Neurodevelopmental and Psychiatric Symptoms in Patients with a Cyst Compressing the Cerebellum: an Ongoing Enigma

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Neurodevelopmental and psychiatric symptoms in patients with a cyst compressing the cerebellum: an ongoing enigma

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ABSTRACT

A patient diagnosed with developmental delay, intellectual disability, and autistic and obsessive-compulsive symptoms was found to have a posterior fossa arachnoid cyst (PFAC) compressing the cerebellum. The patient was referred to our Ataxia Unit for consideration of surgical drainage of the cyst to improve his clinical constellation. This scenario led to an in-depth analysis including a literature review, functional resting-state MRI analysis of our patient compared to a group of controls, and genetic testing. While it is reasonable to consider that there may be a causal relationship between PFAC and neurodevelopmental or psychiatric symptoms in some patients, there is also a nontrivial prevalence of PFAC in the asymptomatic population, and a significant possibility that many PFAC are incidental findings in the context of primary cognitive or psychiatric symptoms. Our functional MRI analysis is the first to examine brain function, and to report cerebellar dysfunction, in a patient presenting with cognitive/psychiatric symptoms found to have a structural abnormality compressing the cerebellum. These neuroimaging findings are inherently limited due to their correlational nature, but provide unprecedented evidence suggesting that cerebellar compression may be associated with cerebellar dysfunction. Exome gene sequencing revealed additional etiological possibilities, highlighting the complexity of this field of cerebellar clinical and scientific practice. Our findings and discussion may guide future investigations addressing an important knowledge gap – namely, is there a link between cerebellar compression (including arachnoid cysts, and possibly other forms of cerebellar compression such as Chiari malformation), cerebellar dysfunction (including fMRI abnormalities reported here), and neuropsychiatric symptoms?

Keywords: Cerebellum; fMRI; Arachnoid cyst; Neuropsychiatry; Behavioral neurology.

1. INTRODUCTION

A patient with a life-long history of neurodevelopmental / psychiatric symptoms was found to have a retrocerebellar posterior fossa arachnoid cyst (PFAC) compressing the cerebellum. The patient was referred to the Massachusetts General Hospital Ataxia Unit for consideration of surgical drainage of the cyst to improve his neurological and neuropsychiatric symptoms. This scenario led to an in-depth analysis including a review of the literature, functional MRI resting-state analysis comparing our patient to 36 healthy controls, and genetic testing.

1.1 Case presentation

A 32-year-old left-handed male presented with a constellation of neurodevelopmental and psychiatric symptoms and the diagnosis of a retrocerebellar PFAC compressing the cerebellum (**Fig.1**). Relevant past medical history included bilateral hypotonia and gross motor deficiency which were observed at age 6-9 months. There was no history of fetal or perinatal distress, or maternal abuse of alcohol or other substances. A muscle biopsy at that time revealed no abnormal findings, and hypotonia improved over time. However, developmental milestones were delayed - sitting started after 12 months, walking at 24 months, and talking between 12 and 24 months. Fine motor skills such as dressing, using small buttons, or threading a belt through trouser loops were delayed and never fully developed, although other motor skills such as bicycle riding were noted to be normal in adulthood. Educational difficulties were present from primary school until the end of high school, requiring participation in special educational programs. Social interactions were difficult in early school, and social awkwardness and difficulty

remained a major issue in recent years. Psychological evaluation at the age of 22 revealed verbal and nonverbal IQ scores at or below the 5th percentile. Additional abnormalities at present included occasional verbal and physical aggressive behavior, compulsive behaviors and obsessive thoughts. Previous reports noted worsening of this constellation of problems after the age of 19. The patient reported increased frustration and anxiety over the years. At age 20, brain MRI revealed the presence of a posterior fossa arachnoid cyst with no other morphological brain abnormalities. Family history was negative for formal psychiatric diagnoses. The patient was not taking any medications other than vitamins at the time of our investigations, but multiple medications were used in the past for behavioral symptoms including selective serotonin reuptake inhibitors (SSRIs), benzodiazepines, methylphenidate, antiepileptic and antipsychotic medications. On examination at our institution he demonstrated mild frontal bossing, markedly decreased eye contact with the examiner, intermittent irritable behavior, saccadic intrusions into pursuit eye movements and mild failure of suppression of the vestibulo-ocular reflex, mild dysarthria, reduced right finger tapping and right rapid alternating movements dexterity, minimally widened stance, and occasional stepping off line in tandem gait. Brief Ataxia Rating Scale score was 2.5 (gait 0.5/8, left leg 0/4, right leg 0/4, left arm 0/4, right arm 0.5/4, speech 0.5/4, eye movements 1/2) (1). Neuropsychological testing at the time of the examination using the Cerebellar Cognitive Affective / Schmahmann Syndrome Scale (2) revealed failures in phonemic and category switching fluency, digit span forward and backwards, cube draw and copy, and affect, with preservation of verbal learning and recall, resulting in a total of 6/10 fails and a raw score of 63/120 (semantic fluency patient score = 17/26, failure cutoff = 15/26; phonemic fluency 3/19, cutoff 9/19; category switching 7/15, cutoff 9/15;

digit span forward 4/8, cutoff 5/8; digit span backward 2/6, cutoff 3/6; cube 6/15, cutoff 11/15; verbal recall 15/15, cutoff 10/15; similarities 7/8, cutoff 6/8; go no-go 1/2, cutoff 0/2; affect 1/6, cutoff 4/6). A comprehensive metabolic panel showed no relevant abnormalities. Structural brain MRI was performed at our institution (**Fig. 1**). To further define the essential features of the case and help determine an optimal strategy for clinical management, we conducted a comprehensive review of the literature, obtained experimental resting-state fMRI data, and requested exome sequencing from a private organization (GeneDx).

[FIGURE 1 HERE]

2. MATERIALS AND METHODS

2.1 Literature review

We first performed a literature review to synthetize previous evidence linking PFAC with neurodevelopmental / psychiatric symptoms. We searched PubMed including the keywords acarchnoid cyst, retrocerebellar arachnoid cyst, posterior fossa arachnoid cyst, cerebellar compression, cerebellar decompression, arachnoid cyst surgical decompression, and arachnoid cyst drainage.

Other than clinical and behavioral investigations, no previous study has examined brain function in patients with a PFAC and simultaneous psychiatric or cognitive symptoms. Accordingly, we tested whether fMRI resting-state functional connectivity analysis could detect cerebellar dysconnectivity in our patient compared to a group of controls, as follows.

