

Overlapping Metabolic and Endocrine Dysfunction during Wolff Parkinson White Syndrome: A Cause or Consequence?

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Viewpoint

In North America and globally, 1 out of 10 people suffer from orphan/rare diseases. Among these patients which are mostly children, 30% of the children die within the first decade. According to National Organization for Rare Disease database (NORD), there are around approximately 7000 rare diseases (<https://rarediseases.org>). This viewpoint would definitely shed light into the importance of metabolic and endocrine abnormalities that co-exist with a rare disease. Some of the rare diseases which have been shown to be accompanied by metabolic abnormalities include Bartter's syndrome, Schindler disease, Incontinentia Pigmenti, Cystinosis, Marfan disease and Wolff Parkinson White syndrome. This article will specially focus on the cardiovascular complication- WPW syndrome.

WPW syndrome is a rare congenital heart disease that is accompanied by irregularities in cardiac conduction systems and with most significant clinical manifestation being supraventricular tachycardia accompanied by dyspnea and syncope. The causes of WPW being mostly genetic with 50% chance of inheriting the disease if just one of the parents have the disease. Even though genetic factor has been shown to be the major culprit, there are many known and unknown gene targets that could contribute towards this complication. Major emphasis has been on the PRKAG2 (AMPK gene) mutations that results in WPW syndrome or WPW like phenotype. PRKAG2 mutations have been accompanied by a major metabolic defect with excess glycogen accumulation in the form of granules in the cardiac tissue and pathophysiological defect involving cardiac hypertrophy [1]. It can also be accompanied by major structural and functional defects including atrial septal defects especially the tricuspid valve allowing the retrograde flow of blood back into the atrium [1,2]. The PRKAG gene is responsible for synthesis of AMPK protein. AMPK, the known master metabolic regulator or metabolic switch maintains the systemic glucose and fatty acid balance especially with regard to cardiovascular tissue. AMPK consists of the α , β and γ subunits, α considered a catalytic subunit comprising of $\alpha 1$ and $\alpha 2$, β being non catalytic made up of $\beta 1$ and $\beta 2$ and γ being the non-catalytic regulatory subunit consisting of $\gamma 1$, $\gamma 2$ and $\gamma 3$.

PRKAG2 mutations follow dominant pattern of inheritance with 50% of off springs inheriting the mutation. The metabolic dysfunction in WPW syndrome is a major contribution due to the PRKAG2 mutation. Following PRKAG2 mutation, there is an unregulated AMPK activity [2], mostly with an enhanced AMPK function leading to increased glucose uptake, enhanced fatty acid uptake and fatty acid oxidation, especially in the cardiac tissues with WPW syndrome utilizing more fatty acids than glucose. This enhanced utilization of fatty acids by oxidation in the presence of an enhanced glucose uptake due to increased AMPK activity results in storage of glucose in the form of glycogen [3].

Some of the evidences in mice models and in clinical subjects with WPW syndrome support the claim that WPW disorder is accompanied by metabolic dysfunction-mostly a PRKAG2/AMPK mediated effect. Arad et al. showed in a well validated animal model over expressing PRKAG 2 N488I missense human mutation in mice aged 8-10 week old showed the LV hypertrophy with accumulation of glycogen granules in

cardiac tissue [4]. This work in rodent model was followed by studies in human subjects, and one of the interesting study is the one by Akman et al. [5], where they showed heart tissue of human infant aged 5 months with a novel R384T heterozygous mutation in PRKAG2, affecting an arginine residue in the N-terminal AMP-binding domain of AMPK with unregulated AMPK activity was accompanied by severe ventricular hypertrophy and glycogen accumulation in the cardiovascular tissue [5]. Because of the tremendous ability of PRKAG2 mutation to alter metabolism and accumulate glycogen in cardiovascular tissue, there is a substantial overlap of this mutation induced cardiac complication with other glycogen storage diseases.

