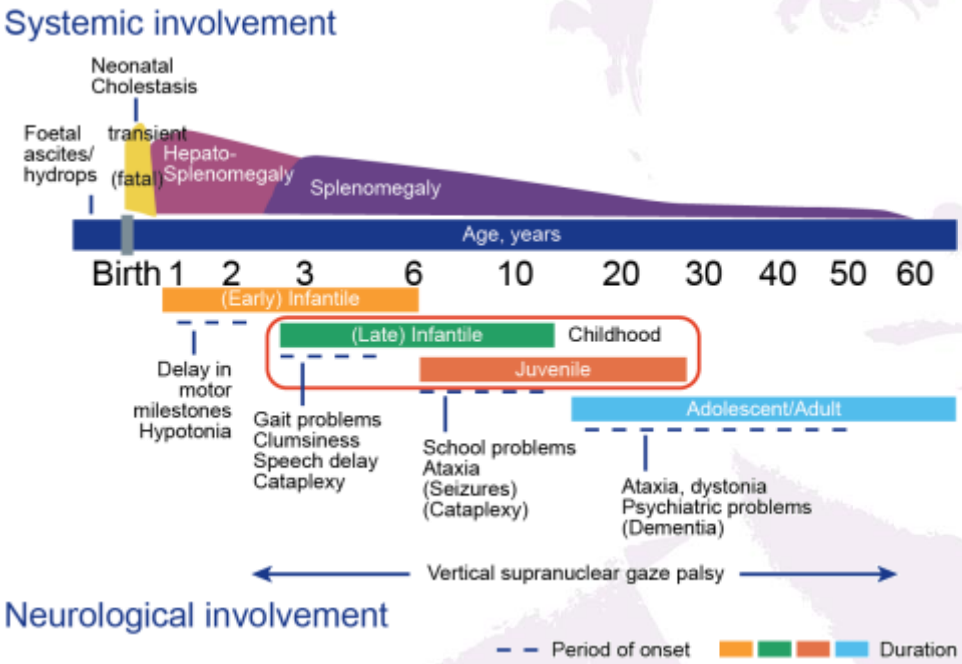
References: 1. Patterson et al, *Mol Genet Metab* 2012; 2. Patterson et al, Lancet 2007; 3. Wraith and Imrie, 2007

NP-C symptoms can present at any age and in different combinations[1]

- The age of onset of visceral symptoms occurs along a continuous spectrum[1]
  - Considerable overlap between the age categories
  - Independence from the onset of neurological disease

- NP-C can be defined by the age at onset of neurological symptoms:[1]
  - **early infantile onset** (age 3 months to ≤ 2 years)
  - **late infantile onset** (2 years to < 6 years)
  - **juvenile onset** (6 to 15 years)
  - **adolescent/adult onset** (> 15 years)



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References: 1. Patterson et al, *Mol Genet Metab* 2012

Linking symptoms together can facilitate fast and differential diagnosis of NP-C[1]

Splenomegaly	Ataxia	Psychotic symptoms
• Vertical supranuclear gaze palsy • Hypotonia • Schizophrenia-like psychosis • Gelastic cataplexy • Developmental delay • Dystonia	• Dysarthria • Cognitive decline	• Cognitive decline

The combination of one of the symptoms on the top with at least one symptom underneath is strongly suggestive of NP-C