2.2 fMRI data acquisition and analysis

2.2.1 Participants

Resting-state fMRI data from our patient (see section 1.1) was compared to a group of 36 healthy controls with no history of psychiatric or neurological illness using the same scanner and scanning parameters (22 male and 14 female; age average = 26.36, SD=4.57; years of education were not available; note that education matching in our control sample is not possible in the context of educational difficulties that required participation in special education programs in our patient, and educational difficulties are part of the psychopathology that is studied in this case of cerebellar compression that was detected in the context of neurodevelopmental and psychiatric issues). All participants provided written, informed consent in accordance with the Massachusetts Institute of Technology Committee on the Use of Humans as Experimental Subjects (COUHES). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

2.2.2 Rationale of fMRI analysis

No previous study using tools other than clinical or behavioral measures has tested whether cerebellar dysfunction exists in patients with cerebellar compression and simultaneous psychiatric or cognitive symptoms. To address this question, we adopted an initial data-driven approach to identify brain regions with the most abnormal functional connectivity patterns using whole-brain multi-voxel pattern analysis (MVPA). Within the limits of strict statistical thresholds ($p<0.05$ FDR voxel-level correction and

cluster p<0.001 FWE correction), the bigger (and hence more statistically reliable) cluster within the cerebellum that emerged from this initial whole-brain exploration was retained for further investigation. This approach enabled our analysis to potentially identify an optimal cerebellar region of interest, and explore for the first time the possibility of cerebellar dysconnectivity in a patient with cerebellar compression and simultaneous psychiatric / cognitive symptoms.

2.2.3 Details of fMRI data acquisition and analysis

MRI data were acquired using a Siemens 3T Tim Trio MRI scanner with a 32-channel head coil. Functional MRI (gradient echo T2*-weighted echo planar imaging) resting-state acquisition parameters were as follows: repetition time = 1.09s, echo time = 30ms, flip angle = 61°, voxel size = 2mm isotropic, 300 time points, field of view = 216mm x 216mm, using simultaneous multislice acquisition (slice acquisition factor = 5). Structural MRI T1w acquisition parameters were as follows: repetition time = 2.53s, inversion time = 1.4s, echo time = 0.00164s, flip angle = 7°, voxel size = 1mm isotropic.

While the scanner model and parameters were the same for all participants, the patient and 7 controls were scanned at the same scanner, while 29 controls were scanned at a different scanner (of the same model) at the same institution. Of note, scanner was included as a regressor of no interest in all analyses in order to account for potential differences between scanners, as noted below.

fMRI analysis included the following steps: (i) Fieldmap correction using FLS topup and applytopup commands (3). (ii) Image preprocessing as implemented by default in the

Conn toolbox (4), which includes the following computations for functional MRI data: realignment and unwarp (including motion estimation and correction), centering to (0, 0, 0) coordinates, outlier detection (ART-based identification of outlier scans for scrubbing), and smoothing (spatial convolution with Gaussian kernel). Structural MRI data preprocessing steps include translation to (0, 0, 0) coordinates, and segmentation and normalization (using gray/white/CSF segmentation and MNI normalization) (functional images were segmented and registered to MNI space following structural segmentation and normalization parameters). For this step we selected the following parameters: global signal z value threshold = 3, subject-motion threshold = 0.5mm, smoothing = 4mm (4mm of smoothing corresponds to twice the voxel size, consistent with common analytical strategies in fMRI (5)). (iii) Denoising as implemented by default in Conn (4) (aCompCor method (6), using automatically generated regressors including 5 white matter components, 5 CSF components, and movement regressors), in addition to 0.008-0.09 Hz band-pass filtering (which correspond to default band-pass filtering values in Conn). (iv) First level whole-brain voxel-to-voxel MVPA using 64 PCA components and retaining 4 factors, as implemented in Conn (within Conn's category of voxel-to-voxel analyses) (4). The first step using 64 components corresponds to subject-level dimensionality reduction; the second step retaining 4 components is calculated jointly across all subjects (after dimensionality reduction to 64 components for each subject) for each voxel, and captures between-subject variability (i.e., these 4 components characterize between-subject variability in functional connections for each voxel, and are extracted from single-subject data that has been previously dimensionality-reduced to 64 components) (for further detail, see https://sites.google.com/view/conn/measures/networks-voxel-level and a previous

description of this method by our group (7)). The number of factors was set to 4 given that this corresponds to approximately 10% of the total number of subjects in the present study, following conventions of previous investigations (8). (v) Second level whole-brain F test using the first 4 MVPA components for a Patient > Controls group contrast, using the following variables as regressors of no interest: scanner, invalid scans (i.e. time points with mean signal intensity outside 3 standard deviations from global mean, or 0.5mm scan-to-scan motion), maximum motion, and mean motion. Results in step 5 were thresholded using $p<0.05$ FDR voxel-level correction and cluster $p<0.001$ FWE correction. The bigger (and hence more statistically reliable) cerebellar cluster is retained for analysis in the following step. (vi) First level whole-brain seed-to-voxel analysis (as implemented in Conn (4), corresponding to Fisher-transformed bivariate correlation coefficients between timeseries of a seed region of interest and individual voxel timeseries) using the cerebellar cluster from step 5 as a seed. (vii) Second level whole-brain seed-to-voxel Patient > Controls group contrast using the cerebellar cluster from step 5 as a seed and including the following variables as regressors of no interest: scanner, invalid scans, maximum motion, and mean motion. Results in step 7 were thresholded using $p<0.05$ FDR voxel-level correction and cluster $p<0.001$ FWE correction, two-tailed (thus, in this two-tailed analysis, positive results corresponded to Patient > Controls and negative results corresponded to Controls > Patient). Voxel-level correction in both MVPA (step 5) and post-hoc seed-to-voxel analyses (step 7) avoids the methodological limitations of cluster-extent based corrections (9). Of note, given that the objective of the present study was to evaluate the possibility of disrupted cerebellar-extracerebellar connectivity, post-hoc analyses were performed using only the bigger (and hence more statistically reliable) cerebellar MVPA

cluster result from step 5 as a seed in steps 6 and 7. Results were visualized using Conn's cerebral cortical surface visualization (4) and cerebellum flat-maps (10). Cerebellar results were also plotted along functional gradients of the cerebellum developed previously by Guell et al. (11). Cerebellar functional gradients provide a low-dimensional representation of functional specialization in cerebellar cortex (gradient 1 corresponds to a progression from motor to default-mode processing; gradient 2 isolates attentional processing) (11). Mapping cerebellar clusters along functional gradients 1 and 2 can be useful to interpret the topographical distribution of cerebellar neuroimaging findings.

T-test as implemented in Conn when one group includes only one subject is equivalent to Crawford's t-test. Crawford's t-test (12) is an optimal statistical method when comparing a single subject against a group of controls given that, in contrast to z values, it does not assume that the parameters and distribution of the population are known (13).

