CASE REPORT

Phelan-McDermid syndrome due to *SHANK3* mutation in an intellectually disabled adult male: successful treatment with lithium

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SUMMARY

For 30 years, Phelan and co-workers described a syndrome characterised by neonatal hypotonia, global developmental delay, strongly impaired speech, sleep disturbances and hyperreactivity to sensory stimuli. This Phelan-McDermid syndrome (PMS), also presenting with symptoms from the autism spectrum and a higher risk of developing seizure disorders, may be caused by a deletion of chromosome 22q13 or by a mutation in the *SHANK3* gene. Its core psychopathological phenotype comprises symptoms from the bipolar spectrum for which generally treatment with a mood-stabilising anticonvulsant in combination with an atypical antipsychotic seems to be most effective. In addition to two elsewhere published adolescent patients, we here describe in detail the history of an adult male patient with PMS caused by a *SHANK3* mutation in whom successive treatment regimens with antipsychotics and mood-stabilising anticonvulsants were all ineffective. Ultimately, addition of lithium to existing olanzapine therapy led to enduring stabilisation of mood and behaviour.

treatment with mood-stabilising agents in combination with an atypical antipsychotic like quetiapine or olanzapine, in addition to contextual measures, has shown promising results.^{8–11} In case of a regressive phenotype, psychotropic medications may be ineffective and associated with multiple side effects. In such an event, Serret *et al*¹² found lithium therapy to be effective in two adolescent patients with PMS due to a *SHANK3* mutation. Also, Darville and colleagues¹³ reported beneficial effects on manic symptoms and attenuation of autistic symptoms in a 12-year-old patient with *SHANK3*-bound PMS.

Here, an adult male patient with a *SHANK3* mutation as well as bipolar-like and regressive features is described in whom successive treatment regimens with antipsychotics and mood-stabilising anticonvulsants were all ineffective and had induced serious side effects.

CASE PRESENTATION

The patient is a 43-year-old male born from non-consanguineous parents. Pregnancy and delivery were undisturbed, although that his mother was known with alcohol and benzodiazepines abuse. He has one paternal half-brother diagnosed with autism spectrum disorder and one healthy older maternal half-sister, who had to adopt the role of primary caregiver during his infant years. Postnatally, no dysmorphisms were noticed, nor were there any indications of childhood hypotonia. Growth curve was normal but development was characterised by mild delayed milestones and progressive destructive, self-injurious and withdrawal behaviours for which he was admitted to a medical child day care centre. Here, his problematic behaviour appeared to be contingent on environmental changes, reason why a descriptive diagnosis of autism spectrum disorder was given. Aged nine, his mother died from an alcohol-related serious fall accident. After she had deceased, the patient was institutionalised permanently. Over subsequent years, his general functioning with limited verbal communication skills kept relatively adequate, provided that no major changes in staff guidance and daily programme occurred, although challenging behaviours and hypersensitivity to sensory stimuli persisted. Most probably due to institutional reorganisation, his behaviour deteriorated, particularly concerning speech and language as well as motor functioning

BACKGROUND

Phelan-McDermid syndrome (PMS (OMIM: 606232)) was initially reported by Phelan and co-workers¹ and can be caused by a heterozygous contiguous gene deletion of chromosome 22q13 or by a mutation in the *SH3 and multiple ankyrin repeat domains 3* (*SHANK3*) gene. Its core phenotype comprises neonatal hypotonia, global developmental delay, impaired to absent speech and expressive language as well as symptoms from the autism spectrum in the absence of major dysmorphisms.^{2–4} In addition, other features can be regularly noticed, such as sleep disturbances and increased reactivity to sensory stimuli, lack of perspiration resulting in a tendency to overheat and high pain threshold.^{5,6} Furthermore, PMS can be associated with structural cardiac and urogenital anomalies as well as a higher risk of developing seizure disorders. The latter may be accompanied by regression in language, motor and behavioural skills. Brain imaging typically shows aspecific white matter changes and sometimes hypoplasia of the cerebellar vermis.⁷

Starting at late adolescence, patients with PMS may develop an atypical bipolar disorder for which

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Figure 1 Phelan-McDermid syndrome caused by a *SHANK3* mutation: face of the patient without any dysmorphisms.