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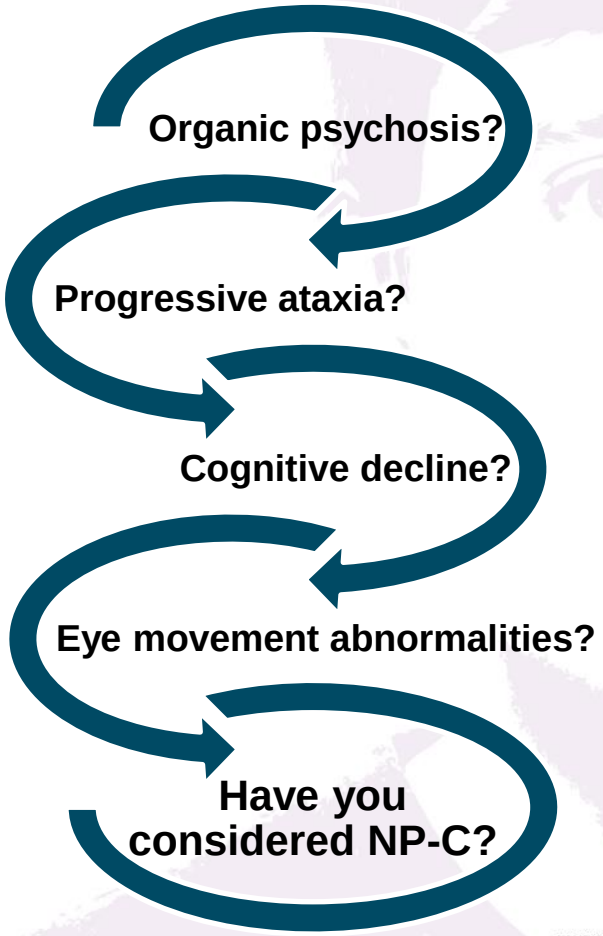
Reference: 1. Mengel et al, *Orphanet J Rare Dis* 2013.

For neurologists – delete as appropriate

Neurologists play a fundamental role in speeding up diagnosis in order to initiate treatment earlier, when it is likely to be most effective[1,2]

- The most common neurological symptom of NP-C is **vertical supranuclear gaze palsy (VSGP)**, present in virtually all patients. However, it often goes undetected[1,3]
- Other neurological symptoms of NP-C include **ataxia, dysarthria, dysphagia, progressive dementia, gelastic cataplexy, dystonia** and **seizures**[1,3]
- The **age of onset of neurological symptoms** correlates with patient prognosis – those with early-onset neurological symptoms progress faster and have a shorter lifespan[1]
- **Early recognition** of these symptoms is therefore critical to improve patient outcomes[4]
- **Disease-specific therapy** is available for the treatment of neurological manifestations and has been shown to help improve or stabilise key parameters in neurological disease[1,2,5]



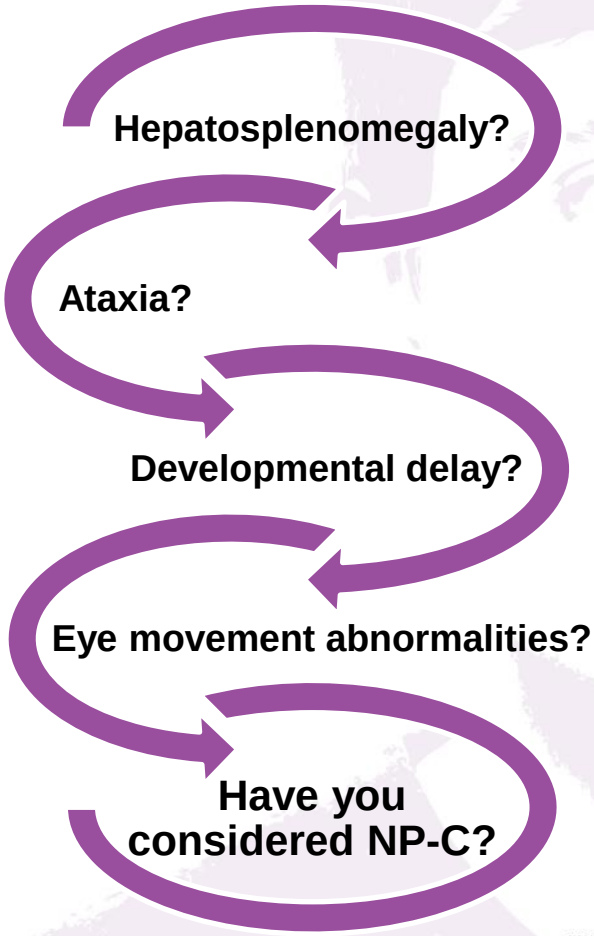
THINK AGAIN
THINK NP-C

References: 1. Patterson et al, *Mol Genet Metab* 2012; 2. Patterson, *Lancet Neurol* 2007; 3. Vanier, *Orphanet J Rare Dis* 2010; 4. Wijburg et al, *Neurology* 2012; 5. Pineda et al, *Mol Genet Metab* 2009.