MVPA has the quality of being a data-driven method to identify brain regions with the most different patterns of whole-brain connectivity when comparing two groups. We used this method in the whole brain in order to identify potential areas of abnormal connectivity in the cerebellum (steps 4 and 5). Post-hoc seed-to-voxel analysis, despite being circular in nature, is useful to *characterize* abnormal patterns of connectivity from our cerebellar MVPA results (steps 6 and 7). Restated, MVPA can identify the presence of clusters with abnormal whole-brain connectivity patterns, and post-hoc seed-to-voxel

analyses are useful to interrogate which brain regions are abnormally connected to a given cluster resulting from an MVPA.

Of note, registration to MNI space in the patient structural and functional data included some aspects of the cerebellar cyst. This does not represent a limitation given that our cerebellar findings are all in lobules I-VI, which are located far from the territory occupied by the cyst, and which were correctly registered to standard space (see **Supplementary figure 1**).

2.3 Genetic analysis

Our fMRI investigation was supplemented by exome sequencing analysis in order to determine whether in this unusual case there were any potentially causative or relevant genetic variants associated with neurodevelopmental / psychiatric phenomena, PFAC, or both. Exome sequencing was performed by a private testing company (GeneDx, using their XomeDxPlus protocol, including massive parallel sequencing on an Illumina system, and their custom-developed analysis tool Xome Analyzer).

2.4 Supplementary analyses

To rule out the possibility that fMRI differences between our patient and controls might be driven by gender differences (patient was male; control sample included 22 males and 14 females) or age differences (patient was 32 years old, control sample age average was 26.36 (SD=4.57), even if age differences were not statistically significant), we repeated the MVPA and post-hoc seed-to-voxel analyses (using the same statistical

parameters as in our main MVPA and post-hoc analyses) including age and gender as additional regressors of no interest.

To rule out the possibility that fMRI differences between our patient and controls might be driven by handedness differences (patient was left-handed, but only 3 out of 27 controls who reported handedness information were left-handed; 9 controls did not provide handedness information), we repeated our analyses using the same parameters described in the fMRI methods section to analyze possible effects of handedness when comparing the 3 left-handed controls to the 24 right-handed controls. Of note, including handedness as a regressor of no interest in our analysis (as in the case of age and gender) would generate a problematic analytical design, given that only 3 out of the 36 controls were confirmed to be left-handed.

To explore the possibility that there may be brain structural differences in our patient compared to our controls, we performed region-based morphometry analyses estimating the total volume of each gray matter parcel from the neuromorphometrics atlas (http://neuromorphometrics.com/; integrated in SPM's CAT12 toolbox (14)) in our patient compared to our controls, as follows: (i) structural T1 scans were entered into the default pipeline of CAT12; (ii) CAT12 provided volumes for each gray matter parcel in the neuromorphometrics atlas; (iii) for each individual participant we divided each parcel's volume by the sum of all grey matter parcel's volume, as a way to normalize for overall larger or smaller brain sizes between participants; (iv) we calculated z scores in our patient and controls for each parcel X as follows: ((normalized brain volume of X in one single participant) – (mean of normalized volume of X across all controls)) /

(standard deviation of normalized volume of X across all controls). Statistical significance testing was performed using Crawford's t-test (two-sided) and FDR correction for multiple comparisons, with a threshold of $p<0.05$, using normalized data as calculated in step (iii). This supplementary exploratory analysis provided a visualization of our patient's normalized brain volume in comparison to our controls for a list of brain territories, which may serve as an indication for future research interested in examining not only functional but also structural MRI in cases of cerebellar compression with concomitant cognitive / psychiatric symptoms.

3. RESULTS

3.1 Posterior fossa arachnoid cysts associated with neurodevelopmental / psychiatric symptoms: a review of the literature

Arachnoid cysts (AC) are collections of cerebrospinal fluid between the layers of the arachnoid membrane (15). They can be located in the posterior fossa adjacent to the cerebellum, or in other regions such as the middle cranial fossa adjacent to the temporal lobe, the vertex adjacent to the frontal lobe, the suprasellar region, and in the ventricles (15). Within the posterior fossa, they are most commonly located in the retro-cerebellar area (16), but can also be found in the cerebellopontine angle or the supravermian area (17). Within the retro-cerebellar area, AC are most commonly found in a midline position, but can also have an asymmetric location (18). A meta-analysis of MRI incidental findings in 19,559 healthy subjects estimated that the prevalence of AC in the apparently asymptomatic population is 0.5% (95% CI 0.21% to 0.87%) (19). The posterior fossa is the second most common location of AC following the middle cranial fossa (20), with some studies estimating a posterior fossa arachnoid cysts (PFAC)

prevalence in the apparently asymptomatic population of 0.3% (21). AC are more common in men, and some studies observed that this sex difference is more prominent in retrocerebellar PFAC (18).

Symptomatic presentations of PFAC in adults in the absence of other radiological abnormalities (such as hydrocephalus or absent septum pellucidum) or significant past medical history (such as prematurity or traumatic delivery) include cranial neuropathies, headache, vomiting, vertigo, and arm and gait dysmetria (20,22). Similar symptoms are reported in the pediatric literature (23). In addition, PFAC in the absence of other radiological or medical history abnormalities can present with agitated behavior, repetitive behaviors, and academic regression in pediatric patients (23), as well as psychosis (24,25) and conversion disorder (26) in the adult population. Other studies report seizures and additional cognitive abnormalities (27–30), but the absence of other radiological abnormalities or significant past medical history was not stated in those cases.

PFAC are sometimes treated with surgical drainage (31), and surgical complications are rare (32). While a large number of studies have reported psychiatric symptoms or cognitive performance improvement after cerebral AC surgical treatment (23,26,32–37), very few of these studies included PFAC patients in their analyses. One of these studies recruited 10 PFAC patients (32), but did not provide information to assess whether symptom improvement had occurred within the PFAC subgroup. Excluding this study, our literature review identified three cases of PFAC patients with pre-surgery and post-surgery psychiatric or cognitive assessment. In these three cases (one adult conversion

disorder (26) and two cases of pediatric cognitive and behavioral abnormalities (23)), symptoms improved after surgery. This paucity of studies investigating cognitive or psychiatric improvement following PFAC treatment might be due to the fact that the medical field recognizes the relevance of the cerebral cortex, but perhaps less often the relevance of the cerebellum, in cognition and emotion.

A large body of anatomical, clinical, behavioral, and neuroimaging evidence has determined that the cerebellum is involved in cognitive and affective functions (38). The cerebellum is anatomically connected to extracerebellar regions involved in cognitive and affective processing (39–44), isolated cerebellar lesions can generate cognitive and affective symptoms (2,45–47), cerebellar neuroimaging activation and functional connectivity is observed in cognitive and affective processes (11,48–51), and cerebellar structural and functional abnormalities exist in many neurological and psychiatric diseases that degrade cognition and affect (7,52–59).