and continence. Starting at the age of 16, marked instability of behaviour and mood, accompanied by sleep disturbances, severe anxieties and attention deficits became prominent for which an array of psychotropics was prescribed such as pipamperone, pimozide, clonidine, haloperidol, lithium, fluvoxamine and zuclopenthixol. Since each compound was prescribed only over a relatively short period of time because of side effects, its effectiveness could not be clearly established. Aged 21, a consultant psychiatrist advised thioridazine because of his hyperarousal state. Three years later, treatment with carbamazepine and/or valproic acid was prescribed and combined with several environmental adjustments, sometimes leading to mild behavioural amelioration, ultimately, however, with equivocal results. During the following decade, permanent sleep disturbances occurred in conjunction with alternating episodes of apathetic behaviours, food refusal and weight loss or impulsive behaviours that were interpreted by the treating physician as typical for maniform dysregulation. For this, in addition to carbamazepine, risperidone was started. Because of lack of effect, the consultant psychiatrist suggested that this type of mood dysregulation could be part of a rapid cycling bipolar disorder. Consequently, carbamazepine was substituted by lamotrigine and risperidone by olanzapine. This sequential combination induced signs of tardive dyskinesia for which the consultant psychiatrist advised clozapine up to a daily dose of 300 mg instead of olanzapine. Shortly thereafter, serious complications of clozapine emerged including severe constipation, recurrent seizures and agranulocytosis. Neurological

examination including CT scanning of the brain and EEG recording showed no abnormalities. As a consequence, psychotropic treatment was temporarily restricted to chlorazepate. At that time, genetic investigation using metabolic screening, microarray analysis and DNA analysis for fragile X syndrome and Lujan-Fryns syndrome was performed from which, however, no aetiological explanation could be discerned. Somatic examination disclosed no dysmorphisms (figure 1). As assessed with the Vineland and the ESSEON, developmental age was 14 months with corresponding scores on scales for communication, daily activities and motor skills of, respectively, 15, 17 and 22 months. Social skills/emotional development were significantly lower (3 months). At the age of 42, a treatment regimen of olanzapine (20 mg; 22 µg/L) in combination with valproic acid (2100 mg; 70 mg/L) and lamotrigine (75 mg; 3 mg/L) was gradually restarted.

Because of persistent instability with intermittent aggressive and apathetic episodes, severely incapacitating medical and nursing staff, and given the patient's history with serious side effects on various psychotropics, expert consultation was requested.

INVESTIGATIONS

Pharmacogenetic analysis was performed that disclosed normal metabolism for CYP1A2, CYP2C9 and 2C19 but intermediate metabolism for CYP2D6 (*1/*4; one active and one inactive allele). Since neither valproic acid nor lamotrigine did induce any behavioural stabilisation, it was advised to successively taper off these anticonvulsants and to continue olanzapine as monotherapy in an initial daily dose of 20 mg that was later reduced to 10 mg (28 µg/L). In terms of his behavioural profile, episodes as before—most probably due to an enhanced sensitivity for environmental stimuli—persisted, despite modifications of contextual parameters and staff approach. Given this situation and his history with seizures, brain imaging was indicated and, because of risk for movement artefacts, performed under general anaesthesia. MRI of the brain showed discrete loss of cerebral tissue predominantly left hemisphere with enlarged sulci, but no focal lesions or abnormalities of corpus callosum and cerebellar vermis could be detected (figure 2).

Aged 44, exome sequencing demonstrated a pathogenic heterozygous truncating mutation in the *SHANK3* gene (c.4523del (p.Thr1508Serfs*36), confirmed by Sanger sequencing) corresponding with a diagnosis of Phelan-McDermid syndrome.

TREATMENT

Because of increasing scientific evidence for atypical bipolar disorder as psychopathological phenotype for this genetic disorder and considering non-response on previous, principally adequate, prescription of mood-stabilising agents (carbamazepine, valproic acid and lamotrigine), it was decided to start lithium carbonate by slowly increasing the dose up to a plasma level of about 0.5 mmol/L that was reached after approximately 3 months (daily dose: 700 mg). Thereafter, over the course of 12 months, close monitoring of daily functioning was performed by the primary caregivers using individual behavioural charting differentiating five stages ranging from primarily apathetic via calm and active cooperative ('normal functioning') towards restless and agitated. During this whole period, general contextual parameters as well as treatment with 10 mg olanzapine daily were kept unchanged.

