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Psychiatric symptoms in alpha-mannosidosis

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Abstract

Alpha-mannosidosis is characterized by mild to moderate intellectual disability (ID), moderate to severe neurosensory hearing loss, frequent infections, psychomotor disturbances and skeletal dysmorphism. For the first time, a panel of nine alpha-mannosidosis patients with psychiatric symptoms is presented. The clinical picture has several similarities: a physical or psychological stressor precedes a rapid development of a state of confusion, delusions, hallucinations, anxiety and often depression leading to a severe loss of function. This usually lasts 3–12 weeks, and is followed by a period of somnolence and asthenia. It may be more prevalent in females. In four of the described patients search for organic causes of the syndrome was performed, but revealed only negative findings. Because of the limited number of cases no firm conclusion about the benefit of various psychotropic drugs can be drawn from our observation.

Psychiatric symptoms could affect as many as 25% of patients with alpha-mannosidosis. First onset is typically in late puberty to early adolescence. The episodes may be recurrent, and of limited duration although medication may be necessary to alleviate symptoms. Our observations indicate that alpha-mannosidosis is associated with an increased risk of psychiatric symptoms. These should not be dismissed as part of the ID but should give rise to the initiation of adequate diagnostic work-up, treatment and support.

Keywords cognitive disorders, lysosomal, mannosidosis, mental disorders, psychosis

Alpha-mannosidosis (MIM 2485000) is an autosomal recessive lysosomal storage disease resulting from the deficient activity of lysosomal alpha-mannosidase (LAMAN) (EC 3.2.1.24) (Nilssen *et al.* 1997). It is characterized by mild to moderate intellectual disability (ID), moderate to severe neurosensory hearing loss, psychomotor disturbances and skeletal dysmorphism (Malm *et al.* 2001). It is further associated with an immunodeficiency leading to frequent infections of the gastrointestinal and respiratory tract (Malm *et al.* 2000).

Hitherto, psychiatric symptoms have not been perceived as a part of the disease. We have, however, accumulated reports on psychiatric symptoms among subjects with alpha-mannosidosis and the purpose of this paper is to describe and bring to attention the clinical presentation and natural course of this facet of the disease. We present nine cases from a cohort of 70 patients.

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Method

Patients with alpha-mannosidosis were recruited through The International Society for Mannosidosis and Related Diseases (ISMRD) where families affected with alpha-mannosidisis received a questionnaire on general clinical information. All patients or their caregivers had signed an 'Informed Consent Form', and the local ethical committee and the National Data Inspectorate approved the study.

Of 140 affected families known to us, 70 filled out a detailed questionnaire.

Among these, 45 of the patients were 15 years or older when the questionnaire was completed. A history of psychiatric disorders was specifically inquired about, and was found to be positive in 11 persons. Subsequently, a more specific questionnaire was sent to the families of the patients with suspected psychiatric disturbance. This enabled us to record and make a detailed description of the mental and behavioural symptoms observed in nine of these patients.

Results

Out of a total of 45 subjects aged 15 years and older with alpha-mannosidosis, 11 had a positive history of mental disturbance. This suggests that this problem could affect as many as 25% of affected individuals.

The typical age of first onset of the syndrome is in the teens. In many cases it is recurrent, lasting typically 1–3 months (Table 1). General and behavioural symptoms with impaired abilities of daily living are almost always present (Table 2). Mental symptoms often associated with organic brain disorder are very common (Table 3), as are depressive symptoms (Table 4). Frank psychotic symptoms are also observed in the majority of the cases (Table 5).

In order to illustrate the clinical picture we present three fairly typical case descriptions.

Case 1

This is a now 21-year-old Norwegian girl. She had hydrocephalus at 18 months, and later inguinal hernias and frequent infections. She had a mild ID and scored an IQ of 70. She reads and writes, but poorly, and attends special class at school. Ordinarily she is well functioning and masters most aspects of daily life, walks to and from school alone and does household chores.