Taken together, the current state of the literature shows that the cerebellum has a role in cognitive and affective functions, that PFAC compressing the cerebellum can be present in patients with cognitive or psychiatric abnormalities, and that these abnormalities may resolve after PFAC treatment. At the same time, there is a nontrivial prevalence of PFAC in the asymptomatic population, and a significant possibility that many PFAC are incidental findings in the context of primary cognitive or psychiatric symptoms. This duality of evidence, namely, a reasonable possibility of a causal relationship between PFAC and neurodevelopmental or psychiatric symptoms in some

patients, and a contrasting possibility that the PFAC is incidental, highlights the need to investigate brain function alterations in patients with PFAC.

3.2 fMRI analyses

Motion analyses revealed the following results when comparing our patient versus our 36 controls (p values that follow are two-sided): mean motion T=1.61, p=0.116; max motion T=1.85, p=0.073; invalid scans (scan-to-scan motion threshold = 0.5mm) T=2.99, p=0.005. All the aforementioned parameters were included as regressors of no interest in all subsequent analyses, as specified in the methods section. Age differences were not statistically significant (T = 0.55, two-sided p = 0.584).

Whole-brain MVPA contrasting our patient against a group of 36 controls revealed multiple clusters of abnormal functional connectivity within the cerebral cortex, and also a cluster of abnormal functional connectivity in lobules I-VI in the cerebellum that survived our strict statistical thresholding ($p<0.05$ FDR voxel-level correction and cluster $p<0.001$ FWE correction) (**Table 1**, **Figure 2a, b**). Having identified the bigger (and hence more statistically reliable) region of cerebellar abnormal connectivity in our patient using an additional thresholding level of cluster size of >300, functional connectivity from cerebellum was characterized in more detail. Specifically, post-hoc seed-to-voxel analysis using the cerebellar MVPA cluster as a seed revealed multiple areas of hyper and hypoconnectivity from cerebellum to cerebral cortex in our patient when compared to a group of 36 controls (**Table 2**, **Figure 2c, d**). Mapping our cerebellar MVPA cluster against cerebellar functional gradients previously developed by Guell and colleagues (11) revealed cluster extension throughout low gradient 1 / low

gradient 2 values as well as high gradient 2 values (**Figure 3**). Additional cerebral cortical and cerebellar clusters with size k<300 that also survived our statistical thresholds are not reported; larger clusters are more likely to be true positives (9), and our largest cerebellar cluster result (k=334) was sufficient to test for the presence of disrupted cerebellar functional connectivity in our patient compared to controls.

[TABLE 1 HERE]

[TABLE 2 HERE]

[FIGURE 2 HERE]

[FIGURE 3 HERE]

3.3 Exome sequencing

GeneDx XomeDx evaluation metrics revealed a quality threshold of 98.2%; average quality thresholds for this system range from 90 to 95%, and the remaining percentage (1.8% in this case) indicates exome target regions that may not be covered with sufficient quality.

Exome sequencing revealed a KAT6A de novo mutation (variant p.P528S, coding DNA c.1582 C>T) classified by GeneDx as a likely pathogenic variant, and an inherited USP9X X-linked mutation (variant p.E903G, coding DNA c.2708 A>G) classified by the testing company as a variant of uncertain significance.

3.4 Supplementary analyses

MVPA and post-hoc seed-to-voxel analyses (using the same statistical parameters as in our main MVPA and post-hoc analyses) including age and gender as additional regressors of no interest revealed virtually identical results (**Supplementary Figure 2**),

indicating that findings reported in section 3.2 are not driven by gender or age differences between our patient and controls.

MVPA analysis investigating handedness effects when comparing left handed versus right handed controls revealed no statistically significant findings. The lack of an MVPA effect of handedness in our control sample indicates that our analytical strategies are unlikely to be affected by effects of handedness.

Region-based morphometry analysis revealed some structural differences in our patient when compared to controls (**Supplementary Figure 3**), although no differences survived statistical significance testing (Crawford's t-test, two-sided, with FDR correction for multiple comparisons and a threshold of $p<0.05$). The differences observed in some brain territories (such as insula and cingulate gyrus) may serve as an indication for future research interested in examining not only functional but also structural MRI in cases of cerebellar compression with concomitant cognitive / psychiatric symptoms.

4. DISCUSSION

A patient with a life-long history of neurodevelopmental / psychiatric symptoms was found to have a PFAC compressing the cerebellum. The patient was referred to our clinical unit for consideration of surgical drainage of the cyst to improve his clinical constellation. An in-depth analysis of this case was performed including a literature review, resting-state functional MRI analysis, and genetic testing. The results presented here and discussion that follows may guide future investigations addressing an important knowledge gap – namely, is there a link between cerebellar compression

(including arachnoid cysts, and possibly other forms of cerebellar compression such as Chiari malformation), cerebellar dysfunction (including fMRI abnormalities reported here), and neuropsychiatric symptoms?

4.1 Literature review: a duality of evidence

Review of current literature (section 3.1) does not resolve the issue. Publications that describe neuropsychiatric phenomenology in the setting of a cerebellar arachnoid cyst could be harmonious with the current understanding of the cerebellar role in cognition and emotion. Clinical improvements reported after PFAC fenestration sound encouraging. In contrast, however, there is considerable evidence that these cysts may be entirely asymptomatic in healthy individuals showing no symptoms of cognitive or neuropsychiatric disorder. This is a clinical conundrum that has not yet been brought to satisfactory resolution. Specifically for this reason, we proceeded to research imaging to obtain a better understandment of the neurobiology of cerebrocerebellar connections in this specific patient.