Figure 2 Transversal T2 weighted MR image (A) and coronal T2 weighted (inverted recovery) MR image (B) of the patient with Phelan-McDermid syndrome caused by a *SHANK3* mutation showing asymmetric (left hemisphere) marked tissue loss with enlarged sulci.

OUTCOME AND FOLLOW-UP

Multidisciplinary analysis after 6 months showed attenuation of stage variations on which it was decided to continue the treatment regimen. Further stabilisation was achieved during the subsequent semesters leading to the conclusion that lithium, indeed, had resulted in a marked stabilisation of behaviour, mood and affect. This was corroborated by the patient's half sister who was best familiarised with his full life course. Given this consensus, lithium was considered to be the long-term treatment of first choice with yearly follow-up through expert consultation. To assess possible deterioration, additional neuropsychological assessment was performed. From this, developmental age was established at 14 months, a result similar to that obtained for more than 20 years. In addition, interpersonal functioning was best typified within the psychopathological domains of 'inappropriate mental adjustment', 'affective disorders' and 'anxiety disorders' (Psychopathology Inventory for Mentally Retarded Adults total score=24 (max 56)). Systematic evaluation of affective information processing including social cognition was in line with these results and was used to formulate refined tools for enhancing awareness and clinical management by the nursing staff.

DISCUSSION

Here, an adult male patient is described with a genetic diagnosis of PMS caused by a *SHANK3* mutation and a long history of therapy-resistant psychopathology within the bipolar and regressive spectrum together with intermittent challenging behaviour. Despite multiple interventions over several decades with environmental adaptations and with psychotropics and/or anticonvulsants, some leading to life-threatening adverse events, no improvements could be achieved. Therefore, it was decided to initiate treatment with lithium that ultimately resulted in observable improvement of general functioning including stabilisation of mood and affect and a gradual diminishing of the regressive

features. Neuropsychological assessment did not reveal any signs of a neurodegenerative course.

This case observation strongly underlines the psychopathological phenotype with enhanced susceptibility to mood dysregulation in patients with PMS. Similarly, it corroborates the effectiveness of long-term treatment with mood-stabilising agents next to contextual measures for reducing the risk for relapse of a bipolar-like episode with possible regressive features. This is also substantiated by the observation of Liu and Smith,¹⁴ who described positive effects on behavioural and adaptive skills in 15 patients with fragile X syndrome that to some extent shows similar psychopathological phenomena as PMS.

In general, it had to be stressed that extensive aetiological investigation is warranted, even in intellectually disabled patients at older age, given its instrumental role in treatment design and its consequent potential for enhancing therapeutic impact.

In conclusion, pharmacological treatment of first choice for the psychopathology in patients with PMS has to be a mood-stabilising agent in combination with a low dose of an atypical

Learning points

- ▶ Full understanding of the behavioural repertoire of adult patients with intellectual disability requires knowledge of syndrome-related psychopathology.
- ▶ The psychopathological phenotype of Phelan-McDermid syndrome comprises atypical bipolar disorder, for which treatment with mood-stabilising agents is primarily indicated.
- ▶ In case of non-response to mood-stabilising anticonvulsants in patients with PMS, lithium therapy may still regulate mood and behaviour and prevent relapses.
- ▶ At present, aetiological diagnostics in intellectually disabled patients should also include exome sequencing, even in patients at older age.

antipsychotic like olanzapine or quetiapine and, in those with a *SHANK3* mutation, perhaps primarily with lithium.

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Contributors JIME and WMAV conceptualised and designed the study and collected and reviewed the literature. JIME, WMAV and RG-R assessed the patient, acquired the data and discussed the initial findings. WMAV planned additional assessments. SGK performed and interpreted the genetic analysis. JIME and WMAV reported the case history and drafted the manuscript. RG-R and SGK commented on the literature review and critically reviewed the manuscript. All authors read and approved the final version of the manuscript.

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