How We Can Put Forward the Diagnosis of NPC Disease: Suspicion Index

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Niemann-pick disease type C (NPC disease) is a rare heritable neurometabolic disorder. One of special features of this disorder is heterogeneous manifestations. Overall various clinical manifestation of NPC disease can be categorized in three main groups: Visceral or systemic, neurological and psychiatric. The most important clinical features of each group are as follow: Visceral (prolonged neonatal jaundice, unexplained splenomegaly with or without hepatomegaly), neurological (vertical supranuclear gaze palsy, gelastic cataplexy), Psychiatric (early cognitive decline or dementia).

In addition of variable clinical features, NPC disease has a wide range of age manifestation, from neonatal period through adulthood. Neurologic features unlike visceral symptoms are not common under early infancy period. After that neurological symptoms become prominent and finally from juvenile period through adolescent/adult age psychiatric symptoms in addition of neurological signs will present.

Therefore with considering the variability in clinical presentations and age manifestation of NPC disease, it seems a little hard to diagnose the disease. The NP-C Guidelines Working Group revised the recommendations for the diagnosis and management of Niemann-Pick type C disease in 2012, to provide the most up-to-date information about NP-C. A new tool – the NP-C Suspicion Index – has also been developed for healthcare professionals to help identify patients for whom further investigation is required. This will hopefully help to achieve earlier and improved diagnosis of NP-C in patients suspected of having the disease. Suspicion index is one of important tools for early diagnosis of NPC disease that developed in 2012 by Wijburg et al. Early diagnosis is important, because it help us to start early treatment with Miglustat (the only available drug for NPC disease that acts as a substrate reduction therapy). This process finally helps to patients with reducing the progression of disease. From a physician's point of view the Suspicion Index works both as a reminder of the complex and varied symptoms characteristic of NP-C, as well as support in making the right referral decision.

It is our hope that the Suspicion Index will contribute to reducing the time to diagnosis for more patients to ensure that they can receive the support and treatment they require."

Suspicion index likes a checklist and fill it tells us the NPC risk prediction score. The three main categories of disease symptoms have been ranked into five groups according it's importance. Co-Occurrence of symptoms (within and

across categories) and family history are also taken into account to define the Risk Prediction Score.
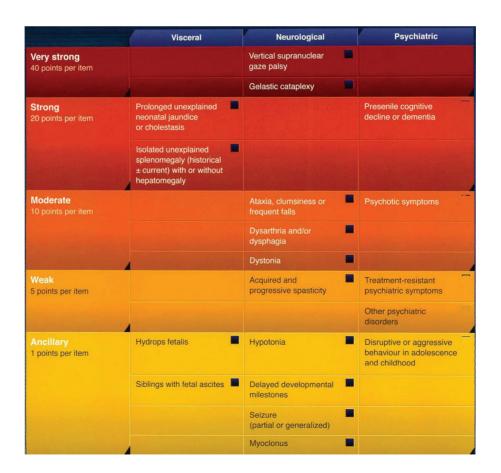
How we can to interpret this scoring system?

1. A total Risk Prediction Score of ≥70 indicates a high suspicion of having NP-C and should lead to immediate referral of the patient to a NP-C center for testing about NP-C according to local practice.

2. A total Risk Prediction Score of 40–69 indicates a Moderate suspicion of having NP-C, and should lead to further follow-up, including discussion with a NP-C center.

3. A total Risk Prediction Score of <40 indicates a low probability of having NP-C, and alternative causes should be considered before further investigation for NP-C.

   Analysis of SI discriminatory ability by age groups showed a high performance in study patients aged >4 years, but the discriminatory performance was low for patients aged ≤4 years. Due to a lower sensitivity in patients below 4 years old, a prediction score below 70 is not conclusive in this group of patients.
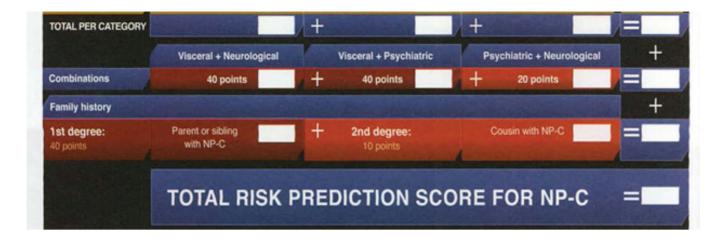
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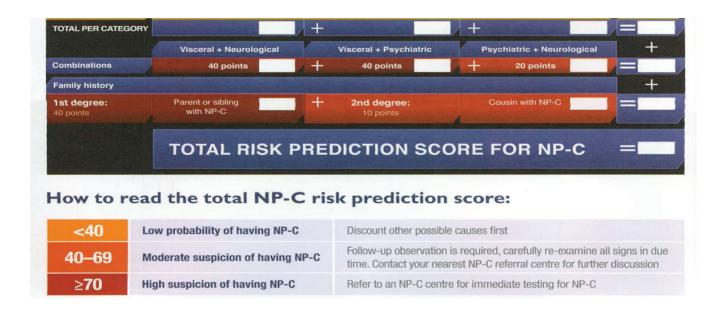
Keywords: NPC disease, Suspicion Index, Visceral, Neurological, Psychiatric

	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 ■		Presenile 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
		Dysarthria and/or dysphagia ■	
		Dystonia ■	
Weak 5 points per item		Acquired and progressive spasticity ■	Treatment-resistant psychiatric symptoms
			Other psychiatric disorders
Ancillary 1 points per item	Hydrops fetalis ■	Hypotonia ■	Disruptive or aggressive behaviour in adolescence and childhood
	Siblings with fetal ascites ■	Delayed developmental milestones ■	
		Seizure (partial or generalized) ■	
		Myoclonus ■	

(a)

(b)

(c)

Fig1 (a,b,c). The NPC suspicion index scoring