For paediatricians – delete as appropriate

Paediatricians play a fundamental role in making links between symptoms, which might present at different times in a child's life[1-3]

- **History of prolonged neonatal cholestasis**, **hepatomegaly** and presence of **splenomegaly** in combination with **clumsiness, frequent falls** or **developmental delay** could indicate NP-C
- Symptoms might present at different times; some symptoms may appear to have been resolved
- Patient medical histories can often reveal **unexplained cholestatic jaundice**
- Although vertical supranuclear gaze palsy (VSGP) is a characteristic symptom of NP-C and is present in nearly all cases, it is often missed, especially among younger patients



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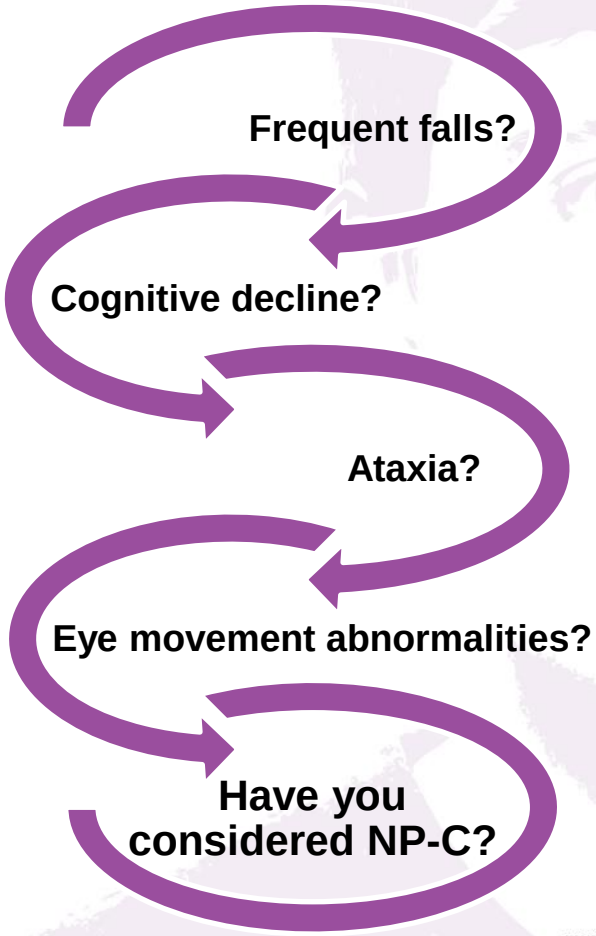
References: 1. Patterson et al, *Mol Genet Metab* 2012; 2. Vanier, *Orphanet J Rare Dis* 2010; 3. Wijburg et al, *Neurology* 2012.

For paediatric neurologists – delete as appropriate

Paediatric neurologists play a fundamental role in speeding up diagnosis in order to initiate treatment earlier, when it is likely to be most effective[1,2]

- The most common neurological symptom of NP-C is **vertical supranuclear gaze palsy (VSGP)** but it often goes undetected
- Other neurological symptoms of NP-C include **ataxia, dysarthria, dysphagia, progressive dementia, gelastic cataplexy, dystonia** and **seizures**
- The **age of onset of neurological symptoms** correlates with patient prognosis – those with early-onset neurological symptoms deteriorate faster and have a shorter lifespan
- **Early recognition** of these symptoms is therefore is critical to improve patient outcomes



THINK AGAIN
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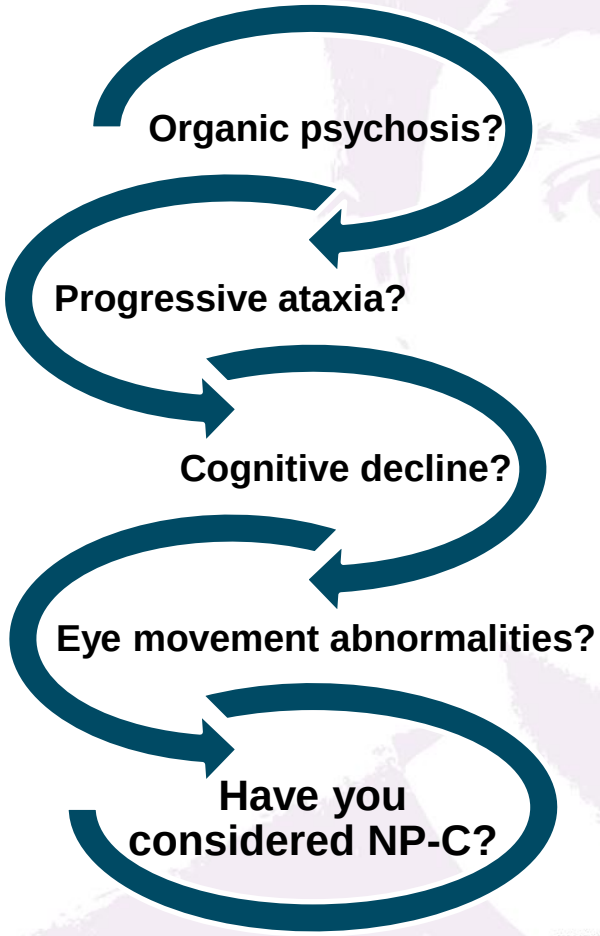
References: 1. Patterson et al, *Mol Genet Metab* 2012; 2. Wijburg et al, *Neurology* 2012.