4.2 Functional neuroimaging findings: first evidence of abnormal cerebellar function in a case of cerebellar compression with concomitant cognitive / psychiatric symptoms

Our resting-state fMRI MVPA revealed abnormal patterns of whole-brain functional connectivity in multiple areas of the cerebral cortex (**Fig. 2a**) and some aspects of cerebellar lobules I-VI in our patient (**Fig. 2b**). A post-hoc seed-to-voxel functional connectivity analysis using our cerebellar MVPA cluster as a seed revealed multiple cerebral cortical regions that were abnormally hypo- or hyper-connected to those

aspects of the cerebellum (**Fig. 2c, 2d**). Cerebellar MVPA cluster in lobules I-VI included regions of the cerebellum involved in motor processing (lobules I-VI). Some aspects of lobule VI have also been shown to be engaged in non-motor processing (60,61). Accordingly, mapping of this cluster along cerebellar functional gradients (obtained from a previous study by Guell and colleagues (11,62)) revealed a majority of low gradient 1 and low gradient 2 values (corresponding to motor processing (11)), but also high gradient 2 values in some voxels (corresponding to focused, as opposed to unfocused / mind wandering, cognitive processing areas (11)) (**Fig. 3c**). Similarly, MVPA findings overlapped mostly with somatomotor network (as defined in a cerebellar resting-state network atlas (49)), but also with some aspects of ventral attention and frontoparietal networks (**Fig. 3b**). Consistent with this distribution, post-hoc seed-to-voxel analysis using our cerebellar MVPA cluster as a seed revealed abnormal connectivity with multiple cerebral cortical regions involved in unimodal information processing (such as precentral and postcentral gyrus) as well as multiple aspects of multimodal information processing (such as supramarginal gyrus, inferior frontal gyrus, angular gyrus, and cingulate cortex; see **Table 2**). In this way, the apparent contradiction between cerebellar MVPA findings (that were localized in motor territories) and our patient's symptomatology (that affected multiple aspects of non-motor processing) may be resolved when considering the distribution of cerebellar MVPA findings towards some aspects of non-motor cerebellar functional territories (**Fig. 3**), as well as the wide distribution of cerebral cortical abnormalities in post-hoc analyses (**Fig. 2c**). To our knowledge, this is the first report of cerebellar functional abnormalities in a patient presenting with neurodevelopmental or psychiatric symptoms found to have a structural abnormality causing cerebellar compression.

Of note, functional connectivity abnormalities were detected in cerebellum but also in cerebral cortex, and it cannot be established whether cerebellar dysfunction is linked to abnormal connectivity in cerebral cortex or whether cerebral cortical dysfunction is unrelated to cerebellar compression. It is reasonable to consider that cerebral cortical findings in our MVPA results might be a result of cerebellar compression, and this possibility is consistent with the fact that cerebral cortical MVPA findings shown in **Fig. 2a** revealed a spatial distribution similar to post-hoc connectivity findings from our cerebellar cortex MVPA cluster shown in **Fig. 2c.** It did not escape our attention that common regions of abnormality between our MVPA findings (**Fig. 2a**) and post-hoc cerebral cortical results (**Fig. 2c**) (including left and right supramarginal gyrus, left and right precentral gyrus, and cingulate cortex) corresponded to areas of hyperconnectivity in post-hoc analyses in our patient (yellow clusters in **Fig. 2c**), while regions of post-hoc analysis that did not overlap with MVPA cerebral cortical results (including left and right occipital cortex and left frontal pole) corresponded predominantly to areas of hypoconnectivity in post-hoc analyses (purple clusters in **Fig. 2c**). Future developments in this field, perhaps including dynamic causal modeling analyses of resting-state timeseries that can determine the direction and strength of influence between brain territories, may further study the nature of cerebellar hyperconnectivity as opposed to hypoconnectivity in cases of cerebellar compression. Future studies examining the relationship between abnormal fMRI findings and behavioral variables across subjects with cerebellar compression might also attempt to dissociate pathological changes (that often positively correlate with higher symptom severity) as opposed to compensatory reorganization changes (that often negatively correlate with higher symptom severity) –

such a distinction is not possible based on our current findings. In addition, future investigations might explore the relationship between functional and structural changes in cerebellar compression. A visualization of volume across multiple brain territories in our patient compared to controls presented here (**Supplementary Fig. 3**) may serve as an indication for future research interested in examining not only functional but also structural MRI in cases of cerebellar compression with concomitant cognitive / psychiatric symptoms. The hypothesis that structural abnormalities may be related to functional abnormalities needs to be investigated in future structure-focused studies using analyses such as voxel-based morphometry, deformation-based morphometry, or surface-based morphometry that are beyond the scope of the present investigation.

The novel research imaging findings were intriguing, but did not necessarily explain the totality of the case, particularly some of the dysmorphic features evident on examination. For this reason, and to determine if there could be an underlying gene disorder accounting for the entire presentation, we proceeded to exome sequencing.

4.3 Genetic testing findings: a cautionary note on establishing causal relationships between cerebellar compression, cerebellar dysfunction, and cognitive/psychiatric symptoms

Exome sequencing detected two potentially relevant variants in KAT6A (autosomal) and USP9X (X chromosome) genes. De novo KAT6A mutations have been associated with intellectual disability and hypotonia, both of which are present in our patient. Facial feature abnormalities are also present in KAT6A mutations, and may be related to the mild frontal bossing observed in our patient. This phenotype was introduced in previous

studies of six (63), three (64), and six (65) individuals. KAT6A mutations affect a protein that regulates gene expression through histone acetylation. Importantly, this protein is susceptible to genetic/epigenetic and environmental modifiers, thereby leading to marked phenotype variations across individuals who have a KAT6A mutation (63). Consistent with this characteristic, KAT6A studies report additional abnormalities such as heart defects and microcephaly (63) which are not present in our patient.

USP9X mutations have been associated with intellectual disability, hypotonia, autism, and structural brain abnormalities including retrocerebellar arachnoid cysts, all of which are present in our patient. Specifically, retrocerebellar arachnoid cyst was present in 5 out of 17 female patients with USP9X mutation and developmental delay (66). Mild frontal bossing observed in our patient might also correspond to facial feature abnormalities observed in some USP9X mutation cases (66) – of note, frontal bossing appears to be more prominent in USP9X than in KAT6A reports (see second figure of USP9X paper by Reijnders and colleagues (66), and compare to first figure of KAT6A paper by Tham and colleagues (63)). A study performing X chromosome sequencing in individuals with intellectual disability and an X-linked inheritability pattern (i.e. affected males with no affected females in the family) observed that USP9X mutations could have caused this phenotype in one of their 208 studied families (67). Importantly, this observation indicates that USP9X mutations in the X chromosome can lead to developmental abnormalities in both males and females. No additional clinical characteristics were reported in this study within the USP9X subgroup, and we therefore cannot determine whether retrocerebellar arachnoid cyst was also present in that case. While the USP9X variant in our patient was reported as a variant of uncertain

significance by the genetic testing company, the phenotype in our patient matches previous USP9X mutation reports. Further, as in the KAT6A variant, gene testing report specified that USP9X variant in-silico analyses supported a deleterious effect of this mutation.

Taken together, our exome sequencing findings highlight the utility of performing gene sequencing when investigating etiological possibilities in cases of cerebellar compression or distortion presenting with intellectual disability. A high percentage of intellectual disability cases are thought to be due to monogenic mutations - exome sequencing investigations estimate that relevant monogenic mutations can be identified in approximately 16% of individuals with intellectual disability (68). As exome sequencing databases increase in size, this percentage is expected to increase (69).