At the age of 14, a few days after an uncomplicated ear operation, she complained about hearing sounds, and refused to use her hearing aids. She lost her appetite and became more talkative, although the contents of her speech made little sense. Some days later, she started to walk about during the night, obviously confused and unable to find her room. She had sensory perceptions (seeing, hearing, feeling and smelling) in the absence of outside stimuli. She 'recognized' persons on TV as family or friends and behaved as if she was seeing something threatening under the sofa. Death was a central theme in the few comments she made. She claimed that the food tasted different and she was unable to chew and swallow, which led to a weight loss of 10%.

Examination at the local university hospital showed normal blood tests without signs of infection. CT and examination of the cerebrospinal fluid were normal. Non-specific increase of 'slow waves' was found in the EEG. She was given 2-mg haloperidol a day. Four weeks later, she recovered partly overnight, but had lost many school skills and remained very sleepy for weeks before she regained her usual condition. Since then she has every year had similar episodes, altogether five times. The last episodes lasted 6 to 8 weeks. The episodes were always followed by weeks of sleepiness. When depressive symptoms were predominant, she was successfully treated with 20-mg citalopram. Loss of appetite with consecutive reduction of body weight of 10–15% was improved when olanzapine was administered as an antipsychotic agent.

Case 2

This is a now 31-year-old German girl with no family history of metabolic, neurological or psychiatric disorders who suffered since early childhood from congenital hip dysplasia and reduced hearing which required the use of a hearing aid at the age of six. She developed a reasonable ability at speech and was able to attend the regular classes of primary school until grade 5, when she was referred to a special school because of the reduced hearing. After finishing junior high school she started an apprenticeship as a sales assistant in her parents butcher's shop. One day, when she was 17 years old, she returned from voca-

tional school crying and full of despair because she had received bad marks in mathematics and had been teased by her classmates. Subsequently, she developed delusions of reference, severe anxiety and suspiciousness as well as optical hallucinations. Her speech appeared confused. She was admitted to a psychiatric hospital where she was treated for the following 6 months, and diagnosed with an 'acute paranoid-hallucinatory schizophrenia'. Under treatment with clozapine her condition improved slowly and eventually a complete remission of the psychotic symptoms was achieved. During the following 5 years two similar episodes occurred (age 19 and 23). At the age of 27 her condition again deteriorated dramatically during a journey abroad with her parents. She developed delusions of persecution, visual and auditory hallucinations (hearing of voices), severe anxiety and depressed mood. Her behaviour rapidly switched between states of stupor and restless agitation. She was hospitalized and treated with various antipsychotics (including clozapine, risperidone and quetiapine) as well as antidepressants. Her condition deteriorated further, and she became almost completely mute. During this hospital stay, she developed recurrent infections and septicaemias, and lost weight from 70 to 37 kg. MRI revealed non-specific atrophic cerebral changes; results from lumbar puncture were negative. Eventually, her psychotic symptoms improved slowly but steadily under a treatment with benperidole and lorazepam although she did not regain her previous level of functioning.

Case 3

This is a New Zealand boy, presently aged 30. As a child, he had frequent infections, and a mild ID. He was well functioning, was reading and writing (poorly) and attended special class in school. He used to do sports and bicycling until ataxia made this difficult at the age of 17. He is now living in a sheltered household.

There were times when the smallest incident led to very angry reactions from him, and he would shout and try to hit when annoyed.

At the age of 26 behavioural abnormality symptoms appeared acutely without any prodromal signs. These included wandering at night, talking to and about people who were not present, worrying about people 'under the floorboards and in the ground', rapid counting and crawling on the ground as well as drawing lines with his finger. For several days after the onset of these symptoms he did not sleep well and had reduced appetite with a loss of weight. A possible precipitating factor was a significant emotional upset the prior week about a young woman he was very keen on. He was prescribed Haliperidol 2 mL at night, which stabilized his condition. Increasing the dosage led to agitation, insomnia, ataxia, marked muscle rigidity, and double incontinence. The acute period lasted 3 weeks, remitted gradually and was followed by a 3-week period of lethargy.