For psychiatrists – delete as appropriate

Psychiatrists play a fundamental role in recognising and linking together psychiatric and neurological symptoms[1-3]

- Psychiatric symptoms of NP-C generally present in **adolescence or adulthood**
- **Pre-senile cognitive decline** and/or **dementia, psychotic symptoms**, such as **hallucinations, delusions** and/or **thought disorder** and other psychiatric disorders such as **depression**, are all symptoms of NP-C
- Hallucinations, delusions and/or thought disorder can be **misdiagnosed** as schizophrenia or other forms of psychosis in later-onset disease. It can be useful to monitor atypical signs of psychosis or minor physical signs such as vertical supranuclear ophthalmoplegia[4]
- Visual hallucinations, cognitive impairment or treatment-resistant psychiatric symptoms could have **organic origins** and should prompt assessment for neurological symptoms of NP-C, for example, progressive ataxia
- Patients presenting with **vertical supranuclear gaze palsy (VSGP) and psychosis** should always be referred



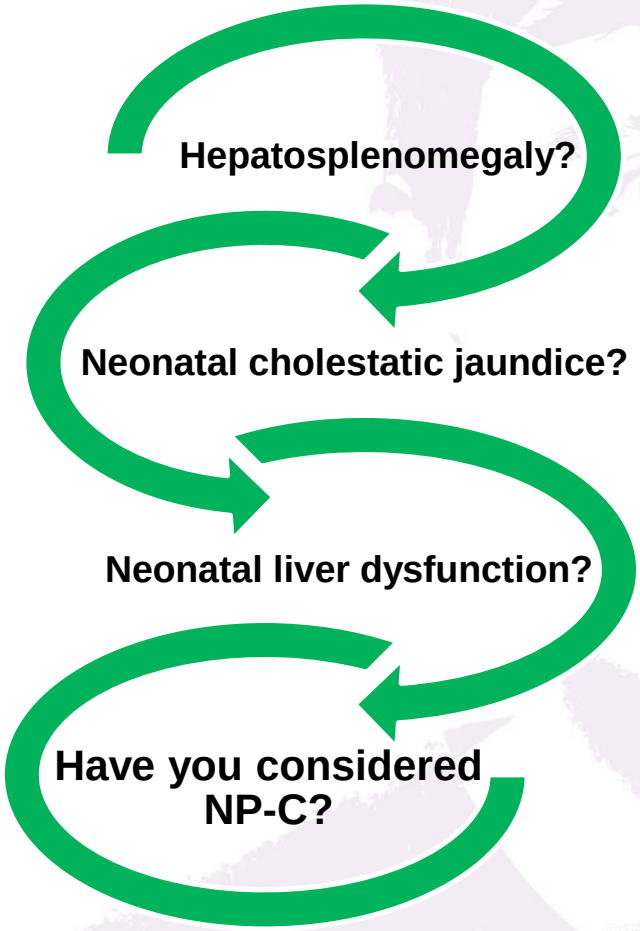
THINK AGAIN
THINK NP-C

References: 1. Patterson et al, *Mol Genet Metab* 2012; 2. Vanier, *Orphanet J Rare Dis* 2010; 3. Wijburg et al, *Neurology* 2012
4. Bonnot *European Psychiatric Review* 2011

For hepatologists/neonatologists – delete as appropriate

Hepatologists and neonatologists play a fundamental role in recognising (hepato)splenomegaly, a key visceral sign present in nearly all patients[1-3]