4.4 Etiological possibilities in our patient exemplify the complexity of this field of cerebellar clinical and scientific practice

[FIGURE 4 HERE]

Our literature review, fMRI analysis, and exome sequencing findings unmask multiple etiological possibilities.

(i) Cerebellar compression could cause or potentially unmask psychiatric and neurodevelopmental symptoms (**Fig. 4a**). Cerebellar tract tracing (39–44), neuroimaging (48–50,61), and clinical (2,45–47) studies have established that the cerebellum plays a role in cognition and affect, and previous studies have reported

cerebellar arachnoid cysts in patients with psychiatric or neurodevelopmental symptoms (23–30) that may improve after cyst drainage (23,26). Further, our fMRI analysis revealed abnormal cerebellar functional connectivity in our patient when compared to a group of 36 controls (**Fig. 2**). Cerebellar dysfunction in our patient is also supported by an intact delayed recall ability in our patient as tested by the Cerebellar Cognitive Affective / Schmahmann Syndrome Scale, a feature consistently observed in cases of isolated cerebellar injury or degeneration (2).

(ii) Genetic abnormalities revealed by exome sequencing testing could also contribute to neurodevelopmental and psychiatric symptoms. KAT6A mutations have been associated with intellectual delay and hypotonia, consistent with the clinical presentation of our patient (**Fig. 4b**). USP9X mutation can also cause intellectual delay, autism, frontal bossing and hypotonia, all of which are present in our patient (**Fig. 4c**). Symptom progression occurred over time in the absence of progression of the dimensions of the cerebellar cyst. This aspect of the patient's history may also argue against a pure cerebellar compression etiology; however, previous reports in the literature have described a delayed onset of psychiatric symptoms in postoperative cases of cerebellar injury (70). While the exome sequencing report in our patient considered KAT6A to be a likely pathogenic variant and USP9X to be a variant of uncertain significance, clinical phenotype of our patient (intellectual delay, hypotonia, autism, retrocerebellar arachnoid cyst) may be more consistent with USP9X than with KAT6A case reports. Genetic/epigenetic and environmental modifiers may attenuate the KAT6A mutation phenotype (63), and it is therefore possible that a major portion of the phenotype of our patient is due to USP9X rather than KAT6A mutation.

(iii) USP9X mutations are also associated with the presence of retrocerebellar arachnoid cysts (66), generating a third etiological possibility (**Fig. 4d**); namely, USP9X may indirectly contribute to psychiatric / neurodevelopmental symptoms by promoting the development of a retrocerebellar cyst that causes cerebellar compression, cerebellar dysfunction, and thereby alterations in neurodevelopment, thought, and affect.

There are few studies investigating USP9X and KAT6A mutations in the literature. First, while USP9X mutation has been described to cause neurodevelopmental symptoms in patients without a retrocerebellar arachnoid cyst (66), a comparison between USP9X mutation patients with and without retrocerebellar arachnoid cysts has not been performed. Second, autism symptoms have not been consistently assessed in USP9X (66,67) and KAT6A (63–65) studies - these studies most commonly test for the presence of intellectual disability, developmental delay, neurological signs, brain structural abnormalities, and other non-neurological pathology, but not social-emotional functioning or restricted/repetitive behaviors. Reports of presence or absence of core autism features in USP9X and KAT6A mutation studies would have been useful in order to further determine which of the two genes is most likely related to the clinical presentation of our patient.

4.5 Decision making in this case

In conventional neurosurgery and radiology, the genetic findings and lack of enlargement of the cyst associated with clinical progression would argue against the

possibility of neurosurgical intervention in this patient. While this is an evolving field of clinical neuroscience, a decision was made not to operate in this case at this time. Clinical monitoring will continue, and changes in the patient's neuropsychiatric constellation or cyst structural characteristics might reopen this discussion. For example, clinical worsening associated with an enlargement of the cyst would argue in favor of surgical intervention. Changes in management guidelines might also lead to a reevaluation of this case – as discussed in the following section, progress within this sphere of cerebellar neuroscience may play a central role in the evolution of clinical decision making in cerebellar neuropsychiatry.

4.6 Implications for future investigations

Our results highlight the need for future studies to examine potential causal relationships between cerebellar compression or distortion, cerebellar dysfunction, and the presence of neurodevelopmental or psychiatric symptoms. First, group studies are needed in order to generalize this single-case fMRI observation to a larger population of patients with PFAC and neurodevelopmental or psychiatric symptoms. Second, future studies might examine other forms of cerebellar compression that may present with concomitant neurodevelopmental or psychiatric symptoms, such as Chiari malformation (71–73), or the rare constellation of Frontotemporal Brain Sagging Syndrome (74). Third, imaging studies examining differences in brain function before and after cyst drainage or cerebellar decompression surgery are needed in order to test a causal relationship between cerebellar compression, cerebellar dysfunction, and the presence of neurodevelopmental or psychiatric symptoms. This line of inquiry would be clinically relevant given the prevalence of PFAC in the general population (21), the existence of

patients with cognitive or psychiatric symptoms and the presence of PFAC (23–30), and the possibility of symptom improvement after cyst drainage (23,26). Psychiatric or neurodevelopmental abnormalities are not currently an indication for neurosurgery in cases of cerebellar compression, and future developments in this field may help establish guidelines to inform these decisions.

5. CONCLUSION

The current state of the literature examining possible relationships between cerebellar compression, cerebellar dysfunction, and cognitive / psychiatric symptoms remains inconclusive. Basic cerebellar cognitive neuroscience establishing a role of the cerebellum in thought and affect, together with reports of neuropsychiatric symptom improvement after PFAC drainage, make it reasonable to consider that PFAC might cause cognitive / psychiatric symptoms in some patients. At the same time, there is a nontrivial prevalence of PFAC in the asymptomatic population, and a significance chance that PFAC are incidental findings in the context of primary cognitive or psychiatric symptoms. The neuroimaging findings presented here are relevant because they report for the first time abnormal cerebellar function using measures other than clinical and behavioral testing in a case of cerebellar compression and concomitant cognitive / psychiatric symptoms. Importantly, these neuroimaging findings do not establish a causal relationship between cerebellar compression and cerebellar dysfunction – future studies comparing brain and behavior measures before and after cyst drainage will be crucial in this evolving field of neuroscience. Exome sequencing revealed that genetic influences might account for our patient's clinical constellation, and perhaps also influence the presence of PFAC, highlighting the complexity of this

area of cerebellar clinical and scientific practice. Taken together, the present report underscores the complexity and unmasks testable questions for an important knowledge gap in the medicine and science of the cerebellum.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest. JDS consults for Bayer, Biogen, Biohaven, and Cadent Pharmaceuticals, and has no conflicts of interest to declare that may be perceived as biasing the content of this manuscript.