Clonazepam was used for 3 weeks to get his sleep patterns restored, and at the end of the sixth week medication was withdrawn as all symptoms were completely remitted. After another 2 weeks he returned to his usual vitality.

The physical examination by a specialist including CT scan of the brain revealed no abnormalities with the exception of an ear infection.

The second episode started 5 months later, after a brief period of anxiety while his parents were away, and coincided with a knee injury with inflammation. Symptoms were limited to mild confusion and disorientation but resolved after a few days with a calm environment and no medication.

The third episode occurred another 15 months later. Again, onset was very sudden with disorientation, confusion and no sleep for over 36 h without any sign of tiredness. Notably, this episode coincided with an emotional upset some days beforehand. He was medicated quickly with clonazepam 0.5 mg at night resulting in 10–12 h sleep every night. Medication was stopped after 3 weeks when sleeping patterns returned to normal. He had mild symptoms of agitation, concentration difficulties, talked about events that had happened many years ago, etc., but this time these symptoms were relatively mild. There was an extended time however, 15 months, before all symptoms were fully resolved and his usual vitality returned.

A list of the psychiatric and behavioural symptoms in the nine subjects for whom a detailed description was available is displayed in Tables 1–5.

Discussion

This is the first description of a panel of alpha-mannosidosis patients presenting with clinically

Table 1 The course of the mental disturbances reported by the observers[1]

Course of disease:	Value
Age at first time psychiatric disturbance of this kind	18 (14–31) years
Age now	23 (19–32) years
Number of episodes of psychiatric disturbance	2 (1–5)
Duration of longest episode of psychiatric disturbance	4 (2–24) months
Duration of shortest episode of psychiatric disturbance	1 (1–3) months
The disturbance subsides quickly (within 3 days)	1 Yes 3 No
The disturbance was followed by a period of weakness/somnolence	8 Yes 1 No

Table 2 Presence of general and behavioural symptoms reported by the observers

Behaviour and general symptoms:	Yes	No	Uncertain
During the disturbance the patient had . . .			
reduced abilities in several areas	8	1	
more violent behaviour towards other persons	1	7	1
increase in self-harming acts	2	6	1
more destructive behaviour towards objects	1	8	
peculiar behaviours	9		

Table 3 Presence of organic symptoms reported by the observers

Organic symptoms:	Yes	No	Uncertain
During the disturbance the patient had . . .			
memory difficulties	9		
difficulty in finding their way in familiar surroundings	4	5	
difficulty in recognizing familiar persons	1	7	1
tendency to mix familiar and unfamiliar persons	2	3	4
difficulty with the use of familiar objects	4	3	1
difficulty in understanding communication from others	7	1	1
difficulty with producing coherent verbal communication	9		
tendency to seem dull or sleepy or have reduced endurance	6	2	1
shifts between agitation and reduced activity	4	3	2
symptoms during night-time	9		

Table 4 Presence of depressive symptoms reported by the observers

Depressive symptoms:	Yes	No	Uncertain
During the disturbance the patient had . . .			
reduced interest and endurance in usually pleasurable activities	9		
reduced appetite or loss of weight	8	1	
reduced sleep during night (> 2 h less than usual)	8	1	
tendency to seem sad or cry	6	1	2
tendency to talk about death or serious illness	5	4	
tendency towards irritation or anger	7	2	
reduced activities in most areas of usual functioning	8	1	
tendency to be silent or speak little or slowly	9		
tendency to move slowly	7	1	1
fear and anxiety	7	2	
guilt or self-reproach	2	7	

significant psychiatric symptoms. The clinical presentation seems to be quite uniform, with first onset during puberty, although one case had a debut at the age of 14 and another at 32 years. Often, but not always, the families describe precipitating factors. These seem to be negative stressors such as change of residence, physical disease, loss or death in the family, changes in school or work, or sibling moving from home. With respect to psychopathology, organic, depressive and psychotic features characterize the symptoms. In some cases indications of a depressive reaction (adjustment disorder) are present

[1]Results from the questionnaire on mental symptoms as reported by the observer. This was normally the family, but could also be a professional. The number of patients is nine. In some cases, questions remained unanswered, and the sum of observations might be eight or less.