- A **history of (hepato)splenomegaly** is a key visceral sign of NP-C, present in nearly all patients
- **Cholestatic jaundice** appears in the first days of life and often persists for more than two weeks. In most cases cholestatic jaundice resolves spontaneously by two to four months of age
- History of cholestatic jaundice is present in 50% of patients
- Neonatal liver failure is found in approximately 10% of patients and is often fatal



THINK AGAIN
THINK NP-C

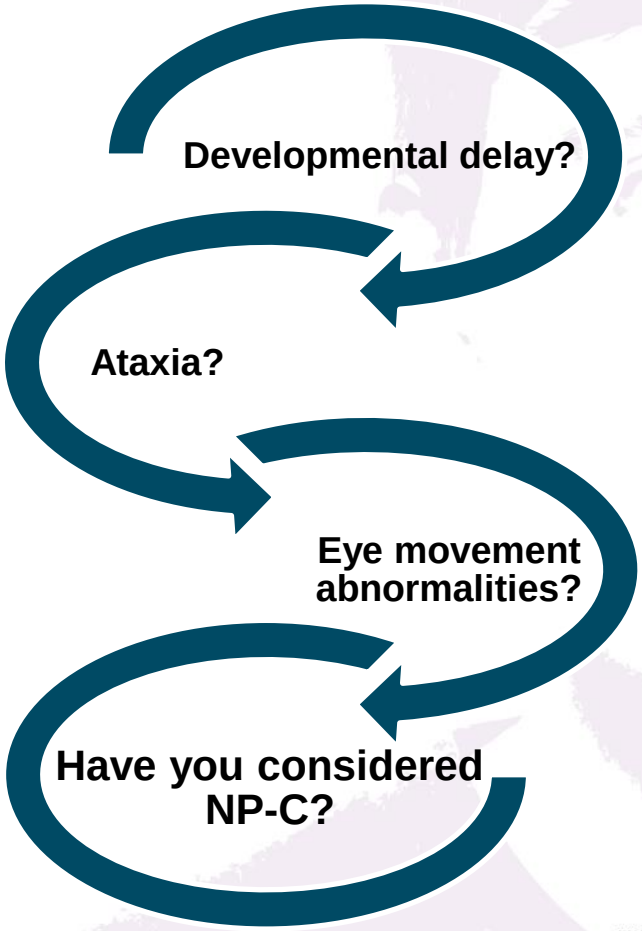
References: 1. Patterson et al, *Mol Genet Metab* 2012; 2. Vanier, *Orphanet J Rare Dis* 2010; 3. Wijburg et al, *Neurology* 2012.

For ophthalmologists – delete as appropriate

Ophthalmologists are fundamental in the diagnosis of NP-C in order to recognise vertical supranuclear gaze palsy (VSGP) in patients[1,2]

- **Ocular-motor abnormalities** are one of the earliest neurological signs of NP-C and are seen in nearly all patients

- A rigorous neurological eye examination of vertical and horizontal voluntary saccades, including smooth pursuit and vergence (movement of the two eyes in opposite directions), will aid recognition of **vertical supranuclear gaze palsy (VSGP)**, a typical symptom of NP-C



THINK AGAIN
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References: 1. Patterson et al, *Mol Genet Metab* 2012; 2. Vanier, *Orphanet J Rare Dis* 2010

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Recognising NP-C

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Vertical supranuclear gaze palsy (VSGP) is a very strong indicator of NP-C[1,2]

- **VSGP often goes undetected**, despite it being simple to detect by testing for voluntary saccades
- The initial sign is usually **impaired voluntary saccadic eye movements (SEM)** in the late-infantile period
- Vertical SEM impairment is affected first followed by horizontal SEM impairment
- A **rigorous neurological examination of VSGP** should include testing of smooth pursuits, saccades and vergence (movement of the two eyes in opposite directions)
- In all patients, saccadic, pursuit and vergence movements should be examined in both vertical and horizontal planes

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References: 1. Wijburg et al Neurology 2011; 2. Patterson et al, *Mol Genet Metab* 2012.