Now the question arises whether it is just a PRKAG2 mutation or any mutations that could contribute towards cardiac glycogen accumulation could result in WPW or WPW like syndromes? There are various glycogen storage diseases including glycogen storage disease GSD III and IV due to changes in the branching and debranching enzyme activity, GSD VIII due to phosphorylase kinase activity indirectly regulating glycogen phosphorylase leading to a decrease in glycogen breakdown, and also the Danon's disease due to dysfunction in LAMP2 protein function and Pompe's disease with alteration in acid glucosidase activity both leading to an altered lysosomal function contributing towards glycogen accumulation induced abnormalities.

Studies by Zhao et al. [6] LAMP2 mutations in Danon's disease show similar phenotype as PRKAG2 mutation in Wolff Parkinson Syndrome in human subjects. Cardiac tissue staining of subject 15 years of age showed glycogen deposition as shown with PAS staining along with hypertrophy in the presence of LAMP2 mutation. Another interesting study by Lee et al. [7] observed and validated the connection put forth in this viewpoint that there is a strong correlation between glycogen storage disease, the Pompe's disease associated with glycogen accumulation and cardiovascular complications like cardiomegaly with features of hypertrophic cardiomyopathy in different subjects between ages 1 year-4 years old. These studies validate the claim that the metabolic abnormalities we perceive in WPW syndrome could result not only because of PRKAG2/AMPK mutation but also other proteins like LAMP2, Phosphorylase kinase and acid glucosidase that could result in similar phenotype with a PRKAG2 mediated WPW phenotype with glycogen accumulation and cardiac hypertrophy (Figure 1).

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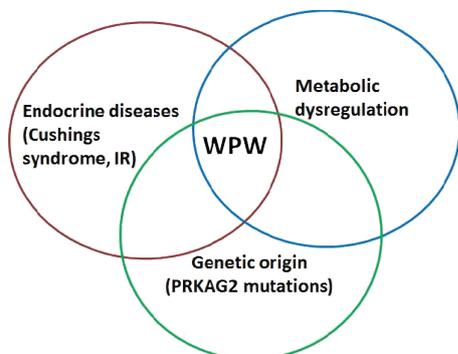


Figure 1: WPW syndrome could be due to genetic origin, but there are contributions from metabolic alterations and endocrine disorders that could lead to glycogen accumulation and cardiac dysfunction as seen with WPW syndrome.

Finally, would like to also focus on the role of endocrine abnormalities contributing towards WPW syndrome. It could also be possible that certain hormones that could induce an unregulated AMPK activity or metabolic alteration could result in WPW like syndrome. Some interesting observations in cardiac cells following glucocorticoids treatment as observed in both *in vitro* and *in vivo* models by Puthanveetil et al. [3,8] showed that a single excess dose of synthetic glucocorticoid dexamethasone was able to alter cardiac cell metabolism with an increased AMPK activity. This enhanced short term AMPK activity was associated with an enhanced GLUT4 mediated glucose uptake, Puthanveetil et al. induction with increased PDH phosphorylation and decrease in glucose oxidation, followed by increased fatty acid oxidation. This channelizes glucose to deposit in the form of glycogen in the cardiac tissue as observed with PAS staining in rat cardiac tissue [8]. These observations give us a strong connection between how endocrine abnormalities like glucocorticoid excess, as seen with endocrine disorders like Cushing's syndrome, adrenal tumors, and insulin resistance could also lead to an alteration in AMPK activity with disturbed metabolism and glycogen accumulation in cardiac tissues as seen in WPW syndrome. The question is whether we should only focus on WPW like features occurring during the first decade of life span or should also look into metabolic and endocrine abnormalities induced disturbance in cardiovascular

metabolism followed by glycogen accumulation and pathological hypertrophy as seen with WPW in any decade of the life span.

This view point sheds light into deeper molecular mechanisms that could aggravate an existing WPW due to genetic origin and also into WPW like indications which could occur due to metabolic and endocrine abnormalities without a known genetic origin. Both from clinical and biomedical perspective a detail study of the overlapping endocrine and metabolic disturbance in WPW syndrome or WPW like indications, we will be able to hinder or slow down the devastating effects seen with this complex cardiac disease, WPW syndrome.

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