Table 5 Presence of psychotic symptoms reported by the observers

Psychotic symptoms:	Yes	No	Uncertain
During the disturbance the patient had . . .			
complaints about sounds other persons can't hear	5	3	1
complaints about voices other persons can't hear	4	2	3
tendency to talk to oneself as if in a conversation	5	4	
tendency to be scared of special objects, persons or places	7	1	1
complaint about seeing things that other people can't see	6	1	2
complaint about seeing things which are impossible	5	4	
tendencies towards seemingly purposeless activities	4	5	
tendencies towards purposeless or inappropriate postures	5	4	
increased suspiciousness	2		

and the outbreaks may carry signs of self-insight, releasing depressive feelings ('Five years ago I could go skiing, now I can hardly walk').

The episodes usually last 1 to 3 months, with a resolution period of days or a week. In one case the symptoms lasted 2 years. Typically, the first episode is experienced as frightening, both to the patient and the family, whereas later episodes are dealt with more easily. The episodes were nearly always followed by weeks of prolonged sleepiness, which could be part of the disturbance or its treatment. Our information of psychotropic drug use in the cases were too fragmentary to assess this with certainty, although there were some cases were sleepiness was reported in the absence of drugs.

We have information about medical examinations in regard to organic brain disease in seven of the nine patients. Three were completely negative. In four cases there were positive but non-specific findings with respect to an organic aetiology. Two had a slowing of the EEG, one an attenuation of the MRI signal in the upper brainstem towards thalamus, and one had atrophic changes on MRI. It is difficult to assess if these EEG and MRI-findings are of causal relevance to the observed psychopathology. In the remaining cases we do not know if EEG or MRI was performed. CT-scans, results from lumbar puncture or blood studies to rule out infections were all negative for the patients in which these investigations had been performed.

Subjects with ID are known to be at increased risk of psychiatric disorder, and they are said to exhibit the full range of such disorders (Borthwick-Duffy 1994). With their increased frequency of inborn errors of metabolism and many other diseases (Webb & Rogers 1999), they are vulnerable to development of organic brain syndromes and diseases. They also have an increased risk for behavioural disturbances (Emerson *et al.* 2001) and psychotic decompensation (Lund 1985) following environmental stressors whether they are biological (Gunsett *et al.* 1989) or psychosocial (Stoddart *et al.* 2002).

Diagnosis of psychiatric disorders in persons with learning disabilities is challenging even for specialists when disturbances occur in persons with ID. The typical symptoms of psychiatric disorders may change, because of a lack of expressive capacity (such as lack of or impairment of language), or they may also be exaggerated because of a lack of adequate coping strategies (insufficient support or help since the description/expression of the problems is difficult). Psychiatric symptoms are also often misinterpreted as a part of the ID (Cooper *et al.* 2003). Diagnostic guidelines in International Classification of Diseases – Tenth Revision (ICD-10; WHO 1993) and The Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV; American Psychiatric Association 1994) both give little help in diagnosing psychiatric disorders among persons with learning disabilities. In addition, the caregiving family members who reported the symptoms were mostly unacquainted with symptoms of mental illnesses. Owing to this limitation with respect to data collection we cannot always be certain about the true nature of the mental disturbance reported by these families.