VSGP may be missed if voluntary saccades are not assessed[1,2]

How to test for VSGP

1. **To assess the smooth pursuit, patients should be tested for their ability to follow an object**
2. **To assess the vertical saccades the physicians will ask the patient to spontaneously move their gaze up and down without following an object** (ask to look between two points fixed by the upper part of their head and at chest level)

- With mild vertical saccades impairment, the patient is still able to look up but cannot look down

- With advanced vertical saccades impairment, the patient can no longer look up or down

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References: 1. Patterson et al, *Mol Genet Metab* 2012; 2. Mengel et al, *Orphanet J Rare Dis* 2013.

Gelastic cataplexy is a very strong indicator of NP-C[1-3]

- **Gelastic cataplexy** is rare but can appear as early as two years of age
  - Patients may experience sudden loss of muscle tone (without loss of consciousness), which is typically triggered by an emotional stimulus
  - Loss of tone may involve the legs, neck or jaw and may manifest as sudden falls, sudden head drop or jaw drop, triggered by laughing
- A general assessment of cranial nerves, muscle bulk, tone, power and stretch reflexes may also help in diagnosing NP-C

Assessing for gelastic cataplexy

History of drop attacks or loss of posture associated with emotional stimuli

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References: 1. Patterson et al, *Mol Genet Metab* 2012; 2. Wijburg et al Neurology 2011; 3. Mengel et al, *Orphanet J Rare Dis* 2013.

Ataxia and dystonia are moderate indicators of NP-C[1,2]

- **Ataxia**, clumsiness or frequent falls may start at any age from late childhood to adulthood and are progressive
  - Children with a mild form of NP-C may appear to be slow e.g. walking instead of running, or cautiously taking objects instead of rapidly grabbing them
- **Dystonia** can cause abnormal dystonic postures in hands, feet or face
  - It occurs more frequently in adolescents and adults with NP-C than in children
- Acquired and progressive spasticity is a weak indicator of NP-C

Tools to assess for ataxia

- 10-m walk test and tandem gait
- International Cooperative Ataxia Rating Scale (ICARS)
- Brief Ataxia Rating Scale

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References: 1. Patterson et al, *Mol Genet Metab* 2012; 2. Mengel et al, *Orphanet J Rare Dis* 2013

Dysphagia and dysarthria are moderate indicators of NP-C[1]

- **Dysphagia** can be present in the early stages of NP-C but typically appears in adulthood[1]
  - Early manifestation can be difficulty in swallowing liquid or simple coughing or choking during feeding[1,2]
  - Increasing severity of dysphagia can lead to aspiration and malnutrition[1]
  - It is a major risk factor in NP-C due to the risk of aspiration pneumonia, one of the most common causes of death in NP-C[3,4,5]
- **Dysarthria** results in slurred and irregular speech with impaired pronunciation, due to lack of coordination of the motor-speech system[1]

Tools to assess for dysphagia

- Standardised swallowing assessment of different substances using video fluoroscopy and fiberoptic endoscopic evaluation

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References: 1. Patterson et al, *Mol Genet Metab* 2012; 2. Walterfang et al, *Orphanet J Rare Dis* 2012; 3. Mengel et al, *Orphanet J Rare Dis* 2013.

A number of other neurological symptoms may link to a diagnosis of NP-C

- High frequency sensori-neural hearing loss affects about 20% of patients[1]
- Epileptic seizures most frequently present in late-infantile or juvenile-onset NP-C patients[2]
- Delayed developmental milestones are an ancillary indicator of NP-C[1]

Tools to assess for hearing loss	Tools to assess for epilepsy
• Audiograms • Auditory brainstem potentials	• Electro-encephalogram (EEG)

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References: 1. Patterson et al, *Mol Genet Metab* 2012; 2. Mengel et al, *Orphanet J Rare Dis* 2013

The NP-C Suspicion Index is a simple-to-use and interactive screening tool[1-3]

- The **NP-C Suspicion Index** (SI) tool can help healthcare professionals identify patients with suspected NP-C who should be referred on for further testing
  - It assigns weighted scores according to the different symptoms identified and family history of NP-C
  - It is specific and sensitive for detection of NP-C in patients for whom the most common diseases have been already ruled out
  - It is reliable and has a high detection power in patients >4 years of age

- The NP-C Suspicion Index Tool is available online at www.NPC-SI.com

- The NP-C SI has been developed by Actelion Pharmaceuticals Ltd in collaboration with a group of international experts in the field of NP-C