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TABLES

Brain region of each cluster	Peak cluster coordinates (MNI)	Voxels per cluster	F max
Precentral gyrus, cingulate gyrus, left	-12 -26 +60	2883	9.94
Subcallosal cortex, paracingulate gyrus, right	+24 +26 +10	1067	10.56
Supramarginal gyrus, left	-46 -28 +30	846	9.77
Supramarginal gyrus, right	+64 -42 +42	633	9.28
Precentral gyrus, right	+58 +04 +02	369	7.32
Cerebellum, right	+14 -52 -24	334	9.28

Table 1. MVPA results comparing our patient versus a group of 36 health controls. Clusters are identified in the cerebral cortex and the cerebellum. Cerebellar cluster is present when examining clusters that survived our statistical thresholds (see methods), and is used as a seed for subsequent analyses (Table 2, Figure 2b, 2c). Additional cerebral cortical and cerebellar clusters with size k<300 that also survived our statistical thresholds are not reported; larger clusters are more likely to be true positives (9), and our largest cerebellar cluster result (k=334) was sufficient to test for the presence of disrupted cerebellar functional connectivity in our patient compared to controls.

Cluster number	Brain region of each cluster	Peak cluster coordinates (MNI)	Voxels per cluster	T max
1	Anterior cingulate gyrus, left and right	-02 +00 +50	2544	7.61
2	Supramarginal gyrus, right	+64 -52 +26	944	8.12
3	Occipital pole, left	-40 -80 +00	605	5.76
4	Inferior frontal gyrus, left	-32 +12 +02	557	6.14
5	Lateral occipital cortex, right	+26 -82 +02	432	6.76
6	Inferior frontal gyrus, right	+36 +02 +14	414	6.17
7	Supramarginal gyrus, left	-56 -30 +38	357	6.51
8	Precentral gyrus, right	+34 -06 +34	185	5.77
9	Occipital fusiform gyrus, left	-28 -58 -06	146	5.86

10	Postcentral gyrus, right	+14 -28 +62	138	5.34
11	Frontal pole, left	-24 +60 -18	119	5.50
12	Frontal pole, right	+32 +36 +26	117	6.91
13	Subcallosal cortex, left	-24 +40 -16	97	5.03
14	Angular gyrus, left	-62 -56 +20	88	4.92
15	Lateral occipital/superior parietal cortex, right	+24 -60 +60	87	4.94
16	Frontal pole, left	-02 +66 +14	82	5.76
17	Lateral occipital cortex, left	-32 -64 +36	71	5.61

Table 2. Post-hoc seed-to-voxel results comparing our patient versus a group of 36 healthy controls using the cerebellar MVPA result cluster (Figure 2B, cluster shown in cerebellum flat map) as a seed. Clusters of hyper and hypoconnectivity (i.e. positive and negative findings in our two-tailed Patient > Controls contrast, respectively) are identified in the cerebral cortex.

FIGURES

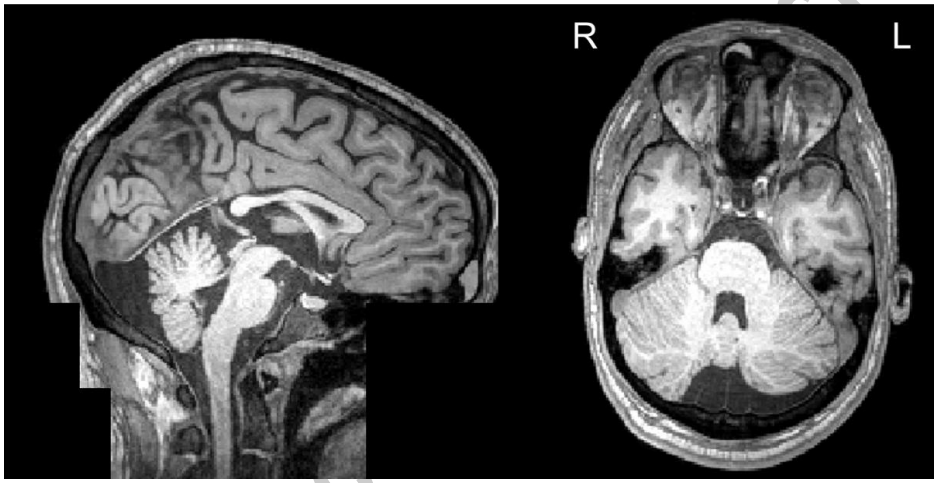

Figure 1. T1w image demonstrating presence of a retrocerebellar arachnoid cyst. Face is removed to preserve anonymity.