The conditions described have similarities with acute and transient psychotic disorder (ICD-10 F23). This condition may or may not be preceded by a stressor, and is usually time-limited. It is characterized by a rapid onset (< 2 weeks), and may have features of perplexity, misidentification, impaired attention and concentration. Anxiety is often severe. There may be also hallucinations and delusions, as well as affective components. The latter is often related to a precipitating stressor.

Another possibility is that the psychiatric symptoms observed in our patients are explained by a disorder of the type delirium (ICD-10 F05) or other organic mental disorder because of brain damage/dysfunction (ICD 10 F06). These conditions are the result of cerebral or systemic disorders, which cause damage or disturbance of brain function with consequences for the mental state. They are usually characterized by a rapid onset, or onset co-occurring with a disturbance of central nervous processes. There is often clouding of consciousness with reduced ability to focus attention, reduced recent memory, disorientation regarding time, place and person, disturbances in psychomotor speed (in both directions), disturbance of sleep–wake cycle and a wide range of psychotic and affective symptoms often varying rapidly (hallucinations, illusions, delusions, anxiety, depression, euphoria, apathy, perplexity). However, delirium typically starts rather abruptly within hours to days, whereas our cases often show a prodromal period of change lasting several weeks. Delirium most often is a sign of acutely compromised brain function, and similar symptoms of less fulminate character can be caused by less abrupt cerebral changes. However, although the symptoms of our subjects are largely compatible with organic pathogenesis, we cannot be certain because both categories require the supposed underlying organic cause to be in a reasonable time-relationship with the psychiatric disturbance. We have no certain knowledge of this in our cases.

Depressive symptoms are very common among our cases. They are however, not isolated, but supplemented by a variety of seemingly organic and/or psychotic symptoms. Primary depressive disorders have been described with varying frequencies among persons with intellectual handicap. The variations have often been assumed to be owing to diagnostic difficulties (Sovner 1986). A major depressive episode may be accompanied by psychotic symptoms. It also represents a major stressor, and may provoke psychotic decompensation in vulnerable individuals. Many reported stressors were situations with potential of real loss and a necessity of adjustment to a new social situation. These are typical stressors leading to depressive decompensation. The precipitating factors in these cases seem moderate, but the impact of such events in the subjective experience of persons with learning disability is difficult to assess. Still, an organic disorder, or an acute transient psychosis could account for most of the depressive symptoms described.

An organic aetiology is further supported by the significant elements of confusion, reduced sensorium, and the long restitution period with asthenia and hypersomnolence, which we assume is part of the disorder. These symptoms are not common in primary depression or acute transient psychotic disorder. Both primary depression and acute transient psychosis are, however, compatible with the seemingly self-limiting nature of the disorder, as well as by its tendency to recur.

In the absence of a clear diagnosis we would recommend thorough physical examinations to rule out cerebral and other possible organic causes which could be treated or lead to a better understanding of this clinical picture.

The difficulty of establishing a clear diagnosis makes the recommendation of pharmacological treatment strategies difficult. Drugs to restore sleep patterns, and carefully titrated antipsychotic medication to control confusion, agitation, repetitive speaking, hallucinations, and disorientation, when present, seem justified in individual cases. Clonazepam seemed useful to restore sleep patterns in case 3 whereas olanzapine was particularly helpful when loss of appetite with significant reduction in body weight was predominant. Treatment with antidepressant drugs has been tried with some success when depressive symptoms dominated the clinical picture.

In conclusion, our observations indicate that alpha-mannosidosis is associated with an increased risk of psychiatric symptoms. The question whether these symptoms are an expression of organic brain dysfunction specifically associated with this disorder or whether they represent true (independent) psychiatric co-morbidity should be addressed in future studies. In any case, caregivers and physicians should be aware that patients with alpha-mannosidosis seem to be vulnerable to certain psychiatric symptoms. Their occurrence should not be dismissed as part of the ID but give rise to the initiation of adequate diagnostic work-up, treatment and support.

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