THINK AGAIN
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References: 1; Wijburg et al, *Neurology* 2012; 2. Patterson et al, *Mol Genet Metab* 2012; 3. Wraith et al, submitted to *J Inherit Metab Dis 2013.*

The NP-C SI calculates a Risk Prediction Score, which correlates with the likelihood of having NP-C[1]

≥70 should prompt immediate referral to a specialist centre for testing for NP-C[1]

40–69 indicates that further follow-up observation and discussion with a specialist centre is required[1]

<40 indicates a low probability of having NP-C and alternative causes should be considered before further investigation for NP-C[1]

Visit www.think-npc.com to find your nearest specialist centre

	Visceral	Neurological	Psychiatric
Very strong 40 points per item		Vertical supranuclear gaze palsy ☐	
		Gelastic cataplexy ☐	
Strong 20 points per item	Prolonged unexplained neonatal jaundice or cholestasis ☐		Pre-senile cognitive decline or dementia ☐
	Isolated unexplained splenomegaly (historical ± current) with or without hepatomegaly ☐		
Moderate 10 points per item		Ataxia, clumsiness or frequent falls ☐	Psychotic symptoms (hallucinations, delusions and/or thought disorder) ☐
		Dysarthria and/or dysphagia ☐	
		Dystonia ☐	
Weak 5 points per item		Acquired & progressive spasticity ☐	Treatment-resistant psychiatric symptoms ☐
			Other psychiatric disorders ☐
Ancillary 1 point per item	Hydrops fetalis ☐	Hypotonia ☐	Disruptive or aggressive behaviour in adolescence and childhood ☐
	Siblings with fetal ascites ☐	Delayed developmental milestones ☐	
		Seizures (partial or generalised) ☐	
		Myoclonus ☐	

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Reference: 1. Wijburg et al, *Neurology* 2012.

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Suspect NP-C?

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Patients with suspected NP-C should undergo a comprehensive medical history and general physical examination plus neurological assessment[1]

Medical history and general physical examination

- Evidence of neonatal cholestasis, isolated splenomegaly or hepatosplenomegaly, seizures, cataplexy and impaired academic or work performance (specifically loss of skills)
- Vital signs, body weight, height and head circumference
- Eye movement abnormalities

Neurological assessment[1]

- Ocular motor assessment
- Swallowing function
- Changes in ambulation
- Cognitive function
- Psychiatric evaluation
- Seizure monitoring

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References: 1 Patterson et al, *Mol Genet Metab* 2012.

What to do if you suspect a patient has NP-C

If a patient presents with symptoms related to NP-C, you should refer them to a specialist centre for further testing[1]

- A combination of biochemical testing, histological analysis and genetic testing are used to confirm the diagnosis of NP-C
- Confirmation of diagnosis will not only facilitate access to treatment for the patient but allow family members and carers to seek help and support[2]

Undiagnosed patient with neurological symptoms?[3]

- You should review or re-assess their symptoms
- Look at whether these symptoms can be linked together and, if so, refer to a specialist centre for further testing

Visit www.think-npc.com to find your nearest specialist centre

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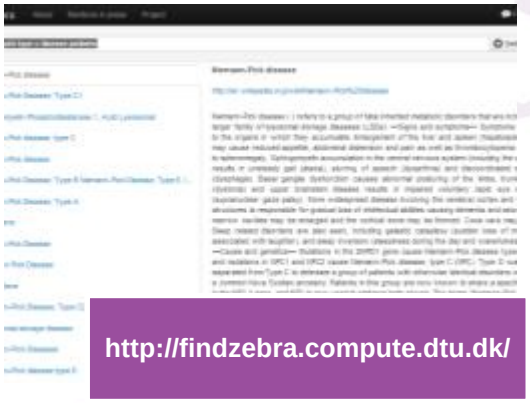
References: 1. Patterson et al, *Mol Genet Metab* 2012; 2. Klünemann et al, *Eur Neurol Rev* 2011; 3. Mengel et al, *Orphanet J Rare Dis* 2013.

A number of resources are available to aid recognition of NP-C and referral to a specialist centre

Visit www.think-npc.com to find out more about Think Again. Think NP-C

www.NPC-info.com

www.NPC-SI.com



http://findzebra.compute.dtu.dk/

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