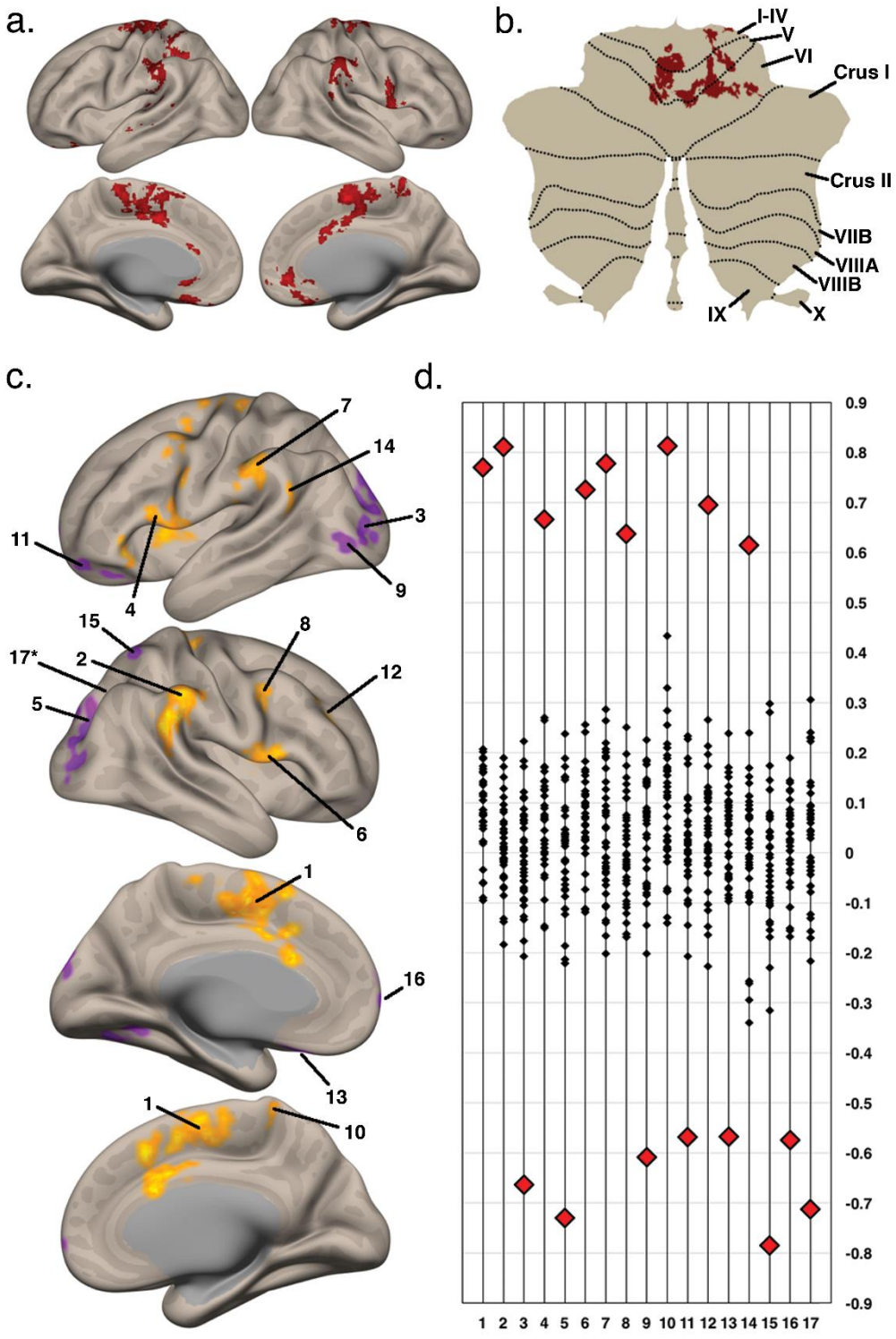

Figure 2. MVPA detected clusters showing abnormal whole-brain connectivity in our patient compared to controls in the cerebral cortex **(a)** and cerebellum **(b)**. **(c)** Post-hoc seed-to-voxel analysis using the cerebellum MVPA cluster (shown in b) as a seed revealed 17 cerebral cortical clusters of hypo (purple) and hyperconnectivity (yellow), labeled here from 1 to 17. **(d)** Plot showing, for each of the 17 clusters shown in (c), connectivity values between each of these clusters and the cerebellum MVPA cluster shown in (a) for the patient (red diamonds) and each of the 36 controls (black diamonds). * cluster 17 is

located at a lateral occipital cortex portion that is not visible in the cerebral cortex representation shown in (c).

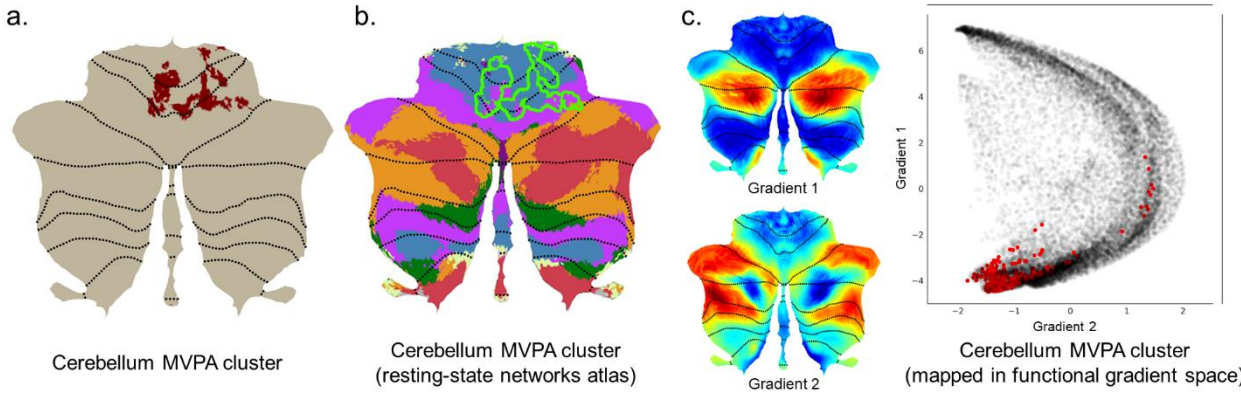

Figure 3. Functional interpretation of the topographical distribution of cerebellar MVPA result. **(a)** Cerebellar MVPA cluster. **(b)** Overlapping our cluster (green outline) with a cerebellar resting-state network map (49) reveals overlap mostly with somatomotor network (blue), and also with some aspects of ventral attention (purple) and frontoparietal network (orange). **(c)** Cerebellum functional gradients as developed by Guell and colleagues (11) (left) and their relationship with our cerebellar MVPA cluster visualized in a scatterplot (right). Each black dot in the scatterplot represents a cerebellar voxel, position of each dot along x and y axis corresponds to position along gradient 1 and gradient 2 for that cerebellar voxel, and dots shown in red correspond to the voxels that are included in our cerebellar MVPA cluster. Cerebellar MVPA cluster is located in motor (low gradient 1 and low gradient 2 values) as well as task-focused cognitive processing regions of the cerebellum (high gradient 2 values).

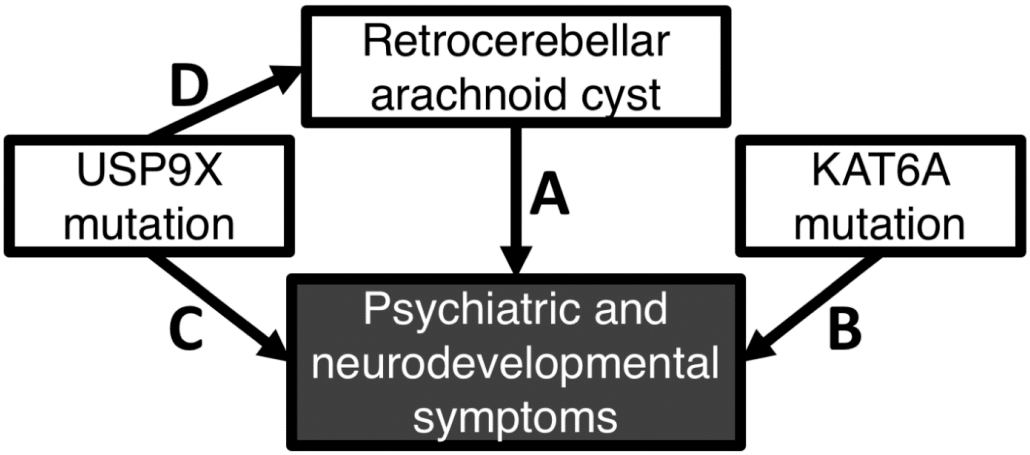

Figure 4. Etiological possibilities in our patient. In the discussion, we examine each possibility independently and